United States
Environmental Protection Agency

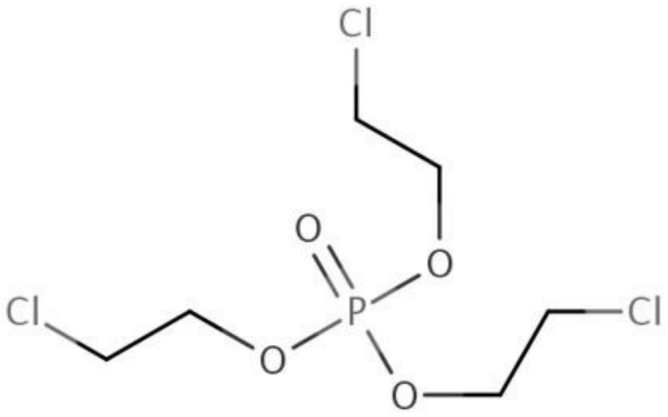
September 2024
Office of Chemical Safety and
Pollution Prevention

Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP)

Systematic Review Supplemental File:

Data Quality Evaluation Information for Human Health Hazard Animal Toxicology

CASRN: 115-96-8



September 2024

This supplemental file contains information regarding the data quality evaluation results for data sources that met the PECO screening criteria for the *Risk Evaluation for Tris(2-chloroethyl) phosphate (TCEP)* and were used to characterize human health hazard. EPA conducted data quality evaluation based on author-reported descriptions and results; additional analyses (*e.g.*, statistical analyses performed during data integration into the risk evaluation) potentially conducted by EPA are not contained in this supplemental file. EPA used the TSCA systematic review process described in the *Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances* (also referred to as '2021 Draft Systematic Review Protocol'). Any updated steps in the systematic review process since the publication of the 2021 Draft Systematic Review Protocol are described in the *Risk Evaluation for Tris(2-chloroethyl) phosphate (TCEP) – Systematic Review Protocol*.

Table of Contents

Study Citation:	Confidential, (1973). Toxicology laboratory report - tris (2-chloroethyl) phosphate.
Health Outcome(s):	Irritation
Reported Health Effect(s):	Skin and Eye Irritation.
Duration:	Acute (less than or equal to 24 hr) Single dose
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	6311026

Domain		Metric	Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	Test substance was identified as tris (2-chloroethyl) phosphate (CASRN 115-96-8).
	Metric 2:	Test Substance Source	Low	The test substance source was not reported.
	Metric 3:	Test Substance Purity	Low	Purity of test substance was not reported.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	N/A	Not necessary for skin and eye irritation testing. The untreated eye served as the control in the eye irritation study.
	Metric 5:	Positive Controls	N/A	Positive Controls do not apply to this study.
	Metric 6:	Randomized Allocation of Animals	N/A	Not necessary for this study type.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Low	Information on preparation and storage of the test substance was not reported.
	Metric 8:	Consistency of Exposure Administration	High	Details of exposure administration were reported and exposures were administered consistently across study groups.
	Metric 9:	Reporting of Doses/Concentrations	Low	For the eye irritation study, 0.1 ml of test substance was instilled into the eye, while 0.5 ml of test substance was applied to the skin for the dermal irritation study. The concentration of TCEP in the applied doses was not reported.
	Metric 10:	Exposure Frequency and Duration	High	Exposure frequency and duration were sufficient for this study.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	N/A	The goal of this study was not to determine a dose-dependent effect.
	Metric 12:	Exposure Route and Method	High	The exposure routes and methods were appropriate for this study.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	Low	New Zealand rabbits weighing 1.6-2.1 kg were used. The sex and source of the test animals was not reported
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Low	Husbandry conditions were not reported.
	Metric 15:	Number of Animals per Group	Medium	Number of animals per group were sufficient for this study.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	Outcome assessment methodology was adequate for this study.

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Study Citation:	Confidential, (1973). Toxicology laboratory report - tris (2-chloroethyl) phosphate.
Health Outcome(s):	Irritation
Reported Health Effect(s):	Skin and Eye Irritation.
Duration:	Acute (less than or equal to 24 hr) Single dose
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	6311026

Domain	Metric		Rating	Comments
	Metric 17:	Consistency of Outcome Assessment	High	Details of the outcome assessment protocol were reported and outcomes were assessed consistently.
	Metric 18:	Sampling Adequacy	High	Reported information indicates the study used adequate sampling.
	Metric 19:	Blinding of Assessors	N/A	Not necessary for this study type.
	Metric 20:	Negative Control Response	N/A	Negative controls are not necessary for this study type.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Low	Confounding variables (body weight, food/water intake) were not reported.
	Metric 22:	Health Outcomes Unrelated to Exposure	Low	4 out of 6 rabbits died during the dermal irritation study. Cause of death was not determined and it is unclear if mortality was due to the test substance or something (e.g., infection) unrelated to exposure.
	Metric 23:	Data Presentation and Analysis	N/A	Statistical analysis was not possible, as only a single treatment group was included in the eye and skin irritation tests.
	Metric 24:	Reporting of Data	High	Quantitative data was reported for the skin irritation study. For eye irritation, study authors clearly state that no evidence of irritation was observed.

Overall Quality Determination Medium

Study Citation:	Confidential, (1973). Toxicology laboratory report - tris (2-chloroethyl) phosphate.
Health Outcome(s):	Mortality
Reported Health Effect(s):	mortality
Duration:	Acute (less than or equal to 24 hr) Single dose
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	6311026

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	Test substance was identified as tris (2-chloroethyl) phosphate (CASRN 115-96-8).
	Metric 2:	Test Substance Source	Low	The test substance source was not reported.
	Metric 3:	Test Substance Purity	Low	Purity of test substance was not reported.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	N/A	Not necessary for skin and eye irritation testing. The untreated eye served as the control in the eye irritation study.
	Metric 5:	Positive Controls	N/A	Not necessary for this study type.
	Metric 6:	Randomized Allocation of Animals	N/A	Not necessary for this study type.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Low	Information on preparation and storage of the test substance was not reported.
	Metric 8:	Consistency of Exposure Administration	High	Details of exposure administration were reported and exposures were administered consistently across study groups.
	Metric 9:	Reporting of Doses/Concentrations	Low	For the eye irritation study, 0.1 ml of test substance was instilled into the eye, while 0.5 ml of test substance was applied to the skin for the dermal irritation study. The concentration of TCEP in the applied doses was not reported.
	Metric 10:	Exposure Frequency and Duration	High	Exposure frequency and duration were sufficient for this study.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	N/A	The goal of this study was not to determine a dose-dependent effect.
	Metric 12:	Exposure Route and Method	High	The exposure routes and methods were appropriate for this study.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	Low	New Zealand rabbits weighing 1.6-2.1 kg were used. The sex and source of the test animals was not reported
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Low	Husbandry conditions were not reported.
	Metric 15:	Number of Animals per Group	Medium	Number of animals per group were sufficient for this study.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	Outcome assessment methodology was adequate for this study. Animals were observed for mortality.
	Metric 17:	Consistency of Outcome Assessment	High	Outcome of study assessment is adequate for this study.
	Metric 18:	Sampling Adequacy	High	All treated animals were observed for mortality.

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Study Citation:	Confidential, (1973). Toxicology laboratory report - tris (2-chloroethyl) phosphate.
Health Outcome(s):	Mortality
Reported Health Effect(s):	mortality
Duration:	Acute (less than or equal to 24 hr) Single dose
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	6311026

Domain	Metric		Rating	Comments
	Metric 19:	Blinding of Assessors	N/A	Not necessary for this study type.
	Metric 20:	Negative Control Response	N/A	Negative controls are not necessary for this study type.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Low	Confounding variables may have played a factor because of the lack of information on animals.
	Metric 22:	Health Outcomes Unrelated to Exposure	Low	4 out of 6 rabbits died. Cause of death was not determined and it is unclear if mortality was due to the test substance or something (e.g., infection) unrelated to exposure.
	Metric 23:	Data Presentation and Analysis	N/A	Statistical analysis was not possible, as only a single treatment group was included in the eye and skin irritation tests.
	Metric 24:	Reporting of Data	Medium	Study authors reported that 4 out of 6 rabbits died following the 4-hr dermal exposure. Animals were observed for up to 96-hours, however, study authors do not report the specific timing of when each rabbit died.

Overall Quality Determination Medium

Study Citation:	Confidential, (1973). Toxicology laboratory report - tris (2-chloroethyl) phosphate.
Health Outcome(s):	Neurological/Behavioral
Reported Health Effect(s):	Narcosis and paralysis.
Duration:	Acute (less than or equal to 24 hr) Single dose
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	6311026

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	Test substance was identified as tris (2-chloroethyl) phosphate (CASRN 115-96-8).
	Metric 2:	Test Substance Source	Low	The test substance source was not reported.
	Metric 3:	Test Substance Purity	Low	Purity of test substance was not reported.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	N/A	Not necessary for skin and eye irritation testing. The untreated eye served as the control in the eye irritation study.
	Metric 5:	Positive Controls	N/A	Not necessary for this study type.
	Metric 6:	Randomized Allocation of Animals	N/A	Not necessary for this study type.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Low	Information on preparation and storage of the test substance was not reported.
	Metric 8:	Consistency of Exposure Administration	High	Details of exposure administration were reported and exposures were administered consistently across study groups.
	Metric 9:	Reporting of Doses/Concentrations	Low	For the eye irritation study, 0.1 ml of test substance was instilled into the eye, while 0.5 ml of test substance was applied to the skin for the dermal irritation study. The concentration of TCEP in the applied doses was not reported.
	Metric 10:	Exposure Frequency and Duration	High	Exposure frequency and duration were sufficient for this study.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	N/A	The goal of this study was not to determine a dose-dependent effect.
	Metric 12:	Exposure Route and Method	High	The exposure routes and methods were appropriate for this study.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	Low	New Zealand rabbits weighing 1.6-2.1 kg were used. The sex and source of the test animals was not reported
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Low	Husbandry conditions were not reported.
	Metric 15:	Number of Animals per Group	Medium	Number of animals per group were sufficient for this study.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	Low	Study authors state that eyes were scored for irritation every 24, 48 and 72 hours. Authors do not state how frequently animals were observed for signs of narcosis and paralysis.

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Study Citation:	Confidential, (1973). Toxicology laboratory report - tris (2-chloroethyl) phosphate.
Health Outcome(s):	Neurological/Behavioral
Reported Health Effect(s):	Narcosis and paralysis.
Duration:	Acute (less than or equal to 24 hr) Single dose
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	6311026

Domain	Metric		Rating	Comments
	Metric 17:	Consistency of Outcome Assessment	Low	Details regarding the execution of the study protocol for outcome assessment were not reported. Study authors do not state when or how frequently animals were observed for signs of narcosis.
	Metric 18:	Sampling Adequacy	High	Reported information indicates the study used adequate sampling.
	Metric 19:	Blinding of Assessors	N/A	Not necessary for this study type.
	Metric 20:	Negative Control Response	N/A	Negative controls are not necessary for this study type.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	Confounding variables (body weight, food/water intake) were not reported.
	Metric 22:	Health Outcomes Unrelated to Exposure	Low	4 out of 6 rabbits died. Cause of death was not determined and it is unclear if mortality was due to the test substance or something (e.g., infection) unrelated to exposure.
	Metric 23:	Data Presentation and Analysis	N/A	Statistical analysis was not possible, as only a single treatment group was included in the eye and skin irritation tests.
	Metric 24:	Reporting of Data	Low	Study authors reported that 4 out of 6 rabbits exhibited signs of narcosis and paralysis following ocular exposure to the test substance. Study authors do not report the timing of when these observations were made.

Overall Quality Determination Low

Study Citation:	Sprague, G. L., Sandvik, L. L., Brookins-Hendricks, M. J., Bickford, A. A. (1981). Neurotoxicity of two organophosphorus ester flame retardants in hens. Journal of Toxicology and Environmental Health, Part A: Current Issues 8(3):507-518.
Health Outcome(s):	Neurological/Behavioral
Reported Health Effect(s):	Inhibition of plasma cholinesterase, Inhibition of neurotoxic esterase
Duration:	Acute (less than or equal to 24 hr) 1 dose
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	656590

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	Medium	No CASRN was identified but the name is specific enough to identify the exact structure.
	Metric 2:	Test Substance Source	High	The manufacturer was identified and chemical structure is not variable.
	Metric 3:	Test Substance Purity	Low	There was no information on purity.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	Low	The controls received corn oil but the dosed group received the test substance neat.
	Metric 5:	Positive Controls	Medium	TOCP was used as a positive control and is appropriate for this test.
	Metric 6:	Randomized Allocation of Animals	Low	The study did not mention random allocation of animals.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Medium	There was limited/no info on preparation/storage but the chemical was administered neat; it appears to be stable; and it was a short term study so it is not expected to result in substantial effects.
	Metric 8:	Consistency of Exposure Administration	Medium	Corn oil in negative control vs. none in dose groups may result in some differences but not likely to be substantial given that this is an acute study.
	Metric 9:	Reporting of Doses/Concentrations	High	Doses were identified as g/kg.
	Metric 10:	Exposure Frequency and Duration	High	Exposure frequency and duration were appropriate to the test.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	A limit test used a dose higher than required.
	Metric 12:	Exposure Route and Method	High	The oral route was used and was acceptable.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	Low	The source of the hens was not reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	Most husbandry information was reported except humidity and whether the animals were acclimatized before treatment (although the figure seems to indicate animals were kept for several days before treatment).
	Metric 15:	Number of Animals per Group	Low	The number of animals was not reported for the acute biochemical portion of the study.
Domain 5: Outcome Assessment				

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Study Citation:	Sprague, G. L., Sandvik, L. L., Brookins-Hendricks, M. J., Bickford, A. A. (1981). Neurotoxicity of two organophosphorus ester flame retardants in hens. Journal of Toxicology and Environmental Health, Part A: Current Issues 8(3):507-518.
Health Outcome(s):	Neurological/Behavioral
Reported Health Effect(s):	Inhibition of plasma cholinesterase, Inhibition of neurotoxic esterase
Duration:	Acute (less than or equal to 24 hr) 1 dose
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	656590

Domain	Metric		Rating	Comments
	Metric 16:	Outcome Assessment Methodology	Low	Several deviations from OECD TG 870.6100 (1998) were noted. The animals were sacrificed at 24 hrs after treatment instead of 48 hrs. A non-tissue blank was not used for the NTE assay. NTE was measured only in brains and not in the spinal cord. AChE was taken from plasma and not the brain.
	Metric 17:	Consistency of Outcome Assessment	Medium	The NTE activity was measured 18-24 hrs after sacrifice, so there was some variation. However, samples for both NTE and AChE were both taken at the same time for the control and TCEP dose group.
	Metric 18:	Sampling Adequacy	Low	No information on sampling (i.e., number of hens) was reported for the acute/biochemical portion of the study.
	Metric 19:	Blinding of Assessors	N/A	Blinding of assessors is not considered necessary for the acute/ biochemical portion of the study because the measures are objective.
	Metric 20:	Negative Control Response	Low	The authors note that mild adverse signs were noted after administration of corn oil in the control group. Given that Marek's disease is related to the outcome of interest, it is not clear whether it may have affected some outcomes; it is assumed chickens in all groups may have been exposed to the virus that causes Marek's disease but the authors don't clearly state this.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	It is unclear how deviations from the protocol and use of corn oil only may have affected the outcome.
	Metric 22:	Health Outcomes Unrelated to Exposure	Medium	Authors mention that the corn-oil treated hens (controls) may have had Marek's disease, which effects the nerves and there were mild adverse effects directly after gavage of the control group. It is assumed that all chickens were likely to have been exposed to the virus that causes Marek's but the authors were not clear about that.
	Metric 23:	Data Presentation and Analysis	High	Statistical methods were described.
	Metric 24:	Reporting of Data	High	Both biochemical measures (NTE from brain and plasma AChE) were reported.

Overall Quality Determination Medium

Study Citation:	Tilson, H. A., Veronesi, B., Mclamb, R. L., Matthews, H. B. (1990). Acute exposure to tris(2-chloroethyl)phosphate produces hippocampal neuronal loss and impairs learning in rats. Toxicology and Applied Pharmacology 106(2):254-269.
Health Outcome(s):	Neurological/Behavioral
Reported Health Effect(s):	TCEP treatment resulted in behavioral effects (convulsions) and histopathological changes in the hippocampus. The seizure-related and neurohistological effects were significantly attenuated by pretreatment with atropine or chlordizepoxide, suggesting that the hippocampal damage was related to the seizure. In a second experiment, rats were mildly impaired in the acquisition of a reference memory task in a water maze, however, rats were consistently impaired in performing a repeated acquisition task in the water maze.
Duration:	Acute (less than or equal to 24 hr) Acute oral (gavage)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	107658

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was identified definitively by name.
	Metric 2:	Test Substance Source	High	The source of the test substance was identified.
	Metric 3:	Test Substance Purity	Low	Test substance purity was not provided.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	This is a single dose study to structural and functional neurotoxic effects
	Metric 5:	Positive Controls	N/A	A positive control was not included or needed.
	Metric 6:	Randomized Allocation of Animals	Low	The study did not report how animals were allocated.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Medium	Preparation/administration of test substance is described, but storage is not reported however the assay is a short-term study and therefore storage is unlikely to affect results.
	Metric 8:	Consistency of Exposure Administration	High	Exposures were administered consistently across study groups.
	Metric 9:	Reporting of Doses/Concentrations	Medium	Only nominal doses were reported.
	Metric 10:	Exposure Frequency and Duration	High	Single exposure was reported.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	Low	Only a single treated group was used.
	Metric 12:	Exposure Route and Method	High	The route and method of exposure were reported and were suited to the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	Medium	Characteristics including starting body weight were not reported, but are unlikely to have a substantial impact on results.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	High	All husbandry conditions were reported (e.g., temperature, humidity, light- dark cycle, diet, water availability) and were adequate and the same for control and exposed populations, such that the only difference was exposure.
	Metric 15:	Number of Animals per Group	Low	The number of animals per study group was not clearly reported for all parameters. It appears to range from 6-8 animals.
Domain 5: Outcome Assessment				

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Study Citation:	Tilson, H. A., Veronesi, B., Mclamb, R. L., Matthews, H. B. (1990). Acute exposure to tris(2-chloroethyl)phosphate produces hippocampal neuronal loss and impairs learning in rats. Toxicology and Applied Pharmacology 106(2):254-269.
Health Outcome(s):	Neurological/Behavioral
Reported Health Effect(s):	TCEP treatment resulted in behavioral effects (convulsions) and histopathological changes in the hippocampus. The seizure-related and neurohistological effects were significantly attenuated by pretreatment with atropine or chlordizepoxide, suggesting that the hippocampal damage was related to the seizure. In a second experiment, rats were mildly impaired in the acquisition of a reference memory task in a water maze, however, rats were consistently impaired in performing a repeated acquisition task in the water maze.
Duration:	Acute (less than or equal to 24 hr) Acute oral (gavage)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	107658

Domain	Metric		Rating	Comments
	Metric 16:	Outcome Assessment Methodology	High	The outcome assessment methodology addressed the intended outcomes of interest.
	Metric 17:	Consistency of Outcome Assessment	High	Details of the outcome assessment protocol were reported and outcomes were assessed consistently across study groups.
	Metric 18:	Sampling Adequacy	High	Reported information indicates the study used adequate sampling for the outcomes of interest.
	Metric 19:	Blinding of Assessors	Low	The study did not report whether assessors were blinded to treatment group.
	Metric 20:	Negative Control Response	High	The biological responses of the negative control group were adequate.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	Although the study did not report all information to determine confounding, reported information did not identify differences.
	Metric 22:	Health Outcomes Unrelated to Exposure	High	There were no differences among groups for health outcomes that could influence the outcome assessment.
	Metric 23:	Data Presentation and Analysis	High	Statistical methods were adequately described.
	Metric 24:	Reporting of Data	High	Data for exposure-related findings were presented for all outcomes.

Overall Quality Determination High

Study Citation:	Umezu, T., Yonemoto, J., Soma, Y., Suzuki, T. (1998). Tris(2-chloroethyl)phosphate increases ambulatory activity in mice: pharmacological analyses of its neurochemical mechanism. Toxicology and Applied Pharmacology 148(1):109-116.
Health Outcome(s):	Neurological/Behavioral
Reported Health Effect(s):	To examine the neurochemical (spontaneous ambulatory activity (AA)) mechanistic effect of TRCP in male mice.
Duration:	Acute (less than or equal to 24 hr) Acute toxicity study
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469219

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	Test substance (tris(2-chloroethyl)phosphate) chemical name and source were identified.
	Metric 2:	Test Substance Source	High	Test substance (tris(2-chloroethyl)phosphate) chemical name and source were identified.
	Metric 3:	Test Substance Purity	Low	Test substance purity not reported.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	Concurrent negative and vehicle control reported as olive oil or saline.
	Metric 5:	Positive Controls	N/A	Not applicable for this study.
	Metric 6:	Randomized Allocation of Animals	Low	No specific information on randomization or allocation of test animals was reported other than: "All experiments in this study were performed with the approval of the Ethic Committee for Experimental Animals of National Institute for Environmental Studies. Mice were put individually in activity cages, and after an adaptation period of 30 min the chemicals were administered."
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Medium	No information on preparation and storage of test material was reported.
	Metric 8:	Consistency of Exposure Administration	High	In all experiments, TRCP was administered consistently intraperitoneally; other drugs were administered consistently subcutaneously at a constant dose volume of 0.1 ml/10 g body weight.
	Metric 9:	Reporting of Doses/Concentrations	High	TRCP was administered intraperitoneally; doses/concentrations were reported.
	Metric 10:	Exposure Frequency and Duration	High	Exposure frequency and duration were reported as either a single i.p. injection of TCEP or in combination with other chemicals.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	The number of exposure groups and dose/concentration were reported for TCEP alone or in combination with other chemicals.
	Metric 12:	Exposure Route and Method	High	The route of administration was i.p. injection.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	High	ICR strain male mice (Clea Japan, Tokyo), 9–12 weeks old and 35–45 g body wt were used in this study.

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Study Citation:	Umezu, T., Yonemoto, J., Soma, Y., Suzuki, T. (1998). Tris(2-chloroethyl)phosphate increases ambulatory activity in mice: pharmacological analyses of its neurochemical mechanism. Toxicology and Applied Pharmacology 148(1):109-116.
Health Outcome(s):	Neurological/Behavioral
Reported Health Effect(s):	To examine the neurochemical (spontaneous ambulatory activity (AA)) mechanistic effect of TRCP in male mice.
Duration:	Acute (less than or equal to 24 hr) Acute toxicity study
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469219

Domain	Metric		Rating	Comments
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	Temperature and light cycle were reported; humidity was not. Each group of 10 animals was housed in a Plexiglas-cage which had a stainless wire mesh top and wooden-flake bedding. Commercial solid food (Clea Japan, Tokyo) and tap water were available ad libitum. The room for breeding animals was artificially illuminated by fluorescentbulbs on a 24-h light-dark schedule (light period: 7 a.m.–7 p.m.), andthe room temperature was 25 6 1.0°C.
	Metric 15:	Number of Animals per Group	Medium	Each group contained 10 animals.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	Outcome assessment methodology address or report the intended outcome(s) of interest. The present study was conducted to clarify the acute effect of tris(2-chloroethyl)phosphate (TRCP), an organophosphate flame retardant, on spontaneous ambulatory activity (AA) in male ICR mice and to examine the neurochemical mechanism of this effect.
	Metric 17:	Consistency of Outcome Assessment	High	The outcome assessment was carried out consistently (i.e., using the same protocol) across study groups (e.g., assessment at the same time after initial exposure in all study groups.
	Metric 18:	Sampling Adequacy	High	Sampling was adequate for the outcome assessment.
	Metric 19:	Blinding of Assessors	N/A	Not applicable for this type of study design.
	Metric 20:	Negative Control Response	High	Negative vehicle control groups were assessed.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	High	No confounding variables reported.
	Metric 22:	Health Outcomes Unrelated to Exposure	High	There were no differences among the study groups in animal attrition or health outcomes unrelated to exposure reported.
	Metric 23:	Data Presentation and Analysis	High	Mean 2-h overall AA counts were first analyzed by one-way analysis of variance (ANOVA), followed by Scheffe´'s multiple comparison test (Yoshimura and Ohashi, 1992). For time course analysis of AA after administration of TRCP, AA counts for each 10 min were plotted from the beginning to the end of the measurement. The time course data were first examined byrepeated measures ANOVA, followed by Fisher's PLSD test to examine the data during the first 10 min after administration of TRCP among all groups. Five percent was used as significance level.
	Metric 24:	Reporting of Data	High	Data for all outcomes measured in this study were reported.

Overall Quality Determination High

Study Citation:	FDRL, (1972). Cholinesterase studies on rats and rabbits with Olin's intermediate for Chemical 58981.
Health Outcome(s):	Immune/Hematological; Immune/Hematological;
Reported Health Effect(s):	Immune/Hematological: Plasma Cholinesterase levels.; Immune/Hematological: Plasma Cholinesterase levels.;
Duration:	Short-term (>1-30 days) 5 days - Rat
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	6311010

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	All Outcomes: The test substance is explained in the document.
	Metric 2:	Test Substance Source	Low	All Outcomes: Origin of test substance is "was supplied by laboratory" but no other information.
	Metric 3:	Test Substance Purity	Low	All Outcomes: There was no indication of purity or if measured, no methods were provided.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	All Outcomes: Control groups had blood drawn prior to treatment to assess baseline cholinesterase levels.
	Metric 5:	Positive Controls	N/A	All Outcomes: No positive controls needed for this study.
	Metric 6:	Randomized Allocation of Animals	Low	All Outcomes: No mention of randomization of animals.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Medium	All Outcomes: Information on test substance preparation indicated the test substance was in corn oil at 10% V/V. No other information was available.
	Metric 8:	Consistency of Exposure Administration	High	All Outcomes: Exposure administration is consistent in this study.
	Metric 9:	Reporting of Doses/Concentrations	High	All Outcomes: Concentrations used were reported.
	Metric 10:	Exposure Frequency and Duration	High	All Outcomes: Exposure frequency and duration were reported.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	N/A	All Outcomes: This was not a dose-dependent study.
	Metric 12:	Exposure Route and Method	High	All Outcomes: Exposure route was appropriate for this study.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	Medium	Immune/Hematological: Test animals species and sex were reported. Strain, and other characteristics (e.g., age, or starting body weight) were not reported but are unlikely to have a substantial impact on results. The test animals were obtained from the laboratory stock from the laboratory conducting the study.; Immune/Hematological: Test animals species and sex were reported. Other characteristics (e.g., age, or starting body weight) were not reported but are unlikely to have a substantial impact on results. The test animals were obtained from the laboratory stock from the laboratory conducting the study.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Low	All Outcomes: No information on animal husbandry conditions was reported.
	Metric 15:	Number of Animals per Group	Medium	All Outcomes: The number of animals was acceptable for this type of study.

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Study Citation:	FDRL, (1972). Cholinesterase studies on rats and rabbits with Olin's intermediate for Chemical 58981.
Health Outcome(s):	Immune/Hematological; Immune/Hematological;
Reported Health Effect(s):	Immune/Hematological: Plasma Cholinesterase levels.; Immune/Hematological: Plasma Cholinesterase levels.;
Duration:	Short-term (>1-30 days) 5 days - Rat
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	6311010

Domain	Metric		Rating	Comments
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	All Outcomes: The outcome methodology addressed the interests sought after in this study.
	Metric 17:	Consistency of Outcome Assessment	High	All Outcomes: Outcome assessment was consistent in this study.
	Metric 18:	Sampling Adequacy	High	All Outcomes: Sampling in this study was adequate.
	Metric 19:	Blinding of Assessors	N/A	All Outcomes: Blinding not required for this study type.
	Metric 20:	Negative Control Response	High	All Outcomes: Negative control response was sufficient for this study.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	High	All Outcomes: No confounding variables were reported.
	Metric 22:	Health Outcomes Unrelated to Exposure	Medium	All Outcomes: Study reported mortality in some animals following treatment.
	Metric 23:	Data Presentation and Analysis	Uninformative	All Outcomes: No mention of statistical analysis or if it was even performed.
	Metric 24:	Reporting of Data	Medium	All Outcomes: Data were reported by day of treatment (RBC and cholinesterase levels). Mortality in some animals was the only other information reported.

Overall Quality Determination Uninformative

Study Citation:	Hazleton Laboratories, (1983). Screening of priority chemicals for potential reproductive hazard (final report) with attachments and cover sheet.
Health Outcome(s):	Neurological/Behavioral; Neurological/Behavioral; Neurological/Behavioral; Lung/Respiratory; Skin/Connective Tissue; Nutritional/Metabolic; Mortality;
Reported Health Effect(s):	Neurological/Behavioral: Tremors, languid, prostrate, ataxia, hunched, head-tilt; Neurological/Behavioral: Tremors, languid, prostrate, ataxia, hunched, head-tilt; Neurological/Behavioral: Tremors, languid, prostrate, ataxia, hunched, head-tilt; Lung/Respiratory: Wheezing, dyspnea; Skin/Connective Tissue: Alopecia, sores, rough hair coat, piloerection; Nutritional/Metabolic: Body Weight; Mortality: Survival/Mortality;
Duration:	Short-term (>1-30 days) 8-day Reproductive study – Skin
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	790471

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	All Outcomes: Test Substances used were listed in the introduction.
	Metric 2:	Test Substance Source	High	All Outcomes: Test Substance was supplied by NIOSH.
	Metric 3:	Test Substance Purity	High	All Outcomes: Each chemical purity was determined by Hazelton laboratory.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	All Outcomes: Vehicle control with corn oil were used for the test substance.
	Metric 5:	Positive Controls	N/A	All Outcomes: Positive Controls for this study were not necessary.
	Metric 6:	Randomized Allocation of Animals	Low	All Outcomes: No mention of allocation of animals in this study.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	All Outcomes: Preparation of test substances for experiment was adequate for study.
	Metric 8:	Consistency of Exposure Administration	High	All Outcomes: Exposure administration was consistent.
	Metric 9:	Reporting of Doses/Concentrations	High	All Outcomes: All doses were reported.
	Metric 10:	Exposure Frequency and Duration	High	All Outcomes: Exposure duration and frequency was suitable for this developmental toxicity study.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	All Outcomes: Dose groups and spacing was adequate for this study.
	Metric 12:	Exposure Route and Method	High	Neurological/Behavioral: Exposure method and method was suitable for this study.; Neurological/Behavioral: Exposure method and method was suitable for this study.; Neurological/Behavioral: Exposure route and method was suitable for this study.; Lung/Respiratory: Exposure route and method was suitable for this study.; Skin/Connective Tissue: Exposure route and method was suitable for this study.; Nutritional/Metabolic: Exposure route and method was suitable for this study.; Mortality: Exposure route and method was suitable for this study.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	High	All Outcomes: Test animal characteristics were explained in detail.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	High	All Outcomes: Animal husbandry conditions were reported.

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Study Citation:	Hazleton Laboratories, (1983). Screening of priority chemicals for potential reproductive hazard (final report) with attachments and cover sheet.
Health Outcome(s):	Neurological/Behavioral; Neurological/Behavioral; Neurological/Behavioral; Lung/Respiratory; Skin/Connective Tissue; Nutritional/Metabolic; Mortality;
Reported Health Effect(s):	Neurological/Behavioral: Tremors, languid, prostrate, ataxia, hunched, head-tilt; Neurological/Behavioral: Tremors, languid, prostrate, ataxia, hunched, head-tilt; Neurological/Behavioral: Tremors, languid, prostrate, ataxia, hunched, head-tilt; Lung/Respiratory: Wheezing, dyspnea; Skin/Connective Tissue: Alopecia, sores, rough hair coat, piloerection; Nutritional/Metabolic: Body Weight; Mortality: Survival/Mortality;
Duration:	Short-term (>1-30 days) 8-day Reproductive study – Skin
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	790471

Domain	Metric		Rating	Comments
	Metric 15:	Number of Animals per Group	Medium	Neurological/Behavioral: This is a developmental study that depends on the birth of new mice. However, there were adequate amounts of pregnant females used to do statistics.; Neurological/Behavioral: This is a developmental study that depends on the birth of new mice. However, there were adequate amounts of pregnant females used to do statistics.; Neurological/Behavioral: An adequate number of animals were utilized for the MED study.; Lung/Respiratory: An adequate number of animals were utilized for the MED study.; Skin/Connective Tissue: An adequate number of animals were utilized for the MED study.; Nutritional/Metabolic: An adequate number of animals were utilized for the MED study; Mortality: An adequate number of animals were utilized for the MED study
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	All Outcomes: The assessment of outcome methodology was suitable for this study.
	Metric 17:	Consistency of Outcome Assessment	High	All Outcomes: Consistency of outcome assessment was suitable for this study.
	Metric 18:	Sampling Adequacy	High	Neurological/Behavioral: Sampling in this study was adequate for this study.; Neurological/Behavioral: Sampling in this study was adequate for this study.; Neurological/Behavioral: Sampling in this study was adequate.; Lung/Respiratory: Sampling in this study was adequate.; Skin/Connective Tissue: Sampling in this study was adequate.; Nutritional/Metabolic: Sampling in this study was adequate for this study.; Mortality: Sampling in this study was adequate for this study.
	Metric 19:	Blinding of Assessors	N/A	All Outcomes: Assessors did not need to be blind for this study.
	Metric 20:	Negative Control Response	High	Neurological/Behavioral: Negative control/vehicle response was how it should be compared to the treated animals.; Neurological/Behavioral: Negative control/vehicle response was how it should be compared to the treated animals.; Neurological/Behavioral: Negative control/vehicle response was appropriately compared to the treated animals.; Lung/Respiratory: Negative control/vehicle response was appropriately compared to the treated animals.; Skin/Connective Tissue: Negative control/vehicle response was appropriately compared to the treated animals.; Nutritional/Metabolic: Negative control/vehicle response was how it should be compared to the treated animals.; Mortality: Negative control/vehicle response was how it should be compared to the treated animals.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	High	All Outcomes: No reported differences in the variables between each animal.
	Metric 22:	Health Outcomes Unrelated to Exposure	High	All Outcomes: No outcomes related to health exposure.
	Metric 23:	Data Presentation and Analysis	High	All Outcomes: Statistical analysis was suitable for this study.
	Metric 24:	Reporting of Data	High	All Outcomes: All data was reported in this study.

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Study Citation:	Hazleton Laboratories, (1983). Screening of priority chemicals for potential reproductive hazard (final report) with attachments and cover sheet.
Health Outcome(s):	Neurological/Behavioral; Neurological/Behavioral; Neurological/Behavioral; Lung/Respiratory; Skin/Connective Tissue; Nutritional/Metabolic; Mortality;
Reported Health Effect(s):	Neurological/Behavioral: Tremors, languid, prostrate, ataxia, hunched, head-tilt; Neurological/Behavioral: Tremors, languid, prostrate, ataxia, hunched, head-tilt; Neurological/Behavioral: Tremors, languid, prostrate, ataxia, hunched, head-tilt; Lung/Respiratory: Wheezing, dyspnea; Skin/Connective Tissue: Alopecia, sores, rough hair coat, piloerection; Nutritional/Metabolic: Body Weight; Mortality: Survival/Mortality;
Duration:	Short-term (>1-30 days) 8-day Reproductive study – Skin
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	790471

Domain	Metric	Rating	Comments
Overall Quality Determination		**High**	

Study Citation:	Hazleton Laboratories, (1983). Screening of priority chemicals for potential reproductive hazard (final report) with attachments and cover sheet.
Health Outcome(s):	Nutritional/Metabolic; Mortality; Lung/Respiratory;
Reported Health Effect(s):	Nutritional/Metabolic: Body Weight; Mortality: Survival/Mortality; Lung/Respiratory: Wheezing, dyspnea;
Duration:	Short-term (>1-30 days) 8-day Reproductive study – Metabolic
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	790471

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	All Outcomes: Test substances used were identified by established nomenclature.
	Metric 2:	Test Substance Source	High	All Outcomes: Test Substance was supplied by NIOSH.
	Metric 3:	Test Substance Purity	High	All Outcomes: Each chemical purity was determined by Hazelton laboratory.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	All Outcomes: Vehicle control with corn oil were used for the test substance.
	Metric 5:	Positive Controls	N/A	All Outcomes: Positive Controls for this study were not necessary.
	Metric 6:	Randomized Allocation of Animals	Low	All Outcomes: No mention of allocation of animals in this study.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	All Outcomes: Preparation of test substances for experiment was adequate for study.
	Metric 8:	Consistency of Exposure Administration	High	All Outcomes: Exposure administration was consistent.
	Metric 9:	Reporting of Doses/Concentrations	High	All Outcomes: All doses were reported.
	Metric 10:	Exposure Frequency and Duration	Low	All Outcomes: There was no premating dosing and gestational dosing was on GD 7- 14.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	N/A	All Outcomes: There is only one exposure dose in the reproductive study.
	Metric 12:	Exposure Route and Method	High	All Outcomes: Exposure route and method was suitable for this study.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	High	All Outcomes: Test animal characteristics were explained in detail.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	High	All Outcomes: Animal husbandry conditions were reported.
	Metric 15:	Number of Animals per Group	Medium	All Outcomes: 50 pregnant mice were dosed at 940 mg/kg-d.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	All Outcomes: The assessment of outcome methodology was suitable for this study.
	Metric 17:	Consistency of Outcome Assessment	High	All Outcomes: Consistency of outcome assessment was suitable for this study.
	Metric 18:	Sampling Adequacy	High	All Outcomes: Sampling in this study was adequate.
	Metric 19:	Blinding of Assessors	N/A	All Outcomes: Assessors did not need to be blind for this study.
	Metric 20:	Negative Control Response	High	All Outcomes: Negative control/vehicle response was appropriately compared to the treated animals.
Domain 6: Confounding / Variable Control				

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Study Citation:	Hazleton Laboratories, (1983). Screening of priority chemicals for potential reproductive hazard (final report) with attachments and cover sheet.
Health Outcome(s):	Nutritional/Metabolic; Mortality; Lung/Respiratory;
Reported Health Effect(s):	Nutritional/Metabolic: Body Weight; Mortality: Survival/Mortality; Lung/Respiratory: Wheezing, dyspnea;
Duration:	Short-term (>1-30 days) 8-day Reproductive study – Metabolic
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	790471

Domain	Metric		Rating	Comments
	Metric 21:	Confounding Variables in Test Design and Procedures	High	All Outcomes: No reported differences in the variables between each animal.
	Metric 22:	Health Outcomes Unrelated to Exposure	High	All Outcomes: No outcomes related to health exposure.
	Metric 23:	Data Presentation and Analysis	High	All Outcomes: Statistical analysis was suitable for this study.
	Metric 24:	Reporting of Data	High	All Outcomes: All data was reported in this study.

Overall Quality Determination High

Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Mortality
Reported Health Effect(s):	Survival
Duration:	Short-term (>1-30 days) 16-days (rats)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was identified definitively as tris(2-chloroethyl phosphate) CASRN 115-96-8. A structure was provided.
	Metric 2:	Test Substance Source	High	The test substance was manufactured by Stauffer Chemical Company and obtained from the analytical chemistry laboratory, Midwest Research Institute. The lot number was provided.
	Metric 3:	Test Substance Purity	High	The test chemical purity was ~98%. The purity was both provided by the supplier and confirmed via analysis (NMR and elemental analysis) by the study laboratory.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	The study included concurrent negative vehicle (corn oil) controls and conditions were consistent with the animals that were treated.
	Metric 5:	Positive Controls	N/A	Positive controls are not required for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	Animals were first assigned to weight groups and then, using random numbers tables, animals were were assigned to cages and then to groups.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) was also stable for 21 days in the dark at room temperature, or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks.
	Metric 8:	Consistency of Exposure Administration	High	All animals were gavaged on the same schedule. Gavage volumes were reported and were consistent across groups.
	Metric 9:	Reporting of Doses/Concentrations	Medium	Animals were dosed with 0, 22, 44, 88, 175, or 350 mg/kg-day, 5 days per week for a total of 12 doses. Adjusted daily doses in mg/kg-day were not reported but can be calculated using the information available. Although dose formulations were analyzed for accuracy in the 16-week and 2-yr experiments (also reported in this reference), there is no indication that the doses in the 16-day study were analyzed.
	Metric 10:	Exposure Frequency and Duration	High	Animals were gavaged 5 days per week over 16 days for a total of 12 doses. Dosing 5 days per week for a gavage study is consistent with NTP guidelines.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	The study tested 5 exposure groups plus a control. The number of groups was consistent with NTP guidelines. The dose spacing was adequate to allow for determination of NOAEL and LOAEL values.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Mortality
Reported Health Effect(s):	Survival
Duration:	Short-term (>1-30 days) 16-days (rats)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 12:	Exposure Route and Method	High	Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	High	The study used male and female F344/N rats. The test animal source (Harlan industries), age at the start of the study (7 weeks), and initial body weights were reported and appropriate.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	The number of animals per cage (5/cage) was reported. Food and water were provided ad libiutm. Animal room environments (temperature, humidity, lighting were reported. The humidity varied considerably, ranging from 26% to 76%. This deviates from NTP guidelines which state humidity should not be below 35% or above 65%. It is unclear whether these deviations had any impact on the study results.
	Metric 15:	Number of Animals per Group	Medium	The number of animals per group (5/sex) was reported and is consistent with NTP guidelines for this study duration
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	Animals were observed for mortality daily; the outcome assessment was considered to be sensitive and appropriate for the outcome of interest.
	Metric 17:	Consistency of Outcome Assessment	High	Sufficient details of the outcome assessment protocols were provided, and outcome assessment was carried out consistently across groups.
	Metric 18:	Sampling Adequacy	High	All animals were assessed for this outcome.
	Metric 19:	Blinding of Assessors	N/A	Blinding is not required. The outcome is not subjective in nature.
	Metric 20:	Negative Control Response	High	No control animals died.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	High	The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP. There were no significant body weight changes that were suggestive of palatability issues.
	Metric 22:	Health Outcomes Unrelated to Exposure	Uninformative	No animals died. Degenerative and inflammatory lesions characteristic of infection with sialodacryoadenitis virus (SDA) were observed in the salivary glands and lungs of most dosed and control rats. Because all groups appeared to be affected and it is unknown how this infection may have impacted the study results, this study is considered to be unacceptable.
	Metric 23:	Data Presentation and Analysis	N/A	Statistical analysis was not necessary. No animals died in the study.
	Metric 24:	Reporting of Data	High	Animal survival was quantitatively reported by sex and exposure group. No animals died in the study.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Mortality
Reported Health Effect(s):	Survival
Duration:	Short-term (>1-30 days) 16-days (rats)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric	Rating	Comments
Overall Quality Determination		**Uninformative**	

Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Nutritional/Metabolic
Reported Health Effect(s):	Body weights
Duration:	Short-term (>1-30 days) 16-days (rats)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was identified definitively as tris(2-chloroethyl phosphate) CASRN 115-96-8. A structure was provided.
	Metric 2:	Test Substance Source	High	The test substance was manufactured by Stauffer Chemical Company and obtained from the analytical chemistry laboratory, Midwest Research Institute. The lot number was provided.
	Metric 3:	Test Substance Purity	High	The test chemical purity was ~98%. The purity was both provided by the supplier and confirmed via analysis (NMR and elemental analysis) by the study laboratory.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	The study included concurrent negative vehicle (corn oil) controls and conditions were consistent with the animals that were treated.
	Metric 5:	Positive Controls	N/A	Positive controls are not required for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	Animals were first assigned to weight groups and then, using random numbers tables, animals were were assigned to cages and then to groups.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) was also stable for 21 days in the dark at room temperature, or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks.
	Metric 8:	Consistency of Exposure Administration	High	All animals were gavaged on the same schedule. Gavage volumes were reported and were consistent across groups.
	Metric 9:	Reporting of Doses/Concentrations	Medium	Animals were dosed with 0, 22, 44, 88, 175, or 350 mg/kg-day, 5 days per week for a total of 12 doses. Adjusted daily doses in mg/kg-day were not reported but can be calculated using the information available. Although dose formulations were analyzed for accuracy in the 16-week and 2-yr experiments (also reported in this reference), there is no indication that the doses in the 16-day study were analyzed.
	Metric 10:	Exposure Frequency and Duration	High	Animals were gavaged 5 days per week over 16 days for a total of 12 doses. Dosing 5 days per week for a gavage study is consistent with NTP guidelines.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	The study tested 5 exposure groups plus a control. The number of groups was consistent with NTP guidelines. The dose spacing was adequate to allow for determination of NOAEL and LOAEL values.
	Metric 12:	Exposure Route and Method	High	Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Nutritional/Metabolic
Reported Health Effect(s):	Body weights
Duration:	Short-term (>1-30 days) 16-days (rats)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	High	The study used male and female F344/N rats. The test animal source (Harlan industries), age at the start of the study (7 weeks), and initial body weights were reported and appropriate.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	The number of animals per cage (5/cage) was reported. Food and water were provided ad libiutm. Animal room environments (temperature, humidity, lighting were reported. The humidity varied considerably, ranging from 26% to 76%. This deviates from NTP guidelines which state humidity should not be below 35% or above 65%. It is unclear whether these deviations had any impact on the study results.
	Metric 15:	Number of Animals per Group	Medium	The number of animals per group (5/sex) was reported and is consistent with NTP guidelines for this study duration
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	Body weights were recorded initially, weekly, and at termination. This is consistent with NTP guidelines and the methods are sensitive and appropriate to assess this outcome of interest.
	Metric 17:	Consistency of Outcome Assessment	High	Sufficient details of the outcome assessment protocols were provided, and outcome assessment was carried out consistently across groups.
	Metric 18:	Sampling Adequacy	High	Measurements were collected from all of the treated animals. Sampling was sufficient for statistical analysis.
	Metric 19:	Blinding of Assessors	N/A	Blinding is not required. The outcome is not subjective in nature.
	Metric 20:	Negative Control Response	High	The negative control responses were reported and and appropriate.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	High	The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP. There were no significant body weight changes that were suggestive of palatability issues.
	Metric 22:	Health Outcomes Unrelated to Exposure	Uninformative	No animals died. Degenerative and inflammatory lesions characteristic of infection with sialodacryoadenitis virus (SDA) were observed in the salivary glands and lungs of most dosed and control rats. Because all groups appeared to be affected and it is unknown how this infection may have impacted the study results, this study is considered to be unacceptable.
	Metric 23:	Data Presentation and Analysis	High	Statistical methods were adequately described and were appropriate for the dataset. Statistical significance was shown where appropriate.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Nutritional/Metabolic
Reported Health Effect(s):	Body weights
Duration:	Short-term (>1-30 days) 16-days (rats)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric	Rating	Comments
	Metric 24: Reporting of Data	High	Body weight data were reported quantitatively for both sexes and all dose groups. Data were presented as means ± SE.

Overall Quality Determination Uninformative

Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Mortality
Reported Health Effect(s):	Survival
Duration:	Short-term (>1-30 days) 16-days (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was identified definitively as tris(2-chloroethyl phosphate) CASRN 115-96-8. A structure was provided.
	Metric 2:	Test Substance Source	High	The test substance was manufactured by Stauffer Chemical Company and obtained from the analytical chemistry laboratory, Midwest Research Institute. The lot number was provided.
	Metric 3:	Test Substance Purity	High	The test chemical purity was ~98%. The purity was both provided by the supplier and confirmed via analysis (NMR and elemental analysis) by the study laboratory.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	The study included concurrent negative vehicle (corn oil) controls and conditions were consistent with the animals that were treated.
	Metric 5:	Positive Controls	N/A	Positive controls are not required for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	Animals were first assigned to weight groups and then, using random numbers tables, animals were were assigned to cages and then to groups.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) was also stable for 21 days in the dark at room temperature, or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks.
	Metric 8:	Consistency of Exposure Administration	High	All animals were gavaged on the same schedule. Gavage volumes were reported and were consistent across groups.
	Metric 9:	Reporting of Doses/Concentrations	Medium	The doses were clearly reported. Animals were exposed to 0, 44, 88, 175, 350, or 700 mg/kg-day, 5 days per week. Time-adjusted doses were not reported but can be determined using the information available. Although dose formulations were analyzed for accuracy in the 16-week and 2-yr experiments (also reported in this reference), there is no indication that the doses in the 16-day study were analyzed.
	Metric 10:	Exposure Frequency and Duration	High	Animals were gavaged 5 days per week over 16 days for a total of 12 doses. Dosing 5 days per week for a gavage study is consistent with NTP guidelines.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	The study tested 5 exposure groups plus a control. The number of groups was consistent with NTP guidelines. The dose spacing was adequate to allow for determination of NOAEL and LOAEL values.
	Metric 12:	Exposure Route and Method	High	Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Mortality
Reported Health Effect(s):	Survival
Duration:	Short-term (>1-30 days) 16-days (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	High	The study used male and female B6C3F1 mice. The test animal source (Harlan industries), age at the start of the study (9 weeks old), and initial body weights were reported and appropriate.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	The number of animals per cage (5/cage) was reported. The NTP guideline specifies that male mice should be housed individually for all studies. Food and water were provided ad libitum. Animal room environments (temperature, humidity, lighting) were reported. The humidity range was large (26% to 76%). This deviates from NTP guidelines which state humidity should not be below 35% or above 65%. It is unclear whether these deviations had a significant impact on the study results.
	Metric 15:	Number of Animals per Group	Medium	The number of animals per group (5/sex) was reported and is consistent with NTP guidelines for this study duration.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	Animals were observed for mortality daily; the outcome assessment was considered to be sensitive and appropriate for the outcome of interest.
	Metric 17:	Consistency of Outcome Assessment	High	Sufficient details of the outcome assessment protocols were provided, and outcome assessment was carried out consistently across groups.
	Metric 18:	Sampling Adequacy	High	All animals were assessed for this outcome.
	Metric 19:	Blinding of Assessors	N/A	Blinding is not required. The outcome is not subjective in nature.
	Metric 20:	Negative Control Response	High	No control animals died.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Low	The initial body weights of female-treated mice were all significantly higher (by 12% - 20%) than the body weights of controls. This is confusing because animals had been distributed into weight classes and then assigned to cages using random numbers tables. It is unclear how the initial body weights of treated animals vs. controls were different to the degree observed. The study authors did not comment on this. The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP. However, the treated animals gained significantly less body weight over the course of the study than the controls. It is unknown if this was related to the fact that their initial body weights were higher, or if there indeed had been decreases in food or water intake.
	Metric 22:	Health Outcomes Unrelated to Exposure	Medium	There were three deaths attributed to gavage trauma. One male each at 175 and 350 mg/kg, and one female at 700 mg/kg. Other than reducing the sample size, these deaths are not expected to have a significant impact on the study results. No other health outcomes unrelated to exposure were reported.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Mortality
Reported Health Effect(s):	Survival
Duration:	Short-term (>1-30 days) 16-days (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric	Rating	Comments
	Metric 23: Data Presentation and Analysis	N/A	Statistical analysis was not necessary. No animal deaths were attributed to TCEP exposure.
	Metric 24: Reporting of Data	High	Mortality data were reported quantitatively. The cause and day of death were specified.

Overall Quality Determination High

Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Nutritional/Metabolic
Reported Health Effect(s):	Body weights
Duration:	Short-term (>1-30 days) 16-days (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was identified definitively as tris(2-chloroethyl phosphate) CASRN 115-96-8. A structure was provided.
	Metric 2:	Test Substance Source	High	The test substance was manufactured by Stauffer Chemical Company and obtained from the analytical chemistry laboratory, Midwest Research Institute. The lot number was provided.
	Metric 3:	Test Substance Purity	High	The test chemical purity was ~98%. The purity was both provided by the supplier and confirmed via analysis (NMR and elemental analysis) by the study laboratory.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	The study included concurrent negative vehicle (corn oil) controls and conditions were consistent with the animals that were treated.
	Metric 5:	Positive Controls	N/A	Positive controls are not required for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	Animals were first assigned to weight groups and then, using random numbers tables, animals were were assigned to cages and then to groups.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) was also stable for 21 days in the dark at room temperature, or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks.
	Metric 8:	Consistency of Exposure Administration	High	All animals were gavaged on the same schedule. Gavage volumes were reported and were consistent across groups.
	Metric 9:	Reporting of Doses/Concentrations	Medium	The doses were clearly reported. Animals were exposed to 0, 44, 88, 175, 350, or 700 mg/kg-day, 5 days per week. Time-adjusted doses were not reported but can be determined using the information available. Although dose formulations were analyzed for accuracy in the 16-week and 2-yr experiments (also reported in this reference), there is no indication that the doses in the 16-day study were analyzed.
	Metric 10:	Exposure Frequency and Duration	High	Animals were gavaged 5 days per week over 16 days for a total of 12 doses. Dosing 5 days per week for a gavage study is consistent with NTP guidelines.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	The study tested 5 exposure groups plus a control. The number of groups was consistent with NTP guidelines. The dose spacing was adequate to allow for determination of NOAEL and LOAEL values.
	Metric 12:	Exposure Route and Method	High	Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Nutritional/Metabolic
Reported Health Effect(s):	Body weights
Duration:	Short-term (>1-30 days) 16-days (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	High	The study used male and female B6C3F1 mice. The test animal source (Harlan industries), age at the start of the study (9 weeks old), and initial body weights were reported and appropriate.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	The number of animals per cage (5/cage) was reported. The NTP guideline specifies that male mice should be housed individually for all studies. Food and water were provided ad libiutm. Animal room environments (temperature, humidity, lighting were reported. The humidity range was large (26% to 76%). This deviates from NTP guidelines which state humidity should not be below 35% or above 65%. It is unclear whether these deviations had a significant impact on the study results.
	Metric 15:	Number of Animals per Group	Medium	The number of animals per group (5/sex) was reported and is consistent with NTP guidelines for this study duration
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	Body weights were recorded initially, weekly, and at termination. This is consistent with NTP guidelines and the methods are sensitive and appropriate for the outcome of interest.
	Metric 17:	Consistency of Outcome Assessment	High	Sufficient details of the outcome assessment protocols were provided, and outcome assessment was carried out consistently across groups.
	Metric 18:	Sampling Adequacy	High	Measurements were collected from all of the treated animals. Due to deaths, necropsy body weights were measured in 4/5 animals in the 175 and 300 mg/kg-day groups (males), and in the 700 mg/kg-day group (females). Sampling was sufficient for statistical analysis.
	Metric 19:	Blinding of Assessors	N/A	Blinding is not required. The outcome is not subjective in nature.
	Metric 20:	Negative Control Response	Medium	The negative control males lost a small amount of weight (~3%) during the 16 days of the study. Control females gained weight (19%) which is a more expected response. The study authors did not discuss these observations. It is unclear whether the response in control males had an impact on the study results. It did not result in any significant differences in final body weights.
Domain 6: Confounding / Variable Control				

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Nutritional/Metabolic
Reported Health Effect(s):	Body weights
Duration:	Short-term (>1-30 days) 16-days (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 21:	Confounding Variables in Test Design and Procedures	Low	The initial body weights of female-treated mice were all significantly higher (by 12% - 20%) than the body weights of controls. This is confusing because animals had been distributed into weight classes and then assigned to cages using random numbers tables. It is unclear how the initial body weights of treated animals vs. controls were different to the degree observed. The study authors did not comment on this. The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP. However, the treated animals gained significantly less body weight over the course of the study than the controls. It is unknown if this was related to the fact that their initial body weights were higher, or if there indeed had been decreases in food or water intake.
	Metric 22:	Health Outcomes Unrelated to Exposure	Medium	There were three deaths attributed to gavage trauma. One male each at 175 and 350 mg/kg, and one female at 700 mg/kg. Other than reducing the sample size, these deaths are not expected to have a significant impact on the study results. No other health outcomes unrelated to exposure were reported.
	Metric 23:	Data Presentation and Analysis	High	Statistical methods were adequately described and were appropriate for the dataset. Statistical significance was shown where appropriate.
	Metric 24:	Reporting of Data	High	Body weight data were reported quantitatively for both sexes and all dose groups. Data were presented as means ± SE.

Overall Quality Determination High

Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Reproductive/Developmental; Gastrointestinal; Musculoskeletal; Thyroid; Ocular/Sensory; Endocrine; Skin/Connective Tissue;
Reported Health Effect(s):	Reproductive/Developmental: Gross necropsy and histopathology (clitoral gland, epididymis, mammary glands, ovary, preputial gland, prostate, seminal vesicle, testis, uterus); Gastrointestinal: Gross necropsy and histopathology (esophagus, gall bladder (mice only), large intestines (cecum, colon, rectum), salivary gland, small intestines (duodenum, ileum, jejunum), stomach, mesentery, tooth); Musculoskeletal: Gross necropsy, histopathology (skeletal muscle, bone); Thyroid: Gross necropsy and histopathology (thyroid); Ocular/Sensory: Gross necropsy, histopathology (harderian gland); Endocrine: Gross necropsy and histopathology (pancreas, adrenal glands, pituitary glands, parathyroid); Skin/Connective Tissue: Gross necropsy, histopathology (skin);
Duration:	Short-term (>1-30 days) 16-days (rats)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	All Outcomes: The test substance was identified definitively as tris(2-chloroethyl phosphate) CASRN 115-96-8. A structure was provided.
	Metric 2:	Test Substance Source	High	All Outcomes: The test substance was manufactured by Stauffer Chemical Company and obtained from the analytical chemistry laboratory, Midwest Research Institute. The lot number was provided.
	Metric 3:	Test Substance Purity	High	All Outcomes: The test chemical purity was ~98%. The purity was both provided by the supplier and confirmed via analysis (NMR and elemental analysis) by the study laboratory.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	All Outcomes: The study included concurrent negative vehicle (corn oil) controls and conditions were consistent with the animals that were treated.
	Metric 5:	Positive Controls	N/A	All Outcomes: Positive controls are not required for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	All Outcomes: Animals were first assigned to weight groups and then, using random numbers tables, animals were were assigned to cages and then to groups.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	All Outcomes: Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) was also stable for 21 days in the dark at room temperature, or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks.
	Metric 8:	Consistency of Exposure Administration	High	All Outcomes: All animals were gavaged on the same schedule. Gavage volumes were reported and were consistent across groups.
	Metric 9:	Reporting of Doses/Concentrations	Medium	All Outcomes: Animals were dosed with 0, 22, 44, 88, 175, or 350 mg/kg-day, 5 days per week for a total of 12 doses. Adjusted daily doses in mg/kg-day were not reported but can be calculated using the information available. Although dose formulations were analyzed for accuracy in the 16-week and 2-yr experiments (also reported in this reference), there is no indication that the doses in the 16-day study were analyzed.
	Metric 10:	Exposure Frequency and Duration	High	All Outcomes: Animals were gavaged 5 days per week over 16 days for a total of 12 doses. Dosing 5 days per week for a gavage study is consistent with NTP guidelines.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Reproductive/Developmental; Gastrointestinal; Musculoskeletal; Thyroid; Ocular/Sensory; Endocrine; Skin/Connective Tissue;
Reported Health Effect(s):	Reproductive/Developmental: Gross necropsy and histopathology (clitoral gland, epididymis, mammary glands, ovary, preputial gland, prostate, seminal vesicle, testis, uterus); Gastrointestinal: Gross necropsy and histopathology (esophagus, gall bladder (mice only), large intestines (cecum, colon, rectum), salivary gland, small intestines (duodenum, ileum, jejunum), stomach, mesentery, tooth); Musculoskeletal: Gross necropsy, histopathology (skeletal muscle, bone); Thyroid: Gross necropsy and histopathology (thyroid); Ocular/Sensory: Gross necropsy, histopathology (harderian gland); Endocrine: Gross necropsy and histopathology (pancreas, adrenal glands, pituitary glands, parathyroid); Skin/Connective Tissue: Gross necropsy, histopathology (skin);
Duration:	Short-term (>1-30 days) 16-days (rats)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	All Outcomes: The study tested 5 exposure groups plus a control. The number of groups was consistent with NTP guidelines. The dose spacing was adequate to allow for determination of NOAEL and LOAEL values.
	Metric 12:	Exposure Route and Method	High	All Outcomes: Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	High	All Outcomes: The study used male and female F344/N rats. The test animal source (Harlan industries), age at the start of the study (7 weeks), and initial body weights were reported and appropriate.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	All Outcomes: The number of animals per cage (5/cage) was reported. Food and water were provided ad libiutm. Animal room environments (temperature, humidity, lighting were reported. The humidity varied considerably, ranging from 26% to 76%. This deviates from NTP guidelines which state humidity should not be below 35% or above 65%. It is unclear whether these deviations had any impact on the study results.
	Metric 15:	Number of Animals per Group	Medium	All Outcomes: The number of animals per group (5/sex) was reported and is consistent with NTP guidelines for this study duration
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	All Outcomes: Histopathological analysis was conducted on tissue(s) from this organ/system and histopathology is considered to be a sensitive and appropriate method to assess this outcome of interest and is consistent with the NTP guidelines for this study type
	Metric 17:	Consistency of Outcome Assessment	High	All Outcomes: Sufficient details of the outcome assessment protocols (organ weights and histopathology) were provided, and outcome assessment was carried out consistently across groups. Blood for measurement of cholinesterase activity was collected from all animals at terminal sacrifice.
	Metric 18:	Sampling Adequacy	Medium	All Outcomes: Histopathology was conducted on controls and high-dose animals only, and no effects were observed at the high dose. The methods report that all animals were examined, but since negative findings were qualitatively reported, the sample size cannot be verified.
	Metric 19:	Blinding of Assessors	N/A	All Outcomes: Blinding is not required for initial histopathology.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Reproductive/Developmental; Gastrointestinal; Musculoskeletal; Thyroid; Ocular/Sensory; Endocrine; Skin/Connective Tissue;
Reported Health Effect(s):	Reproductive/Developmental: Gross necropsy and histopathology (clitoral gland, epididymis, mammary glands, ovary, preputial gland, prostate, seminal vesicle, testis, uterus); Gastrointestinal: Gross necropsy and histopathology (esophagus, gall bladder (mice only), large intestines (cecum, colon, rectum), salivary gland, small intestines (duodenum, ileum, jejunum), stomach, mesentery, tooth); Musculoskeletal: Gross necropsy, histopathology (skeletal muscle, bone); Thyroid: Gross necropsy and histopathology (thyroid); Ocular/Sensory: Gross necropsy, histopathology (harderian gland); Endocrine: Gross necropsy and histopathology (pancreas, adrenal glands, pituitary glands, parathyroid); Skin/Connective Tissue: Gross necropsy, histopathology (skin);
Duration:	Short-term (>1-30 days) 16-days (rats)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 20:	Negative Control Response	Low	All Outcomes: The appropriateness of the negative control response for histopathology cannot be determined because incidence data were not provided. The study authors did not describe any concerns about a high background in controls.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	High	All Outcomes: The study did not measure food or water intake, but these but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP. There were no significant body weight changes that were suggestive of palatability issues.
	Metric 22:	Health Outcomes Unrelated to Exposure	Uninformative	All Outcomes: No animals died. Degenerative and inflammatory lesions characteristic of infection with sialodacryoadenitis virus (SDA) were observed in the salivary glands and lungs of most dosed and control rats. Because all groups appeared to be affected and it is unknown how this infection may have impacted the study results, this study is considered to be unacceptable.
	Metric 23:	Data Presentation and Analysis	High	All Outcomes: Statistical methods were adequately described and were appropriate for the dataset. Statistical significance was shown where appropriate.
	Metric 24:	Reporting of Data	High	All Outcomes: Negative gross necropsy and histopathological findings were reported qualitatively in the text. The study reported that no gross observations or histopathological lesions attributable to exposure were observed. This statement applied to both mice and rats. No organ-specific results were reported, and no quantitative data were provided.

Overall Quality Determination — Uninformative

Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Reproductive/Developmental; Gastrointestinal; Musculoskeletal; Thyroid; Skin/Connective Tissue; Ocular/Sensory; Endocrine;
Reported Health Effect(s):	Reproductive/Developmental: Gross necropsy and histopathology (clitoral gland, epididymis, mammary glands, ovary, preputial gland, prostate, seminal vesicle, testis, uterus); Gastrointestinal: Gross necropsy and histopathology (esophagus, gall bladder (mice only), large intestines (cecum, colon, rectum), salivary gland, small intestines (duodenum, ileum, jejunum), stomach, mesentery, tooth); Musculoskeletal: Gross necropsy, histopathology (skeletal muscle, bone); Thyroid: Gross necropsy and histopathology (thyroid); Skin/Connective Tissue: Gross necropsy, histopathology (skin); Ocular/Sensory: Gross necropsy, histopathology (harderian gland); Endocrine: Gross necropsy and histopathology (pancreas, adrenal glands, pituitary glands, parathyroid);
Duration:	Short-term (>1-30 days) 16-days (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	All Outcomes: The test substance was identified definitively as tris(2-chloroethyl phosphate) CASRN 115-96-8. A structure was provided.
	Metric 2:	Test Substance Source	High	All Outcomes: The test substance was manufactured by Stauffer Chemical Company and obtained from the analytical chemistry laboratory, Midwest Research Institute. The lot number was provided.
	Metric 3:	Test Substance Purity	High	All Outcomes: The test chemical purity was ~98%. The purity was both provided by the supplier and confirmed via analysis (NMR and elemental analysis) by the study laboratory.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	All Outcomes: The study included concurrent negative vehicle (corn oil) controls and conditions were consistent with the animals that were treated.
	Metric 5:	Positive Controls	N/A	All Outcomes: Positive controls are not required for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	All Outcomes: Animals were first assigned to weight groups and then, using random numbers tables, animals were were assigned to cages and then to groups.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	All Outcomes: Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) was also stable for 21 days in the dark at room temperature, or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks.
	Metric 8:	Consistency of Exposure Administration	High	All Outcomes: All animals were gavaged on the same schedule. Gavage volumes were reported and were consistent across groups.
	Metric 9:	Reporting of Doses/Concentrations	Medium	All Outcomes: The doses were clearly reported. Animals were exposed to 0, 44, 88, 175, 350, or 700 mg/kg-day, 5 days per week. Time-adjusted doses were not reported but can be determined using the information available. Although dose formulations were analyzed for accuracy in the 16-week and 2-yr experiments (also reported in this reference), there is no indication that the doses in the 16-day study were analyzed.
	Metric 10:	Exposure Frequency and Duration	High	All Outcomes: Animals were gavaged 5 days per week over 16 days for a total of 12 doses. Dosing 5 days per week for a gavage study is consistent with NTP guidelines.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Reproductive/Developmental; Gastrointestinal; Musculoskeletal; Thyroid; Skin/Connective Tissue; Ocular/Sensory; Endocrine;
Reported Health Effect(s):	Reproductive/Developmental: Gross necropsy and histopathology (clitoral gland, epididymis, mammary glands, ovary, preputial gland, prostate, seminal vesicle, testis, uterus); Gastrointestinal: Gross necropsy and histopathology (esophagus, gall bladder (mice only), large intestines (cecum, colon, rectum), salivary gland, small intestines (duodenum, ileum, jejunum), stomach, mesentery, tooth); Musculoskeletal: Gross necropsy, histopathology (skeletal muscle, bone); Thyroid: Gross necropsy and histopathology (thyroid); Skin/Connective Tissue: Gross necropsy, histopathology (skin); Ocular/Sensory: Gross necropsy, histopathology (harderian gland); Endocrine: Gross necropsy and histopathology (pancreas, adrenal glands, pituitary glands, parathyroid);
Duration:	Short-term (>1-30 days) 16-days (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	All Outcomes: The study tested 5 exposure groups plus a control. The number of groups was consistent with NTP guidelines. The dose spacing was adequate to allow for determination of NOAEL and LOAEL values.
	Metric 12:	Exposure Route and Method	High	All Outcomes: Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	High	All Outcomes: The study used male and female B6C3F1 mice. The test animal source (Harlan industries), age at the start of the study (9 weeks old), and initial body weights were reported and appropriate.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	All Outcomes: The number of animals per cage (5/cage) was reported. The NTP guideline specifies that male mice should be housed individually for all studies. Food and water were provided ad libiutm. Animal room environments (temperature, humidity, lighting were reported. The humidity range was large (26% to 76%). This deviates from NTP guidelines which state humidity should not be below 35% or above 65%. It is unclear whether these deviations had a significant impact on the study results.
	Metric 15:	Number of Animals per Group	Medium	All Outcomes: The number of animals per group (5/sex) was reported and is consistent with NTP guidelines for this study duration
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	All Outcomes: Histopathological analysis was conducted on tissue(s) from this organ/system and histopathology is considered to be a sensitive and appropriate method for this outcome of interest. The methods were consistent with the NTP guidelines for this study type.
	Metric 17:	Consistency of Outcome Assessment	High	All Outcomes: Sufficient details of the outcome assessment protocols were provided, and outcome assessment was carried out consistently across groups.
	Metric 18:	Sampling Adequacy	Medium	All Outcomes: Histopathology was conducted on controls and high-dose animals only, but no effects were observed at the high dose. The methods suggest that all animals were examined, but since negative findings were qualitatively reported, the sample size cannot be verified.
	Metric 19:	Blinding of Assessors	N/A	All Outcomes: Blinding is not required. The outcome is either not subjective in nature (organ weights), or blinding is not required (initial histopathology).
	Metric 20:	Negative Control Response	Low	All Outcomes: The appropriateness of the negative control response for histopathology cannot be determined because the biological responses of the controls were not reported.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Reproductive/Developmental; Gastrointestinal; Musculoskeletal; Thyroid; Skin/Connective Tissue; Ocular/Sensory; Endocrine;
Reported Health Effect(s):	Reproductive/Developmental: Gross necropsy and histopathology (clitoral gland, epididymis, mammary glands, ovary, preputial gland, prostate, seminal vesicle, testis, uterus); Gastrointestinal: Gross necropsy and histopathology (esophagus, gall bladder (mice only), large intestines (cecum, colon, rectum), salivary gland, small intestines (duodenum, ileum, jejunum), stomach, mesentery, tooth); Musculoskeletal: Gross necropsy, histopathology (skeletal muscle, bone); Thyroid: Gross necropsy and histopathology (thyroid); Skin/Connective Tissue: Gross necropsy, histopathology (skin); Ocular/Sensory: Gross necropsy, histopathology (harderian gland); Endocrine: Gross necropsy and histopathology (pancreas, adrenal glands, pituitary glands, parathyroid);
Duration:	Short-term (>1-30 days) 16-days (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric	Rating	Comments
Domain 6: Confounding / Variable Control			
	Metric 21: Confounding Variables in Test Design and Procedures	Low	All Outcomes: The initial body weights of female-treated mice were all significantly higher (by 12% - 20%) than the body weights of controls. This is confusing because animals had been distributed into weight classes and then assigned to cages using random numbers tables. It is unclear how the initial body weights of treated animals vs. controls were different to the degree observed. The study authors did not comment on this. The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP. However, the treated animals gained significantly less body weight over the course of the study than the controls. It is unknown if this was related to the fact that their initial body weights were higher, or if there indeed had been decreases in food or water intake.
	Metric 22: Health Outcomes Unrelated to Exposure	Medium	All Outcomes: There were three deaths attributed to gavage trauma. One male each at 175 and 350 mg/kg, and one female at 700 mg/kg. Other than reducing the sample size, these deaths are not expected to have a significant impact on the study results. No other health outcomes unrelated to exposure were reported.
	Metric 23: Data Presentation and Analysis	High	All Outcomes: Statistical methods were adequately described and were appropriate for the dataset. Statistical significance was shown where appropriate.

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Health Outcome(s):	Reproductive/Developmental; Gastrointestinal; Musculoskeletal; Thyroid; Skin/Connective Tissue; Ocular/Sensory; Endocrine;
Reported Health Effect(s):	Reproductive/Developmental: Gross necropsy and histopathology (clitoral gland, epididymis, mammary glands, ovary, preputial gland, prostate, seminal vesicle, testis, uterus); Gastrointestinal: Gross necropsy and histopathology (esophagus, gall bladder (mice only), large intestines (cecum, colon, rectum), salivary gland, small intestines (duodenum, ileum, jejunum), stomach, mesentery, tooth); Musculoskeletal: Gross necropsy, histopathology (skeletal muscle, bone); Thyroid: Gross necropsy and histopathology (thyroid); Skin/Connective Tissue: Gross necropsy, histopathology (skin); Ocular/Sensory: Gross necropsy, histopathology (harderian gland); Endocrine: Gross necropsy and histopathology (pancreas, adrenal glands, pituitary glands, parathyroid);
Duration:	Short-term (>1-30 days) 16-days (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric	Rating	Comments
	Metric 24: Reporting of Data	High	Reproductive/Developmental: Negative gross necropsy and histopathological findings were reported qualitatively in the text. The study reported that no gross observations or histopathological lesions attributable to exposure were observed. This statement applied to both mice and rats. No organ-specific results were reported.; Gastrointestinal: Negative gross necropsy and histopathological findings were reported qualitatively in the text. The study reported that no gross observations or histopathological lesions attributable to exposure were observed. This statement applied to both mice and rats. No organ-specific results were reported.; Musculoskeletal: Negative gross necropsy and histopathological findings were reported qualitatively in the text. The study reported that no gross observations or histopathological lesions attributable to exposure were observed. No organ-specific results were reported.; Thyroid: Negative gross necropsy and histopathological findings were reported qualitatively in the text. The study reported that no gross observations or histopathological lesions attributable to exposure were observed. This statement applied to both mice and rats. No organ-specific results were reported.; Skin/Connective Tissue: Negative gross necropsy and histopathological findings were reported qualitatively in the text. The study reported that no gross observations or histopathological lesions attributable to exposure were observed. This statement applied to both mice and rats. No organ-specific results were reported.; Ocular/Sensory: Negative gross necropsy and histopathological findings were reported qualitatively in the text. The study reported that no gross observations or histopathological lesions attributable to exposure were observed. This statement applied to both mice and rats. No organ-specific results were reported.; Endocrine: Negative gross necropsy and histopathological findings were reported qualitatively in the text. The study reported that no gross observations or histopathological lesions attributable to exposure were observed. This statement applied to both mice and rats. No organ-specific results were reported.

Overall Quality Determination High

Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Neurological/Behavioral; Cardiovascular; Hepatic/Liver; Renal/Kidney; Lung/Respiratory; Immune/Hematological;
Reported Health Effect(s):	Neurological/Behavioral: Serum cholinesterase activity (special study 16-day and 16-week studies, and as part of serum chemistry in 2-yr study), brain weights, gross necropsy, histopathology (brain); Cardiovascular: Heart organ weights, gross necropsy, histopathology (heart); Hepatic/Liver: Liver weights, gross necropsy, histopathology, clinical chemistry (serum glucose, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, sorbitol dehydrogenase, cholesterol); Renal/Kidney: Serum chemistry (BUN, creatinine), organ weights, gross necropsy, histopathology (kidney, bladder); Lung/Respiratory: Gross necropsy, histopathology (lung, nose, trachea); Immune/Hematological: Hematology (hematocrit, hemoglobin, erythrocytes, leukocytes with differential, MCV, MCH, MCHC, and reticulocyte count), thymus weights, gross pathology, histopathology (spleen, thymus, lymph nodes (mandibular and mesenteric), bone marrow);
Duration:	Short-term (>1-30 days) 16-days (rats)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	All Outcomes: The test substance was identified definitively as tris(2-chloroethyl phosphate) CASRN 115-96-8. A structure was provided.
	Metric 2:	Test Substance Source	High	All Outcomes: The test substance was manufactured by Stauffer Chemical Company and obtained from the analytical chemistry laboratory, Midwest Research Institute. The lot number was provided.
	Metric 3:	Test Substance Purity	High	All Outcomes: The test chemical purity was ~98%. The purity was both provided by the supplier and confirmed via analysis (NMR and elemental analysis) by the study laboratory.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	All Outcomes: The study included concurrent negative vehicle (corn oil) controls and conditions were consistent with the animals that were treated.
	Metric 5:	Positive Controls	N/A	All Outcomes: Positive controls are not required for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	All Outcomes: Animals were first assigned to weight groups and then, using random numbers tables, animals were were assigned to cages and then to groups.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	All Outcomes: Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) was also stable for 21 days in the dark at room temperature, or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks.
	Metric 8:	Consistency of Exposure Administration	High	All Outcomes: All animals were gavaged on the same schedule. Gavage volumes were reported and were consistent across groups.
	Metric 9:	Reporting of Doses/Concentrations	Medium	All Outcomes: Animals were dosed with 0, 22, 44, 88, 175, or 350 mg/kg-day, 5 days per week for a total of 12 doses. Adjusted daily doses in mg/kg-day were not reported but can be calculated using the information available. Although dose formulations were analyzed for accuracy in the 16-week and 2-yr experiments (also reported in this reference), there is no indication that the doses in the 16-day study were analyzed.

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Health Outcome(s):	Neurological/Behavioral; Cardiovascular; Hepatic/Liver; Renal/Kidney; Lung/Respiratory; Immune/Hematological;
Reported Health Effect(s):	Neurological/Behavioral: Serum cholinesterase activity (special study 16-day and 16-week studies, and as part of serum chemistry in 2-yr study), brain weights, gross necropsy, histopathology (brain); Cardiovascular: Heart organ weights, gross necropsy, histopathology (heart); Hepatic/Liver: Liver weights, gross necropsy, histopathology, clinical chemistry (serum glucose, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, sorbitol dehydrogenase, cholesterol); Renal/Kidney: Serum chemistry (BUN, creatinine), organ weights, gross necropsy, histopathology (kidney, bladder); Lung/Respiratory: Gross necropsy, histopathology (lung, nose, trachea); Immune/Hematological: Hematology (hematocrit, hemoglobin, erythrocytes, leukocytes with differential, MCV, MCH, MCHC, and reticulocyte count), thymus weights, gross pathology, histopathology (spleen, thymus, lymph nodes (mandibular and mesenteric), bone marrow);
Duration:	Short-term (>1-30 days) 16-days (rats)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 10:	Exposure Frequency and Duration	High	All Outcomes: Animals were gavaged 5 days per week over 16 days for a total of 12 doses. Dosing 5 days per week for a gavage study is consistent with NTP guidelines.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	All Outcomes: The study tested 5 exposure groups plus a control. The number of groups was consistent with NTP guidelines. The dose spacing was adequate to allow for determination of NOAEL and LOAEL values.
	Metric 12:	Exposure Route and Method	High	All Outcomes: Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	High	All Outcomes: The study used male and female F344/N rats. The test animal source (Harlan industries), age at the start of the study (7 weeks), and initial body weights were reported and appropriate.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	All Outcomes: The number of animals per cage (5/cage) was reported. Food and water were provided ad libiutm. Animal room environments (temperature, humidity, lighting were reported. The humidity varied considerably, ranging from 26% to 76%. This deviates from NTP guidelines which state humidity should not be below 35% or above 65%. It is unclear whether these deviations had any impact on the study results.
	Metric 15:	Number of Animals per Group	Medium	All Outcomes: The number of animals per group (5/sex) was reported and is consistent with NTP guidelines for this study duration
Domain 5: Outcome Assessment				

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Neurological/Behavioral; Cardiovascular; Hepatic/Liver; Renal/Kidney; Lung/Respiratory; Immune/Hematological;
Reported Health Effect(s):	Neurological/Behavioral: Serum cholinesterase activity (special study 16-day and 16-week studies, and as part of serum chemistry in 2-yr study), brain weights, gross necropsy, histopathology (brain); Cardiovascular: Heart organ weights, gross necropsy, histopathology (heart); Hepatic/Liver: Liver weights, gross necropsy, histopathology, clinical chemistry (serum glucose, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, sorbitol dehydrogenase, cholesterol); Renal/Kidney: Serum chemistry (BUN, creatinine), organ weights, gross necropsy, histopathology (kidney, bladder); Lung/Respiratory: Gross necropsy, histopathology (lung, nose, trachea); Immune/Hematological: Hematology (hematocrit, hemoglobin, erythrocytes, leukocytes with differential, MCV, MCH, MCHC, and reticulocyte count), thymus weights, gross pathology, histopathology (spleen, thymus, lymph nodes (mandibular and mesenteric), bone marrow);
Duration:	Short-term (>1-30 days) 16-days (rats)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 16:	Outcome Assessment Methodology	High	Neurological/Behavioral: Serum Cholinesterase activity was determined at study termination. Absolute and relative organ weights were measured, and all animals were subjected to gross necropsy. Brain tissue was examined histologically (other neuronal tissues were not examined). The outcome assessment methodologies were described in sufficient detail and were sensitive to the outcome of interest.; Cardiovascular: Absolute and relative organ weights were recorded and histopathological analysis was conducted on tissue(s) from this organ/system. The outcome assessment methods were sensitive and appropriate for this outcome of interest and were consistent with NTP guidelines.; Hepatic/Liver: Absolute and relative organ weights were recorded and histopathological analysis was conducted on tissue(s) from this organ/system. The outcome assessment methods were sensitive and appropriate for this outcome of interest and were consistent with NTP guidelines.; Renal/Kidney: Absolute and relative organ weights were recorded and histopathological analysis was conducted on tissue(s) from this organ/system. The outcome assessment methods were sensitive and appropriate for this outcome of interest and were consistent with NTP guidelines.; Lung/Respiratory: Absolute and relative organ weights were recorded and histopathological analysis was conducted on tissue(s) from this organ/system. The outcome assessment methods were sensitive and appropriate for this outcome of interest and were consistent with NTP guidelines.; Immune/Hematological: Absolute and relative organ weights were recorded and histopathological analysis was conducted on tissue(s) from this organ/system. The outcome assessment methods were sensitive and appropriate for this outcome of interest and were consistent with NTP guidelines.
	Metric 17:	Consistency of Outcome Assessment	High	All Outcomes: Sufficient details of the outcome assessment protocols (organ weights and histopathology) were provided, and outcome assessment was carried out consistently across groups. Blood for measurement of cholinesterase activity was collected from all animals at terminal sacrifice.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Neurological/Behavioral; Cardiovascular; Hepatic/Liver; Renal/Kidney; Lung/Respiratory; Immune/Hematological;
Reported Health Effect(s):	Neurological/Behavioral: Serum cholinesterase activity (special study 16-day and 16-week studies, and as part of serum chemistry in 2-yr study), brain weights, gross necropsy, histopathology (brain); Cardiovascular: Heart organ weights, gross necropsy, histopathology (heart); Hepatic/Liver: Liver weights, gross necropsy, histopathology, clinical chemistry (serum glucose, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, sorbitol dehydrogenase, cholesterol); Renal/Kidney: Serum chemistry (BUN, creatinine), organ weights, gross necropsy, histopathology (kidney, bladder); Lung/Respiratory: Gross necropsy, histopathology (lung, nose, trachea); Immune/Hematological: Hematology (hematocrit, hemoglobin, erythrocytes, leukocytes with differential, MCV, MCH, MCHC, and reticulocyte count), thymus weights, gross pathology, histopathology (spleen, thymus, lymph nodes (mandibular and mesenteric), bone marrow);
Duration:	Short-term (>1-30 days) 16-days (rats)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 18:	Sampling Adequacy	Medium	Neurological/Behavioral: Organ weights were measured from 5/5 animals from all groups, except for the 88 mg/kg-day group (4/5). Histopathology was conducted on controls and high-dose animals only, but no effects were observed at the high dose.; Cardiovascular: Organ weights were measured from 5/5 animals for all groups except 88 mg/kg-day males (4/5). Histopathology was conducted on controls and high-dose animals only, and no effects were observed at the high dose. The methods suggest that all animals were examined, but since negative findings were qualitatively reported, the sample size for this endpoint cannot be verified.; Hepatic/Liver: Organ weights were measured from 5/5 animals for all groups except 88 mg/kg-day males (4/5). Histopathology was conducted on controls and high-dose animals only, and no effects were observed at the high dose. The methods suggest that all animals were examined, but since negative findings were qualitatively reported, the sample size for this endpoint cannot be verified.; Renal/Kidney: Organ weights were measured from 5/5 animals for all groups except 88 mg/kg-day males (4/5). Histopathology was conducted on controls and high-dose animals only, and no effects were observed at the high dose. The methods suggest that all animals were examined, but since negative findings were qualitatively reported, the sample size for this endpoint cannot be verified.; Lung/Respiratory: Organ weights were measured from 5/5 animals for all groups except 88 mg/kg-day males (4/5). Histopathology was conducted on controls and high-dose animals only, and no effects were observed at the high dose. The methods suggest that all animals were examined, but since negative findings were qualitatively reported, the sample size for this endpoint cannot be verified.; Immune/Hematological: Organ weights were measured from 5/5 animals for all groups except 88 mg/kg-day males (4/5). Histopathology was conducted on controls and high-dose animals only, and no effects were observed at the high dose. The methods suggest that all animals were examined, but since negative findings were qualitatively reported, the sample size for this endpoint cannot be verified.
	Metric 19:	Blinding of Assessors	N/A	Neurological/Behavioral: Blinding is not required. The outcome is either not subjective in nature (organ weights), or blinding is not required (initial histopathology).; Cardiovascular: Blinding is not required for initial histopathology.; Hepatic/Liver: Blinding is not required for initial histopathology.; Renal/Kidney: Blinding is not required for initial histopathology.; Lung/Respiratory: Blinding is not required for initial histopathology.; Immune/Hematological: Blinding is not required for initial histopathology.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Neurological/Behavioral; Cardiovascular; Hepatic/Liver; Renal/Kidney; Lung/Respiratory; Immune/Hematological;
Reported Health Effect(s):	Neurological/Behavioral: Serum cholinesterase activity (special study 16-day and 16-week studies, and as part of serum chemistry in 2-yr study), brain weights, gross necropsy, histopathology (brain); Cardiovascular: Heart organ weights, gross necropsy, histopathology (heart); Hepatic/Liver: Liver weights, gross necropsy, histopathology, clinical chemistry (serum glucose, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, sorbitol dehydrogenase, cholesterol); Renal/Kidney: Serum chemistry (BUN, creatinine), organ weights, gross necropsy, histopathology (kidney, bladder); Lung/Respiratory: Gross necropsy, histopathology (lung, nose, trachea); Immune/Hematological: Hematology (hematocrit, hemoglobin, erythrocytes, leukocytes with differential, MCV, MCH, MCHC, and reticulocyte count), thymus weights, gross pathology, histopathology (spleen, thymus, lymph nodes (mandibular and mesenteric), bone marrow);
Duration:	Short-term (>1-30 days) 16-days (rats)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 20:	Negative Control Response	Medium	Neurological/Behavioral: The appropriateness of the negative control response for histopathology cannot be determined because incidence data were not provided. The study authors did not describe any concerns about a high background in controls. The control responses for organ weights and cholinesterase activity were appropriate.; Cardiovascular: The appropriateness of the negative control responses for histopathology cannot be determined because incidence data were not provided. The study authors did not describe any concerns about high background in controls. Organ weight data for controls appeared to be appropriate.; Hepatic/Liver: The appropriateness of the negative control responses for histopathology cannot be determined because incidence data were not provided. The study authors did not describe any concerns about high background in controls. Organ weight data for controls appeared to be appropriate.; Renal/Kidney: The appropriateness of the negative control responses for histopathology cannot be determined because incidence data were not provided. The study authors did not describe any concerns about high background in controls. Organ weight data for controls appeared to be appropriate.; Lung/Respiratory: The appropriateness of the negative control responses for histopathology cannot be determined because incidence data were not provided. The study authors did not describe any concerns about high background in controls. Organ weight data for controls appeared to be appropriate.; Immune/Hematological: The appropriateness of the negative control responses for histopathology cannot be determined because incidence data were not provided. The study authors did not describe any concerns about high background in controls. Organ weight data for controls appeared to be appropriate.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	High	All Outcomes: The study did not measure food or water intake, but these but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP. There were no significant body weight changes that were suggestive of palatability issues.
	Metric 22:	Health Outcomes Unrelated to Exposure	Uninformative	All Outcomes: No animals died. Degenerative and inflammatory lesions characteristic of infection with sialodacryoadenitis virus (SDA) were observed in the salivary glands and lungs of most dosed and control rats. Because all groups appeared to be affected and it is unknown how this infection may have impacted the study results, this study is considered to be unacceptable.

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Health Outcome(s):	Neurological/Behavioral; Cardiovascular; Hepatic/Liver; Renal/Kidney; Lung/Respiratory; Immune/Hematological;
Reported Health Effect(s):	Neurological/Behavioral: Serum cholinesterase activity (special study 16-day and 16-week studies, and as part of serum chemistry in 2-yr study), brain weights, gross necropsy, histopathology (brain); Cardiovascular: Heart organ weights, gross necropsy, histopathology (heart); Hepatic/Liver: Liver weights, gross necropsy, histopathology, clinical chemistry (serum glucose, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, sorbitol dehydrogenase, cholesterol); Renal/Kidney: Serum chemistry (BUN, creatinine), organ weights, gross necropsy, histopathology (kidney, bladder); Lung/Respiratory: Gross necropsy, histopathology (lung, nose, trachea); Immune/Hematological: Hematology (hematocrit, hemoglobin, erythrocytes, leukocytes with differential, MCV, MCH, MCHC, and reticulocyte count), thymus weights, gross pathology, histopathology (spleen, thymus, lymph nodes (mandibular and mesenteric), bone marrow);
Duration:	Short-term (>1-30 days) 16-days (rats)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 23:	Data Presentation and Analysis	High	All Outcomes: Statistical methods were adequately described and were appropriate for the dataset. Statistical significance was shown where appropriate.
	Metric 24:	Reporting of Data	High	Neurological/Behavioral: Brain weight and serum cholinesterase data were reported quantitatively for both sexes and all dose groups. Data were presented as means ± SE. Negative gross necropsy and histopathological findings were reported qualitatively in the text. The study reported that no gross observations or histopathological lesions attributable to exposure were observed. This statement applied to both mice and rats; no organ-specific results were reported, and no quantitative data were provided.; Cardiovascular: Organ weight data were reported quantitatively. Data were presented as means ± SE. Negative gross necropsy and histopathological findings were reported qualitatively in the text. The study reported that no gross observations or histopathological lesions attributable to exposure were observed. This statement applied to both mice and rats.; Hepatic/Liver: Organ weight data were reported quantitatively. Data were presented as means ± SE. Negative gross necropsy and histopathological findings were reported qualitatively in the text. The study reported that no gross observations or histopathological lesions attributable to exposure were observed. This statement applied to both mice and rats.; Renal/Kidney: Organ weight data were reported quantitatively. Data were presented as means ± SE. Negative gross necropsy and histopathological findings were reported qualitatively in the text. The study reported that no gross observations or histopathological lesions attributable to exposure were observed. This statement applied to both mice and rats.; Lung/Respiratory: Organ weight data were reported quantitatively. Data were presented as means ± SE. Negative gross necropsy and histopathological findings were reported qualitatively in the text. The study reported that no gross observations or histopathological lesions attributable to exposure were observed. This statement applied to both mice and rats.; Immune/Hematological: Organ weight data were reported quantitatively. Data were presented as means ± SE. Negative gross necropsy and histopathological findings were reported qualitatively in the text. The study reported that no gross observations or histopathological lesions attributable to exposure were observed. This statement applied to both mice and rats.

Overall Quality Determination Uninformative

Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Cardiovascular; Hepatic/Liver; Renal/Kidney; Lung/Respiratory; Immune/Hematological;
Reported Health Effect(s):	Cardiovascular: Heart organ weights, gross necropsy, histopathology (heart); Hepatic/Liver: Liver weights, gross necropsy, histopathology, clinical chemistry (serum glucose, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, sorbitol dehydrogenase, cholesterol); Renal/Kidney: Serum chemistry (BUN, creatinine), organ weights, gross necropsy, histopathology (kidney, bladder); Lung/Respiratory: Gross necropsy, histopathology (lung, nose, trachea); Immune/Hematological: Hematology (hematocrit, hemoglobin, erythrocytes, leukocytes with differential, MCV, MCH, MCHC, and reticulocyte count), thymus weights, gross pathology, histopathology (spleen, thymus, lymph nodes (mandibular and mesenteric), bone marrow);
Duration:	Short-term (>1-30 days) 16-days (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	All Outcomes: The test substance was identified definitively as tris(2-chloroethyl phosphate) CASRN 115-96-8. A structure was provided.
	Metric 2:	Test Substance Source	High	All Outcomes: The test substance was manufactured by Stauffer Chemical Company and obtained from the analytical chemistry laboratory, Midwest Research Institute. The lot number was provided.
	Metric 3:	Test Substance Purity	High	All Outcomes: The test chemical purity was ~98%. The purity was both provided by the supplier and confirmed via analysis (NMR and elemental analysis) by the study laboratory.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	All Outcomes: The study included concurrent negative vehicle (corn oil) controls and conditions were consistent with the animals that were treated.
	Metric 5:	Positive Controls	N/A	All Outcomes: Positive controls are not required for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	All Outcomes: Animals were first assigned to weight groups and then, using random numbers tables, animals were were assigned to cages and then to groups.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	All Outcomes: Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) was also stable for 21 days in the dark at room temperature, or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks.
	Metric 8:	Consistency of Exposure Administration	High	All Outcomes: All animals were gavaged on the same schedule. Gavage volumes were reported and were consistent across groups.
	Metric 9:	Reporting of Doses/Concentrations	Medium	All Outcomes: The doses were clearly reported. Animals were exposed to 0, 44, 88, 175, 350, or 700 mg/kg-day, 5 days per week. Time-adjusted doses were not reported but can be determined using the information available. Although dose formulations were analyzed for accuracy in the 16-week and 2-yr experiments (also reported in this reference), there is no indication that the doses in the 16-day study were analyzed.
	Metric 10:	Exposure Frequency and Duration	High	All Outcomes: Animals were gavaged 5 days per week over 16 days for a total of 12 doses. Dosing 5 days per week for a gavage study is consistent with NTP guidelines.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Cardiovascular; Hepatic/Liver; Renal/Kidney; Lung/Respiratory; Immune/Hematological;
Reported Health Effect(s):	Cardiovascular: Heart organ weights, gross necropsy, histopathology (heart); Hepatic/Liver: Liver weights, gross necropsy, histopathology, clinical chemistry (serum glucose, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, sorbitol dehydrogenase, cholesterol); Renal/Kidney: Serum chemistry (BUN, creatinine), organ weights, gross necropsy, histopathology (kidney, bladder); Lung/Respiratory: Gross necropsy, histopathology (lung, nose, trachea); Immune/Hematological: Hematology (hematocrit, hemoglobin, erythrocytes, leukocytes with differential, MCV, MCH, MCHC, and reticulocyte count), thymus weights, gross pathology, histopathology (spleen, thymus, lymph nodes (mandibular and mesenteric), bone marrow);
Duration:	Short-term (>1-30 days) 16-days (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	All Outcomes: The study tested 5 exposure groups plus a control. The number of groups was consistent with NTP guidelines. The dose spacing was adequate to allow for determination of NOAEL and LOAEL values.
	Metric 12:	Exposure Route and Method	High	All Outcomes: Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	High	All Outcomes: The study used male and female B6C3F1 mice. The test animal source (Harlan industries), age at the start of the study (9 weeks old), and initial body weights were reported and appropriate.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	All Outcomes: The number of animals per cage (5/cage) was reported. The NTP guideline specifies that male mice should be housed individually for all studies. Food and water were provided ad libiutm. Animal room environments (temperature, humidity, lighting were reported. The humidity range was large (26% to 76%). This deviates from NTP guidelines which state humidity should not be below 35% or above 65%. It is unclear whether these deviations had a significant impact on the study results.
	Metric 15:	Number of Animals per Group	Medium	All Outcomes: The number of animals per group (5/sex) was reported and is consistent with NTP guidelines for this study duration
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	All Outcomes: Absolute and relative organ weights were measured, and all animals were subjected to gross necropsy. The outcome assessment methodologies were sensitive to the outcome of interest.
	Metric 17:	Consistency of Outcome Assessment	High	All Outcomes: Sufficient details of the outcome assessment protocols (organ weights and histopathology) were provided, and outcome assessment was carried out consistently across groups.
	Metric 18:	Sampling Adequacy	Medium	All Outcomes: Organ weights were measured from all surviving animals. Histopathology was conducted on controls and high-dose animals only, and no effects were observed at the high dose. The methods suggest that all animals were examined, but since negative findings were qualitatively reported, the sample size for this endpoint (histopathology) cannot be verified.
	Metric 19:	Blinding of Assessors	N/A	All Outcomes: Blinding is not required. The outcome is either not subjective in nature (organ weights), or blinding is not required (initial histopathology).

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Cardiovascular; Hepatic/Liver; Renal/Kidney; Lung/Respiratory; Immune/Hematological;
Reported Health Effect(s):	Cardiovascular: Heart organ weights, gross necropsy, histopathology (heart); Hepatic/Liver: Liver weights, gross necropsy, histopathology, clinical chemistry (serum glucose, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, sorbitol dehydrogenase, cholesterol); Renal/Kidney: Serum chemistry (BUN, creatinine), organ weights, gross necropsy, histopathology (kidney, bladder); Lung/Respiratory: Gross necropsy, histopathology (lung, nose, trachea); Immune/Hematological: Hematology (hematocrit, hemoglobin, erythrocytes, leukocytes with differential, MCV, MCH, MCHC, and reticulocyte count), thymus weights, gross pathology, histopathology (spleen, thymus, lymph nodes (mandibular and mesenteric), bone marrow);
Duration:	Short-term (>1-30 days) 16-days (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 20:	Negative Control Response	Medium	All Outcomes: The appropriateness of the negative control response for histopathology cannot be determined because the biological responses of the negative controls were not reported. The control responses for organ weights were appropriate.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Low	All Outcomes: The initial body weights of female-treated mice were all significantly higher (by 12% - 20%) than the body weights of controls. This is confusing because animals had been distributed into weight classes and then assigned to cages using random numbers tables. It is unclear how the initial body weights of treated animals vs. controls were different to the degree observed. The study authors did not comment on this. The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP. However, the treated animals gained significantly less body weight over the course of the study than the controls. It is unknown if this was related to the fact that their initial body weights were higher, or if there indeed had been decreases in food or water intake.
	Metric 22:	Health Outcomes Unrelated to Exposure	Medium	Cardiovascular: There were three deaths attributed to gavage trauma. One male each at 175 and 350 mg/kg, and one female at 700 mg/kg. Other than reducing the sample size, these deaths are not expected to have a significant impact on the study results. No other health outcomes unrelated to exposure were reported.; Hepatic/Liver: There were three deaths attributed to gavage trauma. One male each at 175and 350 mg/kg, and one female at 700 mg/kg. Other than reducing the sample size, these deaths are not expected to have a significant impact on the study results. No other health outcomes unrelated to exposure were reported.; Renal/Kidney: There were three deaths attributed to gavage trauma. One male each at 175 and 350 mg/kg, and one female at 700 mg/kg. Other than reducing the sample size, these deaths are not expected to have a significant impact on the study results. No other health outcomes unrelated to exposure were reported.; Lung/Respiratory: There were three deaths attributed to gavage trauma. One male each at 175and 350 mg/kg, and one female at 700 mg/kg. Other than reducing the sample size, these deaths are not expected to have a significant impact on the study results. No other health outcomes unrelated to exposure were reported.; Immune/Hematological: There were three deaths attributed to gavage trauma. One male each at 175 and 350 mg/kg, and one female at 700 mg/kg. Other than reducing the sample size, these deaths are not expected to have a significant impact on the study results. No other health outcomes unrelated to exposure were reported.
	Metric 23:	Data Presentation and Analysis	High	All Outcomes: Statistical methods were adequately described and were appropriate for the dataset. Statistical significance was shown where appropriate.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Cardiovascular; Hepatic/Liver; Renal/Kidney; Lung/Respiratory; Immune/Hematological;
Reported Health Effect(s):	Cardiovascular: Heart organ weights, gross necropsy, histopathology (heart); Hepatic/Liver: Liver weights, gross necropsy, histopathology, clinical chemistry (serum glucose, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, sorbitol dehydrogenase, cholesterol); Renal/Kidney: Serum chemistry (BUN, creatinine), organ weights, gross necropsy, histopathology (kidney, bladder); Lung/Respiratory: Gross necropsy, histopathology (lung, nose, trachea); Immune/Hematological: Hematology (hematocrit, hemoglobin, erythrocytes, leukocytes with differential, MCV, MCH, MCHC, and reticulocyte count), thymus weights, gross pathology, histopathology (spleen, thymus, lymph nodes (mandibular and mesenteric), bone marrow);
Duration:	Short-term (>1-30 days) 16-days (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric	Rating	Comments
	Metric 24: Reporting of Data	High	All Outcomes: Organ weight data were reported quantitatively. Data were presented as means ± SE. Negative gross necropsy and histopathological findings were reported qualitatively in the text. The study reported that no gross observations or histopathological lesions attributable to exposure were observed.

Overall Quality Determination High

Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Neurological/Behavioral
Reported Health Effect(s):	Serum cholinesterase activity (special study 16-day and 16-week studies, and as part of serum chemistry in 2-yr study), brain weights, gross necropsy, histopathology (brain)
Duration:	Short-term (>1-30 days) 16-days (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was identified definitively as tris(2-chloroethyl phosphate) CASRN 115-96-8. A structure was provided.
	Metric 2:	Test Substance Source	High	The test substance was manufactured by Stauffer Chemical Company and obtained from the analytical chemistry laboratory, Midwest Research Institute. The lot number was provided.
	Metric 3:	Test Substance Purity	High	The test chemical purity was ~98%. The purity was both provided by the supplier and confirmed via analysis (NMR and elemental analysis) by the study laboratory.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	The study included concurrent negative vehicle (corn oil) controls and conditions were consistent with the animals that were treated.
	Metric 5:	Positive Controls	N/A	Positive controls are not required for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	Animals were first assigned to weight groups and then, using random numbers tables, animals were were assigned to cages and then to groups.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) was also stable for 21 days in the dark at room temperature, or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks.
	Metric 8:	Consistency of Exposure Administration	High	All animals were gavaged on the same schedule. Gavage volumes were reported and were consistent across groups.
	Metric 9:	Reporting of Doses/Concentrations	Medium	The doses were clearly reported. Animals were exposed to 0, 44, 88, 175, 350, or 700 mg/kg-day, 5 days per week. Time-adjusted doses were not reported but can be determined using the information available. Although dose formulations were analyzed for accuracy in the 16-week and 2-yr experiments (also reported in this reference), there is no indication that the doses in the 16-day study were analyzed.
	Metric 10:	Exposure Frequency and Duration	High	Animals were gavaged 5 days per week over 16 days for a total of 12 doses. Dosing 5 days per week for a gavage study is consistent with NTP guidelines.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	The study tested 5 exposure groups plus a control. The number of groups was consistent with NTP guidelines. The dose spacing was adequate to allow for determination of NOAEL and LOAEL values.
	Metric 12:	Exposure Route and Method	High	Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Neurological/Behavioral
Reported Health Effect(s):	Serum cholinesterase activity (special study 16-day and 16-week studies, and as part of serum chemistry in 2-yr study), brain weights, gross necropsy, histopathology (brain)
Duration:	Short-term (>1-30 days) 16-days (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	High	The study used male and female B6C3F1 mice. The test animal source (Harlan industries), age at the start of the study (9 weeks old), and initial body weights were reported and appropriate.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	The number of animals per cage (5/cage) was reported. The NTP guideline specifies that male mice should be housed individually for all studies. Food and water were provided ad libiutm. Animal room environments (temperature, humidity, lighting were reported. The humidity range was large (26% to 76%). This deviates from NTP guidelines which state humidity should not be below 35% or above 65%. It is unclear whether these deviations had a significant impact on the study results.
	Metric 15:	Number of Animals per Group	Medium	The number of animals per group (5/sex) was reported and is consistent with NTP guidelines for this study duration
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	Serum Cholinesterase activity was determined at study termination. Absolute and relative organ weights were measured, and all animals were subjected to gross necropsy. Brain tissue was examined histologically (other neuronal tissues were not examined). The outcome assessment methodologies were sensitive to the outcome of interest.
	Metric 17:	Consistency of Outcome Assessment	High	Sufficient details of the outcome assessment protocols (organ weights and histopathology) were provided, and outcome assessment was carried out consistently across groups. Blood for measurement of cholinesterase activity was collected from all animals at terminal sacrifice.
	Metric 18:	Sampling Adequacy	Medium	Organ weights were measured from all surviving animals. Histopathology was conducted on controls and high-dose animals only, and no effects were observed at the high dose. The methods suggest that all animals were examined, but since negative findings were qualitatively reported, the sample size for this endpoint (histopathology) cannot be verified.
	Metric 19:	Blinding of Assessors	N/A	Blinding is not required. The outcome is either not subjective in nature (organ weights), or blinding is not required (initial histopathology).
	Metric 20:	Negative Control Response	Medium	The appropriateness of the negative control response for histopathology cannot be determined because the biological responses of the negative controls were not reported. The control responses for organ weights and cholinesterase activity were appropriate.
Domain 6: Confounding / Variable Control				

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Neurological/Behavioral
Reported Health Effect(s):	Serum cholinesterase activity (special study 16-day and 16-week studies, and as part of serum chemistry in 2-yr study), brain weights, gross necropsy, histopathology (brain)
Duration:	Short-term (>1-30 days) 16-days (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 21:	Confounding Variables in Test Design and Procedures	Low	The initial body weights of female-treated mice were all significantly higher (by 12% - 20%) than the body weights of controls. This is confusing because animals had been distributed into weight classes and then assigned to cages using random numbers tables. It is unclear how the initial body weights of treated animals vs. controls were different to the degree observed. The study authors did not comment on this. The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP. However, the treated animals gained significantly less body weight over the course of the study than the controls. It is unknown if this was related to the fact that their initial body weights were higher, or if there indeed had been decreases in food or water intake.
	Metric 22:	Health Outcomes Unrelated to Exposure	Medium	There were three deaths attributed to gavage trauma. One male each at 175 and 350 mg/kg, and one female at 700 mg/kg. Other than reducing the sample size, these deaths are not expected to have a significant impact on the study results. No other health outcomes unrelated to exposure were reported.
	Metric 23:	Data Presentation and Analysis	High	Statistical methods were adequately described and were appropriate for the dataset. Statistical significance was shown where appropriate.
	Metric 24:	Reporting of Data	Medium	Brain weight and serum cholinesterase data were reported quantitatively for both sexes and all dose groups. Data were presented as means ± SE. Negative gross necropsy and histopathological findings were reported qualitatively in the text. The study reported that no gross observations or histopathological lesions attributable to exposure were observed. No organ-specific results were reported. The text did report transient CNS-related clinical signs the first three days of dosing; incidences and statistical significance were not reported.

Overall Quality Determination — High

Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Unspecified clinical observations
Reported Health Effect(s):	Clinical signs (clinical observations)
Duration:	Short-term (>1-30 days) 16-days (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was identified definitively as tris(2-chloroethyl phosphate) CASRN 115-96-8. A structure was provided.
	Metric 2:	Test Substance Source	High	The test substance was manufactured by Stauffer Chemical Company and obtained from the analytical chemistry laboratory, Midwest Research Institute. The lot number was provided.
	Metric 3:	Test Substance Purity	High	The test chemical purity was ~98%. The purity was both provided by the supplier and confirmed via analysis (NMR and elemental analysis) by the study laboratory.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	The study included concurrent negative vehicle (corn oil) controls and conditions were consistent with the animals that were treated.
	Metric 5:	Positive Controls	N/A	Positive controls are not required for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	Animals were first assigned to weight groups and then, using random numbers tables, animals were were assigned to cages and then to groups.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) was also stable for 21 days in the dark at room temperature, or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks.
	Metric 8:	Consistency of Exposure Administration	High	All animals were gavaged on the same schedule. Gavage volumes were reported and were consistent across groups.
	Metric 9:	Reporting of Doses/Concentrations	Medium	The doses were clearly reported. Animals were exposed to 0, 44, 88, 175, 350, or 700 mg/kg-day, 5 days per week. Time-adjusted doses were not reported but can be determined using the information available. Although dose formulations were analyzed for accuracy in the 16-week and 2-yr experiments (also reported in this reference), there is no indication that the doses in the 16-day study were analyzed.
	Metric 10:	Exposure Frequency and Duration	High	Animals were gavaged 5 days per week over 16 days for a total of 12 doses. Dosing 5 days per week for a gavage study is consistent with NTP guidelines.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	The study tested 5 exposure groups plus a control. The number of groups was consistent with NTP guidelines. The dose spacing was adequate to allow for determination of NOAEL and LOAEL values.
	Metric 12:	Exposure Route and Method	High	Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Unspecified clinical observations
Reported Health Effect(s):	Clinical signs (clinical observations)
Duration:	Short-term (>1-30 days) 16-days (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	High	The study used male and female B6C3F1 mice. The test animal source (Harlan industries), age at the start of the study (9 weeks old), and initial body weights were reported and appropriate.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	The number of animals per cage (5/cage) was reported. The NTP guideline specifies that male mice should be housed individually for all studies. Food and water were provided ad libiutm. Animal room environments (temperature, humidity, lighting were reported. The humidity range was large (26% to 76%). This deviates from NTP guidelines which state humidity should not be below 35% or above 65%. It is unclear whether these deviations had a significant impact on the study results.
	Metric 15:	Number of Animals per Group	Medium	The number of animals per group (5/sex) was reported and is consistent with NTP guidelines for this study duration
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	Medium	Animals were observed daily for unspecified clinical signs. Limited details were available. The NTP guideline specifies that formal clinical signs shall be recorded daily by animal number. It is unclear if this study did this, negative results were qualitatively reported.
	Metric 17:	Consistency of Outcome Assessment	Medium	Based on the information provided, all animals were observed daily. Additional outcome assessment methods (e.g., the time of observations (time of day)) were not provided, but based on the available information, there is no indication that there were differences across groups.
	Metric 18:	Sampling Adequacy	Medium	Based on the study methods, all animals were observed for clinical signs, but since the results were qualitatively reported, the sample size cannot be verified.
	Metric 19:	Blinding of Assessors	Medium	Blinding was not reported and clinical signs can be somewhat subjective in nature; however, lack of blinding is not expected to have a significant impact on results because no clinical signs of toxicity were observed.
	Metric 20:	Negative Control Response	Medium	The appropriateness of the negative control response cannot be determined because the biological responses of the negative controls were not reported.
Domain 6: Confounding / Variable Control				

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Unspecified clinical observations
Reported Health Effect(s):	Clinical signs (clinical observations)
Duration:	Short-term (>1-30 days) 16-days (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 21:	Confounding Variables in Test Design and Procedures	Low	The initial body weights of female-treated mice were all significantly higher (by 12% - 20%) than the body weights of controls. This is confusing because animals had been distributed into weight classes and then assigned to cages using random numbers tables. It is unclear how the initial body weights of treated animals vs. controls were different to the degree observed. The study authors did not comment on this. The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP. However, the treated animals gained significantly less body weight over the course of the study than the controls. It is unknown if this was related to the fact that their initial body weights were higher, or if there indeed had been decreases in food or water intake.
	Metric 22:	Health Outcomes Unrelated to Exposure	Medium	There were three deaths attributed to gavage trauma. One male each at 175 and 350 mg/kg, and one female at 700 mg/kg. Other than reducing the sample size, these deaths are not expected to have a significant impact on the study results. No other health outcomes unrelated to exposure were reported.
	Metric 23:	Data Presentation and Analysis	High	Statistical methods were adequately described and were appropriate for the dataset. Statistical significance was shown where appropriate.
	Metric 24:	Reporting of Data	Low	Exposure-related findings were qualitatively described in the text. Statistical significance was not specified.

Overall Quality Determination High

Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Unspecified clinical observations
Reported Health Effect(s):	Clinical signs (clinical observations)
Duration:	Short-term (>1-30 days) 16-days (rats)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was identified definitively as tris(2-chloroethyl phosphate) CASRN 115-96-8. A structure was provided.
	Metric 2:	Test Substance Source	High	The test substance was manufactured by Stauffer Chemical Company and obtained from the analytical chemistry laboratory, Midwest Research Institute. The lot number was provided.
	Metric 3:	Test Substance Purity	High	The test chemical purity was ~98%. The purity was both provided by the supplier and confirmed via analysis (NMR and elemental analysis) by the study laboratory.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	The study included concurrent negative vehicle (corn oil) controls and conditions were consistent with the animals that were treated.
	Metric 5:	Positive Controls	N/A	Positive controls are not required for this study type.
	Metric 6:	Randomized Allocation of Animals	Missing Conf	Animals were first assigned to weight groups and then, using random numbers tables, animals were were assigned to cages and then to groups.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) was also stable for 21 days in the dark at room temperature, or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks.
	Metric 8:	Consistency of Exposure Administration	High	All animals were gavaged on the same schedule. Gavage volumes were reported and were consistent across groups.
	Metric 9:	Reporting of Doses/Concentrations	Medium	Animals were dosed with 0, 22, 44, 88, 175, or 350 mg/kg-day, 5 days per week for a total of 12 doses. Adjusted daily doses in mg/kg-day were not reported but can be calculated using the information available. Although dose formulations were analyzed for accuracy in the 16-week and 2-yr experiments (also reported in this reference), there is no indication that the doses in the 16-day study were analyzed.
	Metric 10:	Exposure Frequency and Duration	High	Animals were gavaged 5 days per week over 16 days for a total of 12 doses. Dosing 5 days per week for a gavage study is consistent with NTP guidelines.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	The study tested 5 exposure groups plus a control. The number of groups was consistent with NTP guidelines. The dose spacing was adequate to allow for determination of NOAEL and LOAEL values.
	Metric 12:	Exposure Route and Method	High	Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Unspecified clinical observations
Reported Health Effect(s):	Clinical signs (clinical observations)
Duration:	Short-term (>1-30 days) 16-days (rats)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	High	The study used male and female F344/N rats. The test animal source (Harlan industries), age at the start of the study (7 weeks), and initial body weights were reported and appropriate.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	The number of animals per cage (5/cage) was reported. Food and water were provided ad libiutm. Animal room environments (temperature, humidity, lighting were reported. The humidity varied considerably, ranging from 26% to 76%. This deviates from NTP guidelines which state humidity should not be below 35% or above 65%. It is unclear whether these deviations had any impact on the study results.
	Metric 15:	Number of Animals per Group	Medium	The number of animals per group (5/sex) was reported and is consistent with NTP guidelines for this study duration
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	Medium	Animals were observed daily for unspecified clinical signs. Limited details were available. The NTP guideline specifies that formal clinical signs shall be recorded daily by animal number. It is unclear if this study did this; negative results were qualitatively reported.
	Metric 17:	Consistency of Outcome Assessment	Medium	Based on the information provided, all animals were observed daily. Additional outcome assessment methods (e.g., the time of observations (time of day)) were not provided, but based on the available information, there is no indication that there were differences across groups.
	Metric 18:	Sampling Adequacy	Medium	All animals were observed for clinical signs, but since negative findings were qualitatively reported, the sample size cannot be verified.
	Metric 19:	Blinding of Assessors	Medium	Blinding was not reported and clinical signs can be somewhat subjective in nature; however, lack of blinding is not expected to have a significant impact on results because no clinical signs of toxicity were purportedly observed.
	Metric 20:	Negative Control Response	Medium	The appropriateness of the negative control response cannot be definitively determined because incidence data were not reported, but the text indicates that no clinical signs were observed.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	High	The study did not measure food or water intake, but these but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP. There were no significant body weight changes that were suggestive of palatability issues.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Unspecified clinical observations
Reported Health Effect(s):	Clinical signs (clinical observations)
Duration:	Short-term (>1-30 days) 16-days (rats)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 22:	Health Outcomes Unrelated to Exposure	Uninformative	No animals died. Degenerative and inflammatory lesions characteristic of infection with sialodacryoadenitis virus (SDA) were observed in the salivary glands and lungs of most dosed and control rats. Because all groups appeared to be affected and it is unknown how this infection may have impacted the study results, this study is considered to be unacceptable.
	Metric 23:	Data Presentation and Analysis	N/A	Statistical analysis was not necessary; negative findings were qualitatively reported across all groups.
	Metric 24:	Reporting of Data	High	Negative findings were qualitatively reported in the text.

Overall Quality Determination **Uninformative**

Study Citation:	Sala, M., Gu, Z. G., Moens, G., Chouroulinkov, I. (1982). In vivo and in vitro biological effects of the flame retardants tris(2,3-dibromopropyl) phosphate and tris(2-chlorethyl)orthophosphate. European Journal of Cancer & Clinical Oncology 18(12):1337-1344.
Health Outcome(s):	Skin/Connective Tissue
Reported Health Effect(s):	Short term skin test: mouse skin treated with TCEP showed that sebaceous glands were not suppressed and hyperplasia was not induced. Long term skin test: mouse skin treated with TCEP showed negative results for complete carcinogenic or promoting activity on mouse skin.
Duration:	Short-term (>1-30 days) Short term skin test
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469568

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The substance was characterized by nomenclature and commercial name (i.e., Tris(2-chloroethyl), orthophosphate; Genomoll P). The density (chemical property) was also reported.
	Metric 2:	Test Substance Source	High	Source: Hoechst
	Metric 3:	Test Substance Purity	Low	Purity and/or grade of test substance were not reported.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	Concurrent control groups were treated with vehicles: BP, TPA or acetone.
	Metric 5:	Positive Controls	N/A	The study type does not require a positive control.
	Metric 6:	Randomized Allocation of Animals	Low	The study did not report how animals were allocated to study groups.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Medium	There is an omission of details that are unlikely to have a substantial impact on results (e.g. preparation/administration of test substance is described, but storage is not reported however the assay is a short-term study and therefore storage is unlikely to affect results).
	Metric 8:	Consistency of Exposure Administration	High	Details of exposure administration were reported and exposures were administered consistently across study groups.
	Metric 9:	Reporting of Doses/Concentrations	High	Administered doses were reported without ambiguity.
	Metric 10:	Exposure Frequency and Duration	High	The exposure frequency and duration of exposure were reported and appropriate for this study type and/or outcome(s) of interest.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	Medium	There were three dose levels but it is unclear if highest dose was high enough.
	Metric 12:	Exposure Route and Method	High	The route and method of exposure were reported and were suited to the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	High	The test animal species, strain, sex, age, and starting body weight were reported, and the test animal was obtained from a commercial source or laboratory-maintained colony. The test species and strain were an appropriate animal model for the evaluation of the specific outcome(s) of interest (e.g., routinely used for similar study types).
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	Most husbandry conditions were not reported, but this is a short term study.

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Study Citation:	Sala, M., Gu, Z. G., Moens, G., Chouroulinkov, I. (1982). In vivo and in vitro biological effects of the flame retardants tris(2,3-dibromopropyl) phosphate and tris(2-chlorethyl)orthophosphate. European Journal of Cancer & Clinical Oncology 18(12):1337-1344.
Health Outcome(s):	Skin/Connective Tissue
Reported Health Effect(s):	Short term skin test: mouse skin treated with TCEP showed that sebaceous glands were not suppressed and hyperplasia was not induced. Long term skin test: mouse skin treated with TCEP showed negative results for complete carcinogenic or promoting activity on mouse skin.
Duration:	Short-term (>1-30 days) Short term skin test
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469568

Domain	Metric		Rating	Comments
	Metric 15:	Number of Animals per Group	Medium	25 female animals per dose group.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	The outcome assessment methodology addressed the intended outcome(s) of interest and the assessment methodology was sensitive and appropriate for the outcomes(s) of interest.
	Metric 17:	Consistency of Outcome Assessment	High	Outcomes were assessed consistently across study groups
	Metric 18:	Sampling Adequacy	High	Reported information indicates the study used adequate sampling for the outcome(s) of interest. Study authors refer to methods previously published in the literature.
	Metric 19:	Blinding of Assessors	N/A	The number of sebaceous glands and the thickness of the epidermis were measured by standard procedures.
	Metric 20:	Negative Control Response	High	The biological responses of the negative control group(s) were adequate.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Low	Body weight changes, food/water intake and differences in use of surgery were not reported
	Metric 22:	Health Outcomes Unrelated to Exposure	High	There were no adverse effects reported in control or treated animals.
	Metric 23:	Data Presentation and Analysis	High	To compare the mean values Student's t-test was used, p-values were reported to show statistical significance.
	Metric 24:	Reporting of Data	High	Data for exposure-related findings were presented for all outcomes by exposure group.

Overall Quality Determination High

Study Citation:	Sprague, G. L., Sandvik, L. L., Brookins-Hendricks, M. J., Bickford, A. A. (1981). Neurotoxicity of two organophosphorus ester flame retardants in hens. Journal of Toxicology and Environmental Health, Part A: Current Issues 8(3):507-518.
Health Outcome(s):	Mortality
Reported Health Effect(s):	Mortality
Duration:	Short-term (>1-30 days) Two doses - day 1 and day 21
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	656590

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	Medium	No CASRN was identified but the name is specific enough to identify the exact structure.
	Metric 2:	Test Substance Source	High	The manufacturer was identified and chemical structure is not variable.
	Metric 3:	Test Substance Purity	Low	There was no information on purity.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	Low	The controls received corn oil but the dosed group received the test substance neat.
	Metric 5:	Positive Controls	Medium	TOCP was used as a positive control and is appropriate for this test.
	Metric 6:	Randomized Allocation of Animals	Low	The study did not mention random allocation of animals.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Medium	There was limited/no info on preparation/storage but the chemical was administered neat; it appears to be stable; and it was a short term study so it is not expected to result in substantial effects.
	Metric 8:	Consistency of Exposure Administration	Medium	Corn oil in negative control vs. none in dose groups may result in some differences but not likely to be substantial given that there was only one dose.
	Metric 9:	Reporting of Doses/Concentrations	High	Doses were identified as g/kg.
	Metric 10:	Exposure Frequency and Duration	High	Exposure frequency and duration were appropriate to the test.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	A limit test used a dose higher than required.
	Metric 12:	Exposure Route and Method	High	The oral route was used and was acceptable.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	Low	The source of the hens was not reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	Most husbandry information was reported except humidity and whether the animals were acclimatized before treatment (although the figure seems to indicate animals were kept for several days before treatment).
	Metric 15:	Number of Animals per Group	Medium	The number of animals were adequate - more than specified by the TG.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	Deaths are objective and easy to assess.
	Metric 17:	Consistency of Outcome Assessment	High	Deaths easy to determine.

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Study Citation:	Sprague, G. L., Sandvik, L. L., Brookins-Hendricks, M. J., Bickford, A. A. (1981). Neurotoxicity of two organophosphorus ester flame retardants in hens. Journal of Toxicology and Environmental Health, Part A: Current Issues 8(3):507-518.
Health Outcome(s):	Mortality
Reported Health Effect(s):	Mortality
Duration:	Short-term (>1-30 days) Two doses - day 1 and day 21
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	656590

Domain	Metric		Rating	Comments
	Metric 18:	Sampling Adequacy	High	All deaths were reported.
	Metric 19:	Blinding of Assessors	Medium	Blinding of assessors is not reported but not crucial for objective measures (especially deaths).
	Metric 20:	Negative Control Response	Low	The authors note the possibility that mild neurological effects in the corn-oil treated rats (controls) were reminiscent of Marek's disease (a neurological disease); it is not clear whether this could have led to increases ONLY in the negative controls and thus underestimated effects in the test animals. Presumably all animals came from the same source and the treated groups also had the same possible Marek's disease but this is not clear from the article.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	It is unclear how deviations from the protocol and use of corn oil only in controls may have confounded outcomes but would not have been likely to affect whether animals died.
	Metric 22:	Health Outcomes Unrelated to Exposure	Medium	The information on neurological effects on controls could have been related to Marek's disease but details were limited on whether this had a differential effect and the severity not likely to have an effect on deaths.
	Metric 23:	Data Presentation and Analysis	High	Statistical methods were described.
	Metric 24:	Reporting of Data	Medium	Number of deaths were reported but timing of those deaths was not recorded.

Overall Quality Determination Medium

Study Citation:	Sprague, G. L., Sandvik, L. L., Brookins-Hendricks, M. J., Bickford, A. A. (1981). Neurotoxicity of two organophosphorus ester flame retardants in hens. Journal of Toxicology and Environmental Health, Part A: Current Issues 8(3):507-518.
Health Outcome(s):	Neurological/Behavioral
Reported Health Effect(s):	Inhibition of plasma cholinesterase, Inhibition of neurotoxic esterase
Duration:	Short-term (>1-30 days) Two doses - day 1 and day 21
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	656590

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	Medium	No CASRN was identified but the name is specific enough to identify the exact structure.
	Metric 2:	Test Substance Source	High	The manufacturer was identified and chemical structure is not variable.
	Metric 3:	Test Substance Purity	Low	There was no information on purity.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	Low	The controls received corn oil but the dosed group received the test substance neat.
	Metric 5:	Positive Controls	Medium	TOCP was used as a positive control and is appropriate for this test.
	Metric 6:	Randomized Allocation of Animals	Low	The study did not mention random allocation of animals.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Medium	There was limited/no info on preparation/storage but the chemical was administered neat; it appears to be stable; and it was a short term study so it is not expected to result in substantial effects.
	Metric 8:	Consistency of Exposure Administration	Medium	Corn oil in negative control vs. none in dose groups may result in some differences but not likely to be substantial given that there was only one dose.
	Metric 9:	Reporting of Doses/Concentrations	High	Doses were identified as g/kg.
	Metric 10:	Exposure Frequency and Duration	High	Exposure frequency and duration were appropriate to the test.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	A limit test used a dose higher than required.
	Metric 12:	Exposure Route and Method	High	The oral route was used and was acceptable.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	Low	The source of the hens was not reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	Most husbandry information was reported except humidity and whether the animals were acclimatized before treatment (although the figure seems to indicate animals were kept for several days before treatment).
	Metric 15:	Number of Animals per Group	Medium	The number of animals were adequate - more than specified by the TG.
Domain 5: Outcome Assessment				

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Study Citation:	Sprague, G. L., Sandvik, L. L., Brookins-Hendricks, M. J., Bickford, A. A. (1981). Neurotoxicity of two organophosphorus ester flame retardants in hens. Journal of Toxicology and Environmental Health, Part A: Current Issues 8(3):507-518.
Health Outcome(s):	Neurological/Behavioral
Reported Health Effect(s):	Inhibition of plasma cholinesterase, Inhibition of neurotoxic esterase
Duration:	Short-term (>1-30 days) Two doses - day 1 and day 21
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	656590

Domain	Metric		Rating	Comments
	Metric 16:	Outcome Assessment Methodology	Low	The outcome assessment measured the midcervical vs. rostral cervical section of spinal cord (unclear on difference). The animal preparation and staining appear appropriate to identify the sections of the nervous system tissues. Neurobehavioral endpoints were very limited; OPPTS 870.6100 (1998) states that forced motor activity should be measured twice per week to see minimal changes and a 4-level rating scale should be used. Instead the authors only note that they evaluated walking behavior once/week.
	Metric 17:	Consistency of Outcome Assessment	Medium	BW was measured every 3-4 days and walking behavior method not described but done weekly.
	Metric 18:	Sampling Adequacy	Low	5-18 hens were examined - unclear how sampling of hens was done and why these numbers varied (esp. down to 5 because controls/TOCP used 10 animals).
	Metric 19:	Blinding of Assessors	Medium	Blinding of assessors is not specified by the guidelines but examination of walking behavior could be somewhat subjective.
	Metric 20:	Negative Control Response	Low	The authors note the possibility that mild neurological effects in the corn-oil treated rats (controls) were reminiscent of Marek's disease (a neurological disease); it is not clear whether this could have led to increases ONLY in the negative controls and thus underestimated effects in the test animals. Presumably all animals came from the same source and the treated groups also had the same possible Marek's disease but this is not clear from the article.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Low	It is unclear how deviations from the protocol and use of corn oil only in controls may have confounded outcomes.
	Metric 22:	Health Outcomes Unrelated to Exposure	Medium	The information on neurological effects on controls could have been related to Marek's disease but details were limited on whether this had a differential effect.
	Metric 23:	Data Presentation and Analysis	High	Statistical methods were described.
	Metric 24:	Reporting of Data	Low	Only limited details reported on 'walking behavior'

Overall Quality Determination Medium

Study Citation:	Sprague, G. L., Sandvik, L. L., Brookins-Hendricks, M. J., Bickford, A. A. (1981). Neurotoxicity of two organophosphorus ester flame retardants in hens. Journal of Toxicology and Environmental Health, Part A: Current Issues 8(3):507-518.
Health Outcome(s):	Skin/Connective Tissue
Reported Health Effect(s):	Feather loss
Duration:	Short-term (>1-30 days) Two doses - day 1 and day 21
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	656590

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	Medium	No CASRN was identified but the name is specific enough to identify the exact structure.
	Metric 2:	Test Substance Source	High	The manufacturer was identified and chemical structure is not variable.
	Metric 3:	Test Substance Purity	Low	There was no information on purity.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	Low	The controls received corn oil but the dosed group received the test substance neat.
	Metric 5:	Positive Controls	Medium	TOCP was used as a positive control and is appropriate for this test.
	Metric 6:	Randomized Allocation of Animals	Low	The study did not mention random allocation of animals.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Medium	There was limited/no info on preparation/storage but the chemical was administered neat; it appears to be stable; and it was a short term study so it is not expected to result in substantial effects.
	Metric 8:	Consistency of Exposure Administration	Medium	Corn oil in negative control vs. none in dose groups may result in some differences but not likely to be substantial given that there was only one dose.
	Metric 9:	Reporting of Doses/Concentrations	High	Doses were identified as g/kg.
	Metric 10:	Exposure Frequency and Duration	High	Exposure frequency and duration were appropriate to the test.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	A limit test used a dose higher than required.
	Metric 12:	Exposure Route and Method	High	The oral route was used and was acceptable.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	Low	The source of the hens was not reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	Most husbandry information was reported except humidity and whether the animals were acclimatized before treatment (although the figure seems to indicate animals were kept for several days before treatment).
	Metric 15:	Number of Animals per Group	Medium	The number of animals were adequate - more than specified by the TG.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	Low	Not clear when animals were examined for skin/other conditions, clinical signs.
	Metric 17:	Consistency of Outcome Assessment	Medium	Not clear whether animals were examined at different times but severe feather loss occurred in treated animals so lack of details should not significantly affect outcomes.

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Study Citation:	Sprague, G. L., Sandvik, L. L., Brookins-Hendricks, M. J., Bickford, A. A. (1981). Neurotoxicity of two organophosphorus ester flame retardants in hens. Journal of Toxicology and Environmental Health, Part A: Current Issues 8(3):507-518.
Health Outcome(s):	Skin/Connective Tissue
Reported Health Effect(s):	Feather loss
Duration:	Short-term (>1-30 days) Two doses - day 1 and day 21
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	656590

Domain	Metric		Rating	Comments
	Metric 18:	Sampling Adequacy	Low	5-18 animals were sampled with no further explanation about why some groups used less than the number of animals tested. This discrepancy is not explained fully by # deaths.
	Metric 19:	Blinding of Assessors	Medium	Blinding of assessors not reported, but not required by the OPPTS 870.6100 guideline. Identification of severe feather loss not likely to be affected by lack of blinding.
	Metric 20:	Negative Control Response	Medium	The authors note the possibility that mild neurological effects in the corn-oil treated rats (controls) were reminiscent of Marek's disease (a neurological disease). Presumably all animals came from the same source and the treated groups also had the same possible Marek's disease but this is not clear from the article. Severe feather loss occurred only in treated groups so this would not likely affect the outcome.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	There were deviations from the protocol and use of corn oil only in controls but not likely to affect outcomes because the severe feather loss occurred only in treated groups.
	Metric 22:	Health Outcomes Unrelated to Exposure	Medium	The information on neurological effects on controls could have been related to Marek's disease but details were limited on whether this had a differential effect but not likely to affect the outcome of severe feather loss in treated groups.
	Metric 23:	Data Presentation and Analysis	High	Statistical methods were described.
	Metric 24:	Reporting of Data	Low	Timing of feather loss was somewhat unclear; incidence per group not given.

Overall Quality Determination Medium

Study Citation:	Sprague, G. L., Sandvik, L. L., Brookins-Hendricks, M. J., Bickford, A. A. (1981). Neurotoxicity of two organophosphorus ester flame retardants in hens. Journal of Toxicology and Environmental Health, Part A: Current Issues 8(3):507-518.
Health Outcome(s):	Nutritional/Metabolic
Reported Health Effect(s):	Body weightFood consumption
Duration:	Short-term (>1-30 days) Two doses - day 1 and day 21
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	656590

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	Medium	No CASRN was identified but the name is specific enough to identify the exact structure.
	Metric 2:	Test Substance Source	High	The manufacturer was identified and chemical structure is not variable.
	Metric 3:	Test Substance Purity	Low	There was no information on purity.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	Low	The controls received corn oil but the dosed group received the test substance neat.
	Metric 5:	Positive Controls	Medium	TOCP was used as a positive control and is appropriate for this test.
	Metric 6:	Randomized Allocation of Animals	Low	The study did not mention random allocation of animals.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Medium	There was limited/no info on preparation/storage but the chemical was administered neat; it appears to be stable; and it was a short term study so it is not expected to result in substantial effects.
	Metric 8:	Consistency of Exposure Administration	Medium	Corn oil in negative control vs. none in dose groups may result in some differences but not likely to be substantial given that there was only one dose.
	Metric 9:	Reporting of Doses/Concentrations	High	Doses were identified as g/kg.
	Metric 10:	Exposure Frequency and Duration	High	Exposure frequency and duration were appropriate to the test.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	A limit test used a dose higher than required.
	Metric 12:	Exposure Route and Method	High	The oral route was used and was acceptable.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	Low	The source of the hens was not reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	Most husbandry information was reported except humidity and whether the animals were acclimatized before treatment (although the figure seems to indicate animals were kept for several days before treatment).
	Metric 15:	Number of Animals per Group	Medium	The number of animals were adequate - more than specified by the TG.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	Medium	BW and food consumption were measured every 3-4 days.
	Metric 17:	Consistency of Outcome Assessment	Medium	Few details about when collection was made (every 3-4 days) without stating whether this was consistent between controls/dose groups.

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Study Citation:	Sprague, G. L., Sandvik, L. L., Brookins-Hendricks, M. J., Bickford, A. A. (1981). Neurotoxicity of two organophosphorus ester flame retardants in hens. Journal of Toxicology and Environmental Health, Part A: Current Issues 8(3):507-518.
Health Outcome(s):	Nutritional/Metabolic
Reported Health Effect(s):	Body weightFood consumption
Duration:	Short-term (>1-30 days) Two doses - day 1 and day 21
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	656590

Domain	Metric		Rating	Comments
	Metric 18:	Sampling Adequacy	High	5-18 animals were sampled with no further explanation about why some groups used less than the number of animals tested. Although some animals died, the numbers of deaths don't fully describe the discrepancy in # animals sampled/group.
	Metric 19:	Blinding of Assessors	Medium	Blinding of assessors is less important for objective measures.
	Metric 20:	Negative Control Response	Low	The authors note the possibility that mild neurological effects in the corn-oil treated rats (controls) were reminiscent of Marek's disease (a neurological disease). Presumably all animals came from the same source and the treated groups also had the same possible Marek's disease but this is not clear from the article.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Low	It is unclear how deviations from the protocol and use of corn oil only in controls may have confounded outcomes.
	Metric 22:	Health Outcomes Unrelated to Exposure	Medium	The information on neurological effects on controls could have been related to Marek's disease but details were limited on whether this had a differential effect and the severity not likely to have an effect on BW and food consumption.
	Metric 23:	Data Presentation and Analysis	High	Statistical methods were described.
	Metric 24:	Reporting of Data	Low	BW and food consumption were reported only on separate graphs for controls vs. the dosed group and there was no separate table outlining all results. Thus, it was difficult to compare results between groups.

Overall Quality Determination Medium

Study Citation:	Taniai, E., Hayashi, H., Yafune, A., Watanabe, M., Akane, H., Suzuki, K., Mitsumori, K., Shibutani, M. (2012). Cellular distribution of cell cycle-related molecules in the renal tubules of rats treated with renal carcinogens for 28 days: relationship between cell cycle aberration and carcinogenesis. Archives of Toxicology 86(9):1453-1464.
Health Outcome(s):	Renal/Kidney
Reported Health Effect(s):	Immunohistochemical analysis of tubular cells was used to investigate cell cycle-related changes during the early stages of renal carcinogenesis.
Duration:	Short-term (>1-30 days) 28 days
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469208

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	Test substance was identified as tris(2-chloroethyl) phosphate (CAS No. 115-96-8)
	Metric 2:	Test Substance Source	High	Test substance was purchased from Tokyo Chemical Industry Co. (Tokyo, Japan). Batch/lot number was not reported.
	Metric 3:	Test Substance Purity	High	Test substance purity was reported as >97%
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	Low	Authors state "Ten untreated control animals were maintained with basal diet and tap water without any treatment during the experimental period." TCEP was dissolved in corn oil and administered via gavage. It is unclear if a corn oil control was used.
	Metric 5:	Positive Controls	N/A	Positive controls are not needed for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	Study authors state "After 1-week acclimatization period, animals were randomized into groups of 10 animals"
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Medium	Study authors state that TCEP was dissolved in corn oil. No further details regarding test substance preparation or storage were provided.
	Metric 8:	Consistency of Exposure Administration	Medium	TCEP was administered daily by gavage. No details on timing of administration or gavage volume were provided.
	Metric 9:	Reporting of Doses/Concentrations	High	Doses (0 and 350 mg/kg-d) were reported without ambiguity.
	Metric 10:	Exposure Frequency and Duration	High	Animals were administered TCEP for 28 consecutive days.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	N/A	N/A. The goal of this mechanistic study was not to observe a dose-response.
	Metric 12:	Exposure Route and Method	High	TCEP was dissolved in corn oil and administered via oral gavage.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	Medium	Five week old male F344/NSIc rats were purchased from Japan SLC, Inc (Hamamatsu, Japan). Starting body weight was not reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	High	All husbandry conditions were reported (e.g., temperature, humidity, light- dark cycle, diet, water availability) and were adequate.
	Metric 15:	Number of Animals per Group	Medium	10 animals were included per group. This is appropriate for a 28-day study.

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Study Citation:	Taniai, E., Hayashi, H., Yafune, A., Watanabe, M., Akane, H., Suzuki, K., Mitsumori, K., Shibutani, M. (2012). Cellular distribution of cell cycle-related molecules in the renal tubules of rats treated with renal carcinogens for 28 days: relationship between cell cycle aberration and carcinogenesis. Archives of Toxicology 86(9):1453-1464.
Health Outcome(s):	Renal/Kidney
Reported Health Effect(s):	Immunohistochemical analysis of tubular cells was used to investigate cell cycle-related changes during the early stages of renal carcinogenesis.
Duration:	Short-term (>1-30 days) 28 days
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469208

Domain	Metric		Rating	Comments
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	The outcome assessment methodology adequately addressed the outcome of interest.
	Metric 17:	Consistency of Outcome Assessment	High	One day after the 28-day treatment, all animals were sacrificed and kidneys were removed for histopathological and immunohistochemical examination
	Metric 18:	Sampling Adequacy	High	The ten animals included in each treatment group were evaluated for each outcome of interest.
	Metric 19:	Blinding of Assessors	N/A	Blinding is not necessary for initial histopathology review.
	Metric 20:	Negative Control Response	Medium	Biological responses were only reported for some outcomes of interest (i.e., histochemical analyses). Histopathological response data was not reported for the negative control group.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Low	Confounding variables (i.e., body weight, food/water intake values) were not reported.
	Metric 22:	Health Outcomes Unrelated to Exposure	Medium	There was no information either to support or dismiss the suggestion that there were differences among groups in animal attrition or health outcomes unrelated to exposure that could influence the outcome assessment.
	Metric 23:	Data Presentation and Analysis	Low	Statistical methods were clearly described for some outcomes (immunohistochemical analysis). However, it is unclear if a statistical analysis was conducted on the observed histopathological changes.
	Metric 24:	Reporting of Data	Low	Immunohistochemical data is represented graphically as mean +/- standard deviation. A limited description of histopathological findings is described qualitatively in the text, however, incidence data is not provided.

Overall Quality Determination Medium

Study Citation:	Taniai, E., Yafune, A., Hayashi, H., Itahashi, M., Hara-Kudo, Y., Suzuki, K., Mitsumori, K., Shibutani, M. (2012). Aberrant activation of ubiquitin D at G2 phase and apoptosis by carcinogens that evoke cell proliferation after 28-day administration in rats. Journal of Toxicological Sciences 37(6):1093-1111.
Health Outcome(s):	Cancer/Carcinogenesis
Reported Health Effect(s):	Kidney cancer (aim was to identify early prediction markers of carcinogenesis)
Duration:	Short-term (>1-30 days) 28-day oral gavage study
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469521

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	Test substance identified as tris(2-chloroethyl)phosphate (Cas No. 115-96-8)
	Metric 2:	Test Substance Source	High	Test substance was obtained from Tokylo Chemical Industry Corporation (Tokyo, Japan). Batch/lot number were not provided.
	Metric 3:	Test Substance Purity	High	Purity of test substance was reported as >97.0%
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	Low	Untreated controls were used. Figure 1, which outlines the experimental design, indicates that control animals were fed basal diet and tap water. However, TCEP was dissolved in corn oil and administered via gavage. Insufficient details are provided to determine if control animals were gavaged with corn oil.
	Metric 5:	Positive Controls	N/A	Not applicable for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	Study authors state that "animals were randomized into groups of 10 each and treated with carcinogens for non-carcinogens for 28-days"
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Medium	Study authors state that TCEP was dissolved in corn oil. No additional information on preparation or storage of the test substance was provided.
	Metric 8:	Consistency of Exposure Administration	Low	Details of exposure administration are insufficiently reported. No information on gavage volume or timing of test substance administration were reported.
	Metric 9:	Reporting of Doses/Concentrations	High	Doses (0 and 350 mg/kg-d) were reported without ambiguity.
	Metric 10:	Exposure Frequency and Duration	High	TCEP was administered daily for 28 consecutive days. This frequency and duration was considered appropriate for the aim of the study (i.e., to identify early prediction markers of carcinogens).
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	N/A	Not applicable. The goal of the study was to identify early prediction markers of carcinogens, not to achieve a dose-resposne.
	Metric 12:	Exposure Route and Method	High	Test substance was administered via oral gavage.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	Medium	Five week old male F344/NSIc rats were obtained from Japan SLC, Inc. (Shizouka, Japan). They were housed in stainless steel cages in a barrier-maintained animal room on a 12 hr light-dark cycle and conditioned at 23C (+/- 3C) with a relative humidity of 50% (+/-20%). Animal starting body weight was not reported.

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Study Citation:	Taniai, E., Yafune, A., Hayashi, H., Itahashi, M., Hara-Kudo, Y., Suzuki, K., Mitsumori, K., Shibutani, M. (2012). Aberrant activation of ubiquitin D at G2 phase and apoptosis by carcinogens that evoke cell proliferation after 28-day administration in rats. Journal of Toxicological Sciences 37(6):1093-1111.
Health Outcome(s):	Cancer/Carcinogenesis
Reported Health Effect(s):	Kidney cancer (aim was to identify early prediction markers of carcinogenesis)
Duration:	Short-term (>1-30 days) 28-day oral gavage study
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469521

Domain	Metric		Rating	Comments
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	High	All husbandry conditions were reported and were adequate.
	Metric 15:	Number of Animals per Group	Medium	10 rats were included in each treatment group.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	The methodology addressed the intended outcomes.
	Metric 17:	Consistency of Outcome Assessment	High	One day after the 28-day treatment, all animals were sacrificed and kidneys are removed for histopathological and immunohistochemical examination.
	Metric 18:	Sampling Adequacy	High	Kidneys were evaluated from all 10 animals treated with TCEP.
	Metric 19:	Blinding of Assessors	N/A	Blinding is not necessary for initial histopathology review.
	Metric 20:	Negative Control Response	Low	The biological response of the negative control groups were not reported for all outcomes (i.e., histopathology).
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	No information on animal body or food/water intake were reported.
	Metric 22:	Health Outcomes Unrelated to Exposure	Medium	There was no information either to support or dismiss the suggestion that there were differences among groups in animal attrition or health outcomes unrelated to exposure that could influence the outcome assessment.
	Metric 23:	Data Presentation and Analysis	Low	Statistical analysis was clearly described and appropriate for the immunohistochemical staining of kidney cells. Study authors report that TCEP treatment resulted in scattered proximal tubular regeneration in the cortex and OSOM; however, it is unclear if a statistical analysis was performed on the histopathological findings.
	Metric 24:	Reporting of Data	Low	Data for immunohistochemical staining for Mcm3+, Ubd+ and TUNEL+ cells is presented graphically as mean plus standard deviation. Histopathological findings were described qualitatively in the study report, however, incidence data is not provided.

Overall Quality Determination Medium

Study Citation:	Chen, G., Jin, Y., Wu, Y., Liu, L., Fu, Z. (2015). Exposure of male mice to two kinds of organophosphate flame retardants (OPFRs) induced oxidative stress and endocrine disruption. Environmental Toxicology and Pharmacology 40(1):310-318.
Health Outcome(s):	Hepatic/Liver; Nutritional/Metabolic;
Reported Health Effect(s):	Hepatic/Liver: Decreased liver weights, decreased hepatic glutathione (GSH)content, altered activities of hepatic enzymes including glutathione peroxidase (GPX), catalase (CAT) and glutathione S-transferase (GST), altered transcriptional patterns of Sod1, Sod2, Gpx1, Gpx2 and Cat.; Nutritional/Metabolic: Decreased in weights.;
Duration:	Subchronic (>30-91 days) 35 days
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	4199395

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	All Outcomes: The test substance was identified definitively.
	Metric 2:	Test Substance Source	High	All Outcomes: The source of the test substance was reported.
	Metric 3:	Test Substance Purity	High	All Outcomes: The purity was reported as >97%.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	All Outcomes: Control animals were given standard diet.
	Metric 5:	Positive Controls	N/A	All Outcomes: A positive control is not needed for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	All Outcomes: The study reported that animals were randomly allocated into study groups.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Medium	All Outcomes: No information on storage conditions of mixed diet or stability and homogeneity.
	Metric 8:	Consistency of Exposure Administration	High	All Outcomes: Details of exposure administration were reported and exposures were administered consistently across study groups.
	Metric 9:	Reporting of Doses/Concentrations	Low	All Outcomes: Nominal dose was provided rather than the analytical dose and no information was provided on food consumption.
	Metric 10:	Exposure Frequency and Duration	High	All Outcomes: The exposure frequency and duration of exposure were reported and appropriate for this study type.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	Medium	All Outcomes: There were minor limitations regarding the number of exposure groups and/or dose/concentration spacing (i.e., effects were observed at all doses tested).
	Metric 12:	Exposure Route and Method	High	All Outcomes: The route and method of exposure were reported and were suited to the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	High	All Outcomes: The test animal species, strain, sex, age, and starting body weight were reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	High	All Outcomes: Husbandry conditions were reported and were appropriate.
	Metric 15:	Number of Animals per Group	Low	All Outcomes: There were 7 animals per study group. The standard for subchronic studies is 10 animals per group.

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Study Citation:	Chen, G., Jin, Y., Wu, Y., Liu, L., Fu, Z. (2015). Exposure of male mice to two kinds of organophosphate flame retardants (OPFRs) induced oxidative stress and endocrine disruption. Environmental Toxicology and Pharmacology 40(1):310-318.
Health Outcome(s):	Hepatic/Liver; Nutritional/Metabolic;
Reported Health Effect(s):	Hepatic/Liver: Decreased liver weights, decreased hepatic glutathione (GSH)content, altered activities of hepatic enzymes including glutathione peroxidase (GPX), catalase (CAT) and glutathione S-transferase (GST), altered transcriptional patterns of Sod1, Sod2, Gpx1, Gpx2 and Cat.; Nutritional/Metabolic: Decreased in weights.;
Duration:	Subchronic (>30-91 days) 35 days
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	4199395

Domain	Metric		Rating	Comments
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	All Outcomes: The outcome assessment methodology addressed the intended outcome(s) of interest.
	Metric 17:	Consistency of Outcome Assessment	High	All Outcomes: Details of the outcome assessment protocol were reported and outcomes were assessed consistently across study groups.
	Metric 18:	Sampling Adequacy	High	Hepatic/Liver: For liver endpoints, n=7 animals per group; Nutritional/Metabolic: n=7 animals per group
	Metric 19:	Blinding of Assessors	N/A	Hepatic/Liver: Blinding was not required for liver endpoints.; Nutritional/Metabolic: Blinding was not required for body weight and food intake.
	Metric 20:	Negative Control Response	High	All Outcomes: The biological responses of the negative control group was adequate.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Low	Hepatic/Liver: The study does not report food intake. It is not clear whether reduced body weight and liver weights are treatment related or due to reduced food intake. Relative liver weights are not reported, making it difficult to determine whether liver weight changes are proportional to body weight changes or an effect that is specific to the liver.; Nutritional/Metabolic: The study does not report food intake, making it difficult to determine the extent to which body weight reduction may be due to reduced consumption or impacts on food efficiency.
	Metric 22:	Health Outcomes Unrelated to Exposure	High	All Outcomes: There were no differences among groups that could influence the outcome assessment.
	Metric 23:	Data Presentation and Analysis	High	All Outcomes: Statistical methods were clearly described and appropriate.
	Metric 24:	Reporting of Data	Medium	All Outcomes: Most data was only provided in charts.

Overall Quality Determination High

Study Citation:	Chen, G., Jin, Y., Wu, Y., Liu, L., Fu, Z. (2015). Exposure of male mice to two kinds of organophosphate flame retardants (OPFRs) induced oxidative stress and endocrine disruption. Environmental Toxicology and Pharmacology 40(1):310-318.
Health Outcome(s):	Reproductive/Developmental
Reported Health Effect(s):	Decreased testis weights, decrease of testicular testosterone level, decreased gene expression of genes related to testosterone synthesis, histopathological damage (decreased number of leydig cells, Sertoli cells and spermatogenic cells, and disintegration of seminiferous tubule structure at 300 mg/kg TCEP).
Duration:	Subchronic (>30-91 days) 35 days
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	4199395

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was identified definitively.
	Metric 2:	Test Substance Source	High	The source of the test substance was reported.
	Metric 3:	Test Substance Purity	High	The purity was reported as >97%.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	Control animals were given standard diet.
	Metric 5:	Positive Controls	N/A	A positive control is not needed for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	The study reported that animals were randomly allocated into study groups.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Medium	No information on storage conditions of mixed diet or stability and homogeneity.
	Metric 8:	Consistency of Exposure Administration	High	Details of exposure administration were reported and exposures were administered consistently across study groups.
	Metric 9:	Reporting of Doses/Concentrations	Low	Nominal dose was provided rather than the analytical dose and no information was provided on food consumption.
	Metric 10:	Exposure Frequency and Duration	High	The exposure frequency and duration of exposure were reported and appropriate for this study type.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	Medium	There were minor limitations regarding the number of exposure groups and/or dose/concentration spacing (i.e., effects were observed at all doses tested).
	Metric 12:	Exposure Route and Method	High	The route and method of exposure were reported and were suited to the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	High	The test animal species, strain, sex, age, and starting body weight were reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	High	Husbandry conditions were reported and were appropriate.
	Metric 15:	Number of Animals per Group	Low	There were 7 animals per study group. The standard for subchronic studies is 10 animals per group.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	The outcome assessment methodology addressed the intended outcome(s) of interest.
	Metric 17:	Consistency of Outcome Assessment	High	Details of the outcome assessment protocol were reported and outcomes were assessed consistently across study groups.
	Metric 18:	Sampling Adequacy	Low	For testis weight n=7; for histopathological evaluation, n= 2

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Study Citation:	Chen, G., Jin, Y., Wu, Y., Liu, L., Fu, Z. (2015). Exposure of male mice to two kinds of organophosphate flame retardants (OPFRs) induced oxidative stress and endocrine disruption. Environmental Toxicology and Pharmacology 40(1):310-318.
Health Outcome(s):	Reproductive/Developmental
Reported Health Effect(s):	Decreased testis weights, decrease of testicular testosterone level, decreased gene expression of genes related to testosterone synthesis, histopathological damage (decreased number of leydig cells, Sertoli cells and spermatogenic cells, and disintegration of seminiferous tubule structure at 300 mg/kg TCEP).
Duration:	Subchronic (>30-91 days) 35 days
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	4199395

Domain	Metric		Rating	Comments
	Metric 19:	Blinding of Assessors	N/A	Histological evaluations relied on quantitative metrics (the number of seminiferous tubules).
	Metric 20:	Negative Control Response	High	The biological responses of the negative control group was adequate.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Low	The study does not report food intake, making it difficult to determine the extent to which body weight reduction, reduced organ weights, and other effects may be due to reduced consumption.
	Metric 22:	Health Outcomes Unrelated to Exposure	High	There were no differences among groups that could influence the outcome assessment.
	Metric 23:	Data Presentation and Analysis	High	Statistical methods were clearly described and appropriate.
	Metric 24:	Reporting of Data	Medium	Most data was only provided in charts.

Overall Quality Determination High

Study Citation:	Yang, W., Zhao, F., Fang, Y., Li, L., Li, C., Ta, N. (2018). 1H-nuclear magnetic resonance metabolomics revealing the intrinsic relationships between neurochemical alterations and neurobehavioral and neuropathological abnormalities in rats exposed to tris(2-chloroethyl)phosphate. Chemosphere 200(Elsevier):649-659.
Health Outcome(s):	Neurological/Behavioral
Reported Health Effect(s):	Neurotoxic effects (neurochemical alterations, neurobehavioral and neuropathological abnormalities) Neurochemical alterations (dose-dependent increase in alterations of amino acid and neurotransmitter metabolism, energy metabolism, and cell membrane integrity)Neurobehavioral and neuropathological abnormalities (degeneration, necrosis, and loss of neurons in the hippocampal CA1 region of rats), these alterations can lead to functional disorder of learning and memory.
Duration:	Subchronic (>30-91 days) 60-day oral exposure
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469245

Domain		Metric	Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	Identified definitively with nomenclature, CASRN, and structure.
	Metric 2:	Test Substance Source	High	Source was provided and identified as a manufacturer.
	Metric 3:	Test Substance Purity	High	Purity was reported as >95%.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	Control animals were administered corn oil.
	Metric 5:	Positive Controls	N/A	Positive controls were not needed for this study design.
	Metric 6:	Randomized Allocation of Animals	Low	The only detail provided was that littermates were not used in the same experimental group. Unlikely to have a substantial impact.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Medium	Storage is not reported, but unlikely to have substantial impacts.
	Metric 8:	Consistency of Exposure Administration	Medium	Information is not provided on the volume of corn oil used for the controls or gavage administration of the treated groups.
	Metric 9:	Reporting of Doses/Concentrations	Medium	Only nominal doses were reported.
	Metric 10:	Exposure Frequency and Duration	High	The exposure frequency and duration of exposure were reported and appropriate for this study type and/or outcomes of interest.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	A control and three treatment groups were used.
	Metric 12:	Exposure Route and Method	High	Oral gavage is a relevant route of administration. However, a bolus dose may not be relevant for all exposure pathways.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	Medium	Starting body weight was not provided, but unlikely to have a substantial effects on the outcomes measured in this study.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	High	Temperature, humidity, light- dark cycle, diet, and food and water availability were all reported.

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Study Citation:	Yang, W., Zhao, F., Fang, Y., Li, L., Li, C., Ta, N. (2018). 1H-nuclear magnetic resonance metabolomics revealing the intrinsic relationships between neurochemical alterations and neurobehavioral and neuropathological abnormalities in rats exposed to tris(2-chloroethyl)phosphate. Chemosphere 200(Elsevier):649-659.
Health Outcome(s):	Neurological/Behavioral
Reported Health Effect(s):	Neurotoxic effects (neurochemical alterations, neurobehavioral and neuropathological abnormalities) Neurochemical alterations (dose-dependent increase in alterations of amino acid and neurotransmitter metabolism, energy metabolism, and cell membrane integrity)Neurobehavioral and neuropathological abnormalities (degeneration, necrosis, and loss of neurons in the hippocampal CA1 region of rats), these alterations can lead to functional disorder of learning and memory.
Duration:	Subchronic (>30-91 days) 60-day oral exposure
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469245

Domain	Metric		Rating	Comments
	Metric 15:	Number of Animals per Group	Medium	The number of animals was not explicitly stated but was reported to be 10 in may of the data tables.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	10 animals per group
	Metric 17:	Consistency of Outcome Assessment	High	Outcomes were assessed consistently across study groups.
	Metric 18:	Sampling Adequacy	High	The study used adequate sampling for the outcomes of interest.
	Metric 19:	Blinding of Assessors	High	The study did not report whether assessors were blinded to treatment group, however, the outcomes that were assessed are not subjective.
	Metric 20:	Negative Control Response	High	The biological responses of the negative control groups were adequate.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	Although the study did not report all information to determine confounding, the reported information did not identify differences.
	Metric 22:	Health Outcomes Unrelated to Exposure	High	There were no differences reported among groups that could influence the outcome assessment.
	Metric 23:	Data Presentation and Analysis	High	Statistical methods were clearly described.
	Metric 24:	Reporting of Data	Medium	Data for exposure-related findings were presented for most outcomes. However, histopathological results were not adequately described.

Overall Quality Determination High

Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Nutritional/Metabolic; Nutritional/Metabolic;
Reported Health Effect(s):	Nutritional/Metabolic: Body weight; Nutritional/Metabolic: Body weight;
Duration:	Chronic (>91 days) 16 weeks - Rats
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	All Outcomes: The test substance was clearly identified as tris(2-chloroethyl)phosphate.
	Metric 2:	Test Substance Source	High	All Outcomes: The test substance was purchased from Stauffer Chemical Company. The lot and batch number were provided.
	Metric 3:	Test Substance Purity	Low	All Outcomes: The purity was not reported and could not be determined on the manufacturer's website.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	All Outcomes: The study included a concurrent negative vehicle (corn oil) control group.
	Metric 5:	Positive Controls	N/A	All Outcomes: Positive controls are not necessary for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	All Outcomes: Animals were assigned to dose groups and to cages using a random number table. It was not specified whether animals were also normalized to starting body weights.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Medium	All Outcomes: Fresh solutions were made every two weeks by dissolving the test material in 100% pure corn oil. Test solutions were stored at 5 degrees C until use. Details of mixing for homogeneity weren't provided. Testing for stability was not discussed.
	Metric 8:	Consistency of Exposure Administration	High	All Outcomes: Sufficient exposure administration details were reported. A consistent gavage volume of 5 mL/kg was used. The time of day of dosing was not specified.
	Metric 9:	Reporting of Doses/Concentrations	Medium	All Outcomes: Doses were clearly reported. Dosing solutions were analyzed (method and frequency not specified), and the text indicated that the actual concentrations administered remained within 10% of the target. Analytical values were not provided.
	Metric 10:	Exposure Frequency and Duration	Medium	All Outcomes: The study did not mention adherence to a specific guideline, but the text indicated this was an NTP study. Animals were dosed 5 days per week, consistent with the "Specifications for the Conduct of Studies to Evaluate the Toxic and Carcinogenic Potential of Chemical, Biological and Physical Agents in Laboratory Animals for the National Toxicology Program (NTP). The study duration was 16 weeks. The authors did not provide justification for this duration. This is longer than a typical 90-day subchronic study, and shorter than an NTP chronic/carcinogenicity study.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	All Outcomes: The study tested 5 dose groups plus a control. This is consistent with NTP guidelines. The spacing was sufficient to identify NOAEL and LOAEL values

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Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Nutritional/Metabolic; Nutritional/Metabolic;
Reported Health Effect(s):	Nutritional/Metabolic: Body weight; Nutritional/Metabolic: Body weight;
Duration:	Chronic (>91 days) 16 weeks - Rats
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
	Metric 12:	Exposure Route and Method	High	All Outcomes: Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	Medium	Nutritional/Metabolic: The study used male and female F344/N rats. The test animal source (Charles River Breeding Laboratories), and age purchase (5 weeks old), were reported. Initial body weights were not specified. A quarantine period was mentioned, but the duration was not reported.; Nutritional/Metabolic: The study used male and female B6C3F1 mice. The test animal source (Charles River Breeding Laboratories), and age purchase (5 weeks old), were reported. Initial body weights were not specified. A quarantine period was mentioned, but the duration was not reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	Nutritional/Metabolic: Animal husbandry (caging, food and water access, temperature, humidity, and light cycle) were reported. The relative humidity varied from 10% to 78%. This deviates from NTP guidelines that stat humidity should not be below 35% or above 65%. The temperature range in the study was 70 to 81 degrees. NTP indicates temperature should not be above 75 degrees, and that there should be minimal fluctuations. The number of animals per cage (n =5) was appropriate. It is unclear whether the deviations in animal husbandry conditions had an impact on the study results.; Nutritional/Metabolic: Animal husbandry (caging, food and water access, temperature, humidity, and light cycle) were reported. The relative humidity varied from 10% to 78%. This deviates from NTP guidelines that state humidity should not be below 35% or above 65%. The temperature range in the study was 70 to 81 degrees. NTP indicates temperature should not be above 75 degrees, and that there should be minimal fluctuations. The number of animals per cage (n =5) was reported. NTP guidelines specify that male mice should always be housed individually. It is unclear whether the deviations in animal husbandry conditions had an impact on the study results.
	Metric 15:	Number of Animals per Group	Medium	All Outcomes: The number of animals per group (10/sex) was reported and consistent with NTP guidelines.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	All Outcomes: The text indicated that body weights were recorded weekly and body weight gain was determined. The outcome methodology was sensitive for the outcome of interest.
	Metric 17:	Consistency of Outcome Assessment	High	All Outcomes: Details regarding the execution of the study protocol for outcome assessment (weekly) were provided. There is no indication that there were inconsistencies across groups for this outcome.
	Metric 18:	Sampling Adequacy	High	All Outcomes: Final body weights were recorded for all surviving animals. Sampling was adequate in all groups to allow for statistical analysis.

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Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Nutritional/Metabolic; Nutritional/Metabolic;
Reported Health Effect(s):	Nutritional/Metabolic: Body weight; Nutritional/Metabolic: Body weight;
Duration:	Chronic (>91 days) 16 weeks - Rats
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
	Metric 19:	Blinding of Assessors	N/A	All Outcomes: Blinding is not required for this outcome because it is not subjective in nature.
	Metric 20:	Negative Control Response	Medium	All Outcomes: The final body weights of the negative controls were reported and were adequate. Initial body weights were not provided, so the weight gain of control animals could not be assessed.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	All Outcomes: Some information to determine confounding (initial body weights) was not provided. The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP.
	Metric 22:	Health Outcomes Unrelated to Exposure	Low	Nutritional/Metabolic: The study text noted that during week 4, the two highest dose groups were prepared incorrectly, and for the first three days of that week, the animals were administered double the target levels. Animals in the 175 mg/kg-day group, were instead dosed with 350 mg/kg-day, and animals in the 350 mg/kg-day group were dosed with 700 mg/kg-day. As a result, 2 females in each group died, and others showed excessive signs of acute toxicity (e.g., ataxia, excessive salivation, gasping, and convulsions). The overdose caused no deaths in males, and they showed no signs of toxicity. The surviving animals were not dosed on the 4th day of the week to allow them to recover. Dosing resumed on the 5th day. In addition to these deaths, three animals died due to gavage error including 1 male and 1 female at 22 mg/kg-day and 1 female at 175 mg/kg-day.; Nutritional/Metabolic: The study text noted that during week 4, the two highest dose groups were prepared incorrectly, and for the first three days of that week, the animals were administered double the target levels. Animals in the 350 mg/kg group, were instead dosed with 700 mg/kg, and animals in the 700 mg/kg group were dosed with 1,400 mg/kg. No deaths occurred as a result of the dosing error, but two male mice had convulsions and labored breathing on the third day of overdosing. Overdosed females were uncoordinated. These animals were not dosed on the 4th day of the week to allow them to recover. Dosing resumed on the 5th day. Three males and two females died during the study due to gavage trauma. The males were from the 175, 350, and 700 mg/kg groups, and the females were from the 175 and 300 mg/kg groups, respectively.
	Metric 23:	Data Presentation and Analysis	High	Nutritional/Metabolic: Some data were clearly statistically analyzed, but the statistical methods used were not reported; the study text only specifies that the "Significance level was set at $p < 0.05$)."; Nutritional/Metabolic: Some data were clearly statistically analyzed, but the statistical methods used were not reported; the study text only specifies that the "Significance level was set at $p < 0.05$)"

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Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Nutritional/Metabolic; Nutritional/Metabolic;
Reported Health Effect(s):	Nutritional/Metabolic: Body weight; Nutritional/Metabolic: Body weight;
Duration:	Chronic (>91 days) 16 weeks - Rats
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric	Rating	Comments
	Metric 24: Reporting of Data	Medium	Nutritional/Metabolic: Initial body weights and weekly body weight data were not provided. Only final body weights were reported as means ± SE in a table. Body weight gain results were reported qualitatively in the text for females only, indicating that high-dose females gained significantly more weight than controls.; Nutritional/Metabolic: Initial body weights and weekly body weight data were not provided. Only final body weights were reported as means ± SE in a table.

Overall Quality Determination High

Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Renal/Kidney
Reported Health Effect(s):	Histopathology (kidney) and kidney weights
Duration:	Chronic (>91 days) 16 weeks - Mice
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was clearly identified as tris(2-chloroethyl)phosphate.
	Metric 2:	Test Substance Source	High	The test substance was purchased from Stauffer Chemical Company. The lot and batch number were provided.
	Metric 3:	Test Substance Purity	Low	The purity was not reported and could not be determined on the manufacturer's website.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	The study included a concurrent negative vehicle (corn oil) control group.
	Metric 5:	Positive Controls	N/A	Positive controls are not necessary for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	Animals were assigned to dose groups and to cages using a random number table. It was not specified whether animals were also normalized to starting body weights.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Medium	Fresh solutions were made every two weeks by dissolving the test material in 100% pure corn oil. Test solutions were stored at 5 degrees C until use. Details of mixing for homogeneity weren't provided. Testing for stability was not discussed.
	Metric 8:	Consistency of Exposure Administration	High	Sufficient exposure administration details were reported. A consistent gavage volume of 5 mL/kg was used. The time of day of dosing was not specified.
	Metric 9:	Reporting of Doses/Concentrations	Medium	Doses were clearly reported. Dosing solutions were analyzed (method and frequency not specified), and the text indicated that the actual concentrations administered remained within 10% of the target. Analytical values were not provided.
	Metric 10:	Exposure Frequency and Duration	Medium	The study did not mention adherence to a specific guideline, but the text indicated this was an NTP study. Animals were dosed 5 days per week, consistent with the "Specifications for the Conduct of Studies to Evaluate the Toxic and Carcinogenic Potential of Chemical, Biological and Physical Agents in Laboratory Animals for the National Toxicology Program (NTP)." The study duration was 16 weeks. The authors did not provide justification for this duration. This is longer than a typical 90-day subchronic study, and shorter than an NTP chronic/carcinogenicity study.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	The study tested 5 dose groups plus a control. This is consistent with NTP guidelines. The spacing was sufficient to identify NOAEL and LOAEL values.
	Metric 12:	Exposure Route and Method	High	Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				

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Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Renal/Kidney
Reported Health Effect(s):	Histopathology (kidney) and kidney weights
Duration:	Chronic (>91 days) 16 weeks - Mice
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
	Metric 13:	Test Animal Characteristics	Medium	The study used male and female B6C3F1 mice. The test animal source (Charles River Breeding Laboratories), and age purchase (5 weeks old), were reported. Initial body weights were not specified. A quarantine period was mentioned, but the duration was not reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	Animal husbandry (caging, food and water access, temperature, humidity, and light cycle) were reported. The relative humidity varied from 10% to 78%. This deviates from NTP guidelines that state humidity should not be below 35% or above 65%. The temperature range in the study was 70 to 81 degrees. NTP indicates temperature should not be above 75 degrees, and that there should be minimal fluctuations. The number of animals per cage (n =5) was reported. NTP guidelines specify that male mice should always be housed individually. It is unclear whether the deviations in animal husbandry conditions had an impact on the study results.
	Metric 15:	Number of Animals per Group	Medium	The number of animals per group (10/sex) was reported and consistent with NTP guidelines.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	Kidney weights were recorded and histopathology was conducted. The methods were sensitive for this outcome of interest. The study did not specify whether serum chemistry analysis was done.
	Metric 17:	Consistency of Outcome Assessment	High	There is no indication that there were inconsistencies in the outcome assessment across groups. Histopathology and organ weights were recorded at the end of the study.
	Metric 18:	Sampling Adequacy	Medium	Organ weights were measured from all surviving animals. Histopathology was conducted in controls and animals from the high-dose group. This is acceptable because no treatment-related lesions were observed.
	Metric 19:	Blinding of Assessors	N/A	Blinding is not necessary for initial histopathology.
	Metric 20:	Negative Control Response	High	A single control male had nephropathy, and lymphocytic infiltrate was observed in one control female. There was no indication that these were unexpected or abnormal. Negative control organ weights were appropriate.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	Some information to determine confounding (initial body weights) was not provided. The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP.

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Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Renal/Kidney
Reported Health Effect(s):	Histopathology (kidney) and kidney weights
Duration:	Chronic (>91 days) 16 weeks - Mice
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
	Metric 22:	Health Outcomes Unrelated to Exposure	Low	The study text noted that during week 4, the two highest dose groups were prepared incorrectly, and for the first three days of that week, the animals were administered double the target levels. Animals in the 350 mg/kg group, were instead dosed with 700 mg/kg, and animals in the 700 mg/kg group were dosed with 1,400 mg/kg. No deaths occurred as a result of the dosing error, but two male mice had convulsions and labored breathing on the third day of overdosing. Overdosed females were uncoordinated. These animals were not dosed on the 4th day of the week to allow them to recover. Dosing resumed on the 5th day. Three males and two females died during the study due to gavage trauma. The males were from the 175, 350, and 700 mg/kg groups, and the females were from the 175 and 300 mg/kg groups, respectively.
	Metric 23:	Data Presentation and Analysis	Low	Statistical analysis was performed, but the methods used to analyze organ weight and initial histopathology data weren't clearly specified, only that the significance level was set at $p < 0.05$.
	Metric 24:	Reporting of Data	High	Organ weights were adequately reported as means $\pm$ SEM. Kidney histopathology results were qualitatively reported in the text. Only incidences of one lesion type were reported for high-dose animals and the controls, which allows for independent statistical analysis.

Overall Quality Determination High

Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Renal/Kidney; Hepatic/Liver;
Reported Health Effect(s):	Renal/Kidney: Histopathology (kidney) and kidney weights; Hepatic/Liver: Histopathology (liver) and liver weights;
Duration:	Chronic (>91 days) 16 weeks - Rats
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	All Outcomes: The test substance was clearly identified as tris(2-chloroethyl)phosphate.
	Metric 2:	Test Substance Source	High	All Outcomes: The test substance was purchased from Stauffer Chemical Company. The lot and batch number were provided.
	Metric 3:	Test Substance Purity	Low	All Outcomes: The purity was not reported and could not be determined on the manufacturer's website.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	All Outcomes: The study included a concurrent negative vehicle (corn oil) control group.
	Metric 5:	Positive Controls	N/A	All Outcomes: Positive controls are not necessary for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	All Outcomes: Animals were assigned to dose groups and to cages using a random number table. It was not specified whether animals were also normalized to starting body weights.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Medium	All Outcomes: Fresh solutions were made every two weeks by dissolving the test material in 100% pure corn oil. Test solutions were stored at 5 degrees C until use. Details of mixing for homogeneity weren't provided. Testing for stability was not discussed.
	Metric 8:	Consistency of Exposure Administration	High	All Outcomes: Sufficient exposure administration details were reported. A consistent gavage volume of 5 mL/kg was used. The time of day of dosing was not specified.
	Metric 9:	Reporting of Doses/Concentrations	Medium	All Outcomes: Doses were clearly reported. Dosing solutions were analyzed (method and frequency not specified), and the text indicated that the actual concentrations administered remained within 10% of the target. Analytical values were not provided.
	Metric 10:	Exposure Frequency and Duration	Medium	All Outcomes: The study did not mention adherence to a specific guideline, but the text indicated this was an NTP study. Animals were dosed 5 days per week, consistent with the "Specifications for the Conduct of Studies to Evaluate the Toxic and Carcinogenic Potential of Chemical, Biological and Physical Agents in Laboratory Animals for the National Toxicology Program (NTP). The study duration was 16 weeks. The authors did not provide justification for this duration. This is longer than a typical 90-day subchronic study, and shorter than an NTP chronic/carcinogenicity study.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	All Outcomes: The study tested 5 dose groups plus a control. This is consistent with NTP guidelines. The spacing was sufficient to identify NOAEL and LOAEL values
	Metric 12:	Exposure Route and Method	High	All Outcomes: Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				

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Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Renal/Kidney; Hepatic/Liver;
Reported Health Effect(s):	Renal/Kidney: Histopathology (kidney) and kidney weights; Hepatic/Liver: Histopathology (liver) and liver weights;
Duration:	Chronic (>91 days) 16 weeks - Rats
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
	Metric 13:	Test Animal Characteristics	Medium	All Outcomes: The study used male and female F344/N rats. The test animal source (Charles River Breeding Laboratories), and age purchase (5 weeks old), were reported. Initial body weights were not specified. A quarantine period was mentioned, but the duration was not reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	All Outcomes: Animal husbandry (caging, food and water access, temperature, humidity, and light cycle) were reported. The relative humidity varied from 10% to 78%. This deviates from NTP guidelines that stat humidity should not be below 35% or above 65%. The temperature range in the study was 70 to 81 degrees. NTP indicates temperature should not be above 75 degrees, and that there should be minimal fluctuations. The number of animals per cage (n =5) was appropriate. It is unclear whether the deviations in animal husbandry conditions had an impact on the study results.
	Metric 15:	Number of Animals per Group	Medium	All Outcomes: The number of animals per group (10/sex) was reported and consistent with NTP guidelines.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	All Outcomes: The study included organ weights and histopathology was conducted. The methods were sensitive for this outcome of interest.
	Metric 17:	Consistency of Outcome Assessment	High	All Outcomes: There is no indication that there were inconsistencies in the outcome assessment across groups. Organs were weighed and histopathology was performed at the end of the study.
	Metric 18:	Sampling Adequacy	Medium	All Outcomes: Histopathology was conducted in controls and animals from the 175 and 350 mg/kg-day groups. This is acceptable particularly because no treatment-related lesions were observed. The sample size for organ weights was not provided.
	Metric 19:	Blinding of Assessors	N/A	All Outcomes: Blinding is not necessary because the outcomes were either not subjective in nature (organ weights), or blinding is not required for initial histopathology.
	Metric 20:	Negative Control Response	Low	All Outcomes: The biological responses of negative controls were not explicitly reported.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	All Outcomes: Some information to determine confounding (initial body weights) was not provided. The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP.

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Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Renal/Kidney; Hepatic/Liver;
Reported Health Effect(s):	Renal/Kidney: Histopathology (kidney) and kidney weights; Hepatic/Liver: Histopathology (liver) and liver weights;
Duration:	Chronic (>91 days) 16 weeks - Rats
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
	Metric 22:	Health Outcomes Unrelated to Exposure	Low	All Outcomes: The study text noted that during week 4, the two highest dose groups were prepared incorrectly, and for the first three days of that week, the animals were administered double the target levels. Animals in the 175 mg/kg-day group, were instead dosed with 350 mg/kg-day, and animals in the 350 mg/kg-day group were dosed with 700 mg/kg-day. As a result, 2 females in each group died, and others showed excessive signs of acute toxicity (e.g., ataxia, excessive salivation, gasping, and convulsions). The overdose caused no deaths in males, and they showed no signs of toxicity. The surviving animals were not dosed on the 4th day of the week to allow them to recover. Dosing resumed on the 5th day. In addition to these deaths, three animals died due to gavage error including 1 male and 1 female at 22 mg/kg-day and 1 female at 175 mg/kg-day.
	Metric 23:	Data Presentation and Analysis	Low	All Outcomes: Statistical analysis was performed, but the methods used to analyze initial histopathology and organ weight data weren't clearly specified, only that the significance level was set at $p < 0.05$.
	Metric 24:	Reporting of Data	High	All Outcomes: Negative findings for initial histopathology were reported qualitatively in the text. Absolute and relative organ weight data were reported as means $\pm$ SE and statistical significance was indicated.

Overall Quality Determination High

Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Immune/Hematological
Reported Health Effect(s):	Histopathology (spleen, thymus, mesenteric lymph nodes, bone marrow); organs may have been weighed
Duration:	Chronic (>91 days) 16 weeks - Rats
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was clearly identified as tris(2-chloroethyl)phosphate.
	Metric 2:	Test Substance Source	High	The test substance was purchased from Stauffer Chemical Company. The lot and batch number were provided.
	Metric 3:	Test Substance Purity	Low	The purity was not reported and could not be determined on the manufacturer's website.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	The study included a concurrent negative vehicle (corn oil) control group.
	Metric 5:	Positive Controls	N/A	Positive controls are not necessary for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	Animals were assigned to dose groups and to cages using a random number table. It was not specified whether animals were also normalized to starting body weights.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Medium	Fresh solutions were made every two weeks by dissolving the test material in 100% pure corn oil. Test solutions were stored at 5 degrees C until use. Details of mixing for homogeneity weren't provided. Testing for stability was not discussed.
	Metric 8:	Consistency of Exposure Administration	High	Sufficient exposure administration details were reported. A consistent gavage volume of 5 mL/kg was used. The time of day of dosing was not specified.
	Metric 9:	Reporting of Doses/Concentrations	Medium	Doses were clearly reported. Dosing solutions were analyzed (method and frequency not specified), and the text indicated that the actual concentrations administered remained within 10% of the target. Analytical values were not provided.
	Metric 10:	Exposure Frequency and Duration	Medium	The study did not mention adherence to a specific guideline, but the text indicated this was an NTP study. Animals were dosed 5 days per week, consistent with the "Specifications for the Conduct of Studies to Evaluate the Toxic and Carcinogenic Potential of Chemical, Biological and Physical Agents in Laboratory Animals for the National Toxicology Program (NTP). The study duration was 16 weeks. The authors did not provide justification for this duration. This is longer than a typical 90-day subchronic study, and shorter than an NTP chronic/carcinogenicity study.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	The study tested 5 dose groups plus a control. This is consistent with NTP guidelines. The spacing was sufficient to identify NOAEL and LOAEL values
	Metric 12:	Exposure Route and Method	High	Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				

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Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Immune/Hematological
Reported Health Effect(s):	Histopathology (spleen, thymus, mesenteric lymph nodes, bone marrow); organs may have been weighed
Duration:	Chronic (>91 days) 16 weeks - Rats
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
	Metric 13:	Test Animal Characteristics	Medium	The study used male and female F344/N rats. The test animal source (Charles River Breeding Laboratories), and age purchase (5 weeks old), were reported. Initial body weights were not specified. A quarantine period was mentioned, but the duration was not reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	Animal husbandry (caging, food and water access, temperature, humidity, and light cycle) were reported. The relative humidity varied from 10% to 78%. This deviates from NTP guidelines that stat humidity should not be below 35% or above 65%. The temperature range in the study was 70 to 81 degrees. NTP indicates temperature should not be above 75 degrees, and that there should be minimal fluctuations. The number of animals per cage (n =5) was appropriate. It is unclear whether the deviations in animal husbandry conditions had an impact on the study results.
	Metric 15:	Number of Animals per Group	Medium	The number of animals per group (10/sex) was reported and consistent with NTP guidelines.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	The study included thymus weights and histopathology was conducted. The methods were sensitive for this outcome of interest.
	Metric 17:	Consistency of Outcome Assessment	High	There is no indication that there were inconsistencies in the outcome assessment across groups. Organs were weighed and histopathology was performed at the end of the study.
	Metric 18:	Sampling Adequacy	Medium	Histopathology was conducted in controls and animals from the 175 and 350 mg/kg-day groups. This is acceptable particularly because no treatment-related lesions were observed. The sample size for organ weights was not provided.
	Metric 19:	Blinding of Assessors	N/A	Blinding is not necessary because the outcomes were either not subjective in nature (organ weights), or blinding is not required for initial histopathology.
	Metric 20:	Negative Control Response	Low	The biological responses of negative controls were not explicitly reported.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	Some information to determine confounding (initial body weights) was not provided. The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP.

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Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Immune/Hematological
Reported Health Effect(s):	Histopathology (spleen, thymus, mesenteric lymph nodes, bone marrow); organs may have been weighed
Duration:	Chronic (>91 days) 16 weeks - Rats
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
	Metric 22:	Health Outcomes Unrelated to Exposure	Low	The study text noted that during week 4, the two highest dose groups were prepared incorrectly, and for the first three days of that week, the animals were administered double the target levels. Animals in the 175 mg/kg-day group, were instead dosed with 350 mg/kg-day, and animals in the 350 mg/kg-day group were dosed with 700 mg/kg-day. As a result, 2 females in each group died, and others showed excessive signs of acute toxicity (e.g., ataxia, excessive salivation, gasping, and convulsions). The overdose caused no deaths in males, and they showed no signs of toxicity. The surviving animals were not dosed on the 4th day of the week to allow them to recover. Dosing resumed on the 5th day. In addition to these deaths, three animals died due to gavage error including 1 male and 1 female at 22 mg/kg-day and 1 female at 175 mg/kg-day.
	Metric 23:	Data Presentation and Analysis	Low	Statistical analysis was performed, but the methods used to analyze initial histopathology data weren't clearly specified, only that the significance level was set at $p < 0.05$. The significance for thymus weight changes was not specified, and the data were not provided for an independent analysis.
	Metric 24:	Reporting of Data	Medium	Negative findings for initial histopathology were reported qualitatively in the text. A 19% decrease in thymus weight was reported for high-dose females, relative to controls. The significance was not specified.

Overall Quality Determination High

Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Hepatic/Liver
Reported Health Effect(s):	Histopathology (liver) and liver weights
Duration:	Chronic (>91 days) 16 weeks - Mice
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was clearly identified as tris(2-chloroethyl)phosphate.
	Metric 2:	Test Substance Source	High	The test substance was purchased from Stauffer Chemical Company. The lot and batch number were provided.
	Metric 3:	Test Substance Purity	Low	The purity was not reported and could not be determined on the manufacturer's website.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	The study included a concurrent negative vehicle (corn oil) control group.
	Metric 5:	Positive Controls	N/A	Positive controls are not necessary for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	Animals were assigned to dose groups and to cages using a random number table. It was not specified whether animals were also normalized to starting body weights.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Medium	Fresh solutions were made every two weeks by dissolving the test material in 100% pure corn oil. Test solutions were stored at 5 degrees C until use. Details of mixing for homogeneity weren't provided. Testing for stability was not discussed.
	Metric 8:	Consistency of Exposure Administration	High	Sufficient exposure administration details were reported. A consistent gavage volume of 5 mL/kg was used. The time of day of dosing was not specified.
	Metric 9:	Reporting of Doses/Concentrations	Medium	Doses were clearly reported. Dosing solutions were analyzed (method and frequency not specified), and the text indicated that the actual concentrations administered remained within 10% of the target. Analytical values were not provided.
	Metric 10:	Exposure Frequency and Duration	Medium	The study did not mention adherence to a specific guideline, but the text indicated this was an NTP study. Animals were dosed 5 days per week, consistent with the "Specifications for the Conduct of Studies to Evaluate the Toxic and Carcinogenic Potential of Chemical, Biological and Physical Agents in Laboratory Animals for the National Toxicology Program (NTP). The study duration was 16 weeks. The authors did not provide justification for this duration. This is longer than a typical 90-day subchronic study, and shorter than an NTP chronic/carcinogenicity study.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	The study tested 5 dose groups plus a control. This is consistent with NTP guidelines. The spacing was sufficient to identify NOAEL and LOAEL values
	Metric 12:	Exposure Route and Method	High	Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				

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Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Hepatic/Liver
Reported Health Effect(s):	Histopathology (liver) and liver weights
Duration:	Chronic (>91 days) 16 weeks - Mice
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
	Metric 13:	Test Animal Characteristics	Medium	The study used male and female B6C3F1 mice. The test animal source (Charles River Breeding Laboratories), and age purchase (5 weeks old), were reported. Initial body weights were not specified. A quarantine period was mentioned, but the duration was not reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	Animal husbandry (caging, food and water access, temperature, humidity, and light cycle) were reported. The relative humidity varied from 10% to 78%. This deviates from NTP guidelines that state humidity should not be below 35% or above 65%. The temperature range in the study was 70 to 81 degrees. NTP indicates temperature should not be above 75 degrees, and that there should be minimal fluctuations. The number of animals per cage (n =5) was reported. NTP guidelines specify that male mice should always be housed individually. It is unclear whether the deviations in animal husbandry conditions had an impact on the study results.
	Metric 15:	Number of Animals per Group	Medium	The number of animals per group (10/sex) was reported and consistent with NTP guidelines.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	Liver weights were recorded and histopathology was conducted. The methods were sensitive for this outcome of interest. The study did not specify whether serum chemistry analysis was done.
	Metric 17:	Consistency of Outcome Assessment	High	There is no indication that there were inconsistencies in the outcome assessment across groups. Histopathology and organ weights were recorded at the end of the study.
	Metric 18:	Sampling Adequacy	Medium	Organ weights were measured from all surviving animals. Histopathology was conducted in controls and animals from the high-dose group. This is acceptable because no treatment-related lesions were observed.
	Metric 19:	Blinding of Assessors	N/A	Blinding is not necessary for initial histopathology.
	Metric 20:	Negative Control Response	Medium	The biological responses of negative controls were not explicitly reported for histopathology; negative findings were qualitatively reported in the text. Negative control organ weights were appropriate.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	Some information to determine confounding (initial body weights) was not provided. The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP.

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Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Hepatic/Liver
Reported Health Effect(s):	Histopathology (liver) and liver weights
Duration:	Chronic (>91 days) 16 weeks - Mice
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
	Metric 22:	Health Outcomes Unrelated to Exposure	Low	The study text noted that during week 4, the two highest dose groups were prepared incorrectly, and for the first three days of that week, the animals were administered double the target levels. Animals in the 350 mg/kg group, were instead dosed with 700 mg/kg, and animals in the 700 mg/kg group were dosed with 1,400 mg/kg. No deaths occurred as a result of the dosing error, but two male mice had convulsions and labored breathing on the third day of overdosing. Overdosed females were uncoordinated. These animals were not dosed on the 4th day of the week to allow them to recover. Dosing resumed on the 5th day. Three males and two females died during the study due to gavage trauma. The males were from the 175, 350, and 700 mg/kg groups, and the females were from the 175 and 300 mg/kg groups, respectively.
	Metric 23:	Data Presentation and Analysis	Low	Statistical analysis was performed, but the methods used to analyze organ weight and initial histopathology data weren't clearly specified, only that the significance level was set at $p < 0.05$.
	Metric 24:	Reporting of Data	High	Organ weights were adequately reported as means $\pm$ SEM. Negative findings for initial histopathology were reported qualitatively in the text.

Overall Quality Determination High

Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Neurological/Behavioral
Reported Health Effect(s):	Serum cholinesterase, necropsy (including brain weight), brain histopathology
Duration:	Chronic (>91 days) 16 weeks - Mice
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was clearly identified as tris(2-chloroethyl)phosphate.
	Metric 2:	Test Substance Source	High	The test substance was purchased from Stauffer Chemical Company. The lot and batch number were provided.
	Metric 3:	Test Substance Purity	Low	The purity was not reported and could not be determined on the manufacturer's website.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	The study included a concurrent negative vehicle (corn oil) control group.
	Metric 5:	Positive Controls	N/A	Positive controls are not necessary for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	Animals were assigned to dose groups and to cages using a random number table. It was not specified whether animals were also normalized to starting body weights.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Medium	Fresh solutions were made every two weeks by dissolving the test material in 100% pure corn oil. Test solutions were stored at 5 degrees C until use. Details of mixing for homogeneity weren't provided. Testing for stability was not discussed.
	Metric 8:	Consistency of Exposure Administration	High	Sufficient exposure administration details were reported. A consistent gavage volume of 5 mL/kg was used. The time of day of dosing was not specified.
	Metric 9:	Reporting of Doses/Concentrations	Medium	Doses were clearly reported. Dosing solutions were analyzed (method and frequency not specified), and the text indicated that the actual concentrations administered remained within 10% of the target. Analytical values were not provided.
	Metric 10:	Exposure Frequency and Duration	Medium	The study did not mention adherence to a specific guideline, but the text indicated this was an NTP study. Animals were dosed 5 days per week, consistent with the "Specifications for the Conduct of Studies to Evaluate the Toxic and Carcinogenic Potential of Chemical, Biological and Physical Agents in Laboratory Animals for the National Toxicology Program (NTP)." The study duration was 16 weeks. The authors did not provide justification for this duration. This is longer than a typical 90-day subchronic study, and shorter than an NTP chronic/carcinogenicity study.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	The study tested 5 dose groups plus a control. This is consistent with NTP guidelines. The spacing was sufficient to identify NOAEL and LOAEL values.
	Metric 12:	Exposure Route and Method	High	Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				

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Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Neurological/Behavioral
Reported Health Effect(s):	Serum cholinesterase, necropsy (including brain weight), brain histopathology
Duration:	Chronic (>91 days) 16 weeks - Mice
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
	Metric 13:	Test Animal Characteristics	Medium	The study used male and female B6C3F1 mice. The test animal source (Charles River Breeding Laboratories), and age purchase (5 weeks old), were reported. Initial body weights were not specified. A quarantine period was mentioned, but the duration was not reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	Animal husbandry (caging, food and water access, temperature, humidity, and light cycle) were reported. The relative humidity varied from 10% to 78%. This deviates from NTP guidelines that state humidity should not be below 35% or above 65%. The temperature range in the study was 70 to 81 degrees. NTP indicates temperature should not be above 75 degrees, and that there should be minimal fluctuations. The number of animals per cage (n =5) was reported. NTP guidelines specify that male mice should always be housed individually. It is unclear whether the deviations in animal husbandry conditions had an impact on the study results.
	Metric 15:	Number of Animals per Group	Medium	The number of animals per group (10/sex) was reported and consistent with NTP guidelines.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	Low	Brains were weighed. Histopathology was measured in controls and high-dose mice. What animals were microscopically examined and when is unclear. Some animals died due to gavage trauma, and it was not specified whether these animals were examined for histopathology. Additionally, animals in this study were dosed 5 days per week for 16 weeks, yet histopathology images shown in the study indicate they are from rats treated for 90 days (so it is not clear whether this would also be true for mice). Five days per week for 16 weeks would be 80 days. The study also indicated that serum cholinesterase levels were measured and referenced: Ellman, G.L., Courtney, K.D., Andres, V., Jr., and Featherstone, R.M. (1961). A new and rapid colorimetric determination of acetylcholinesterase activity. Biochem. Phamacol. 7,88-95 for methods. Overall, the methods were sensitive for the outcomes of interest, but there were limitations in reporting the details.
	Metric 17:	Consistency of Outcome Assessment	Medium	Details regarding the execution of the study protocols for outcome assessment were partially reported. The time of serum draw for measuring cholinesterase activity wasn't specified. The timing of histopathological examinations is unclear (90 days vs. after 16 weeks). Ogan weights were presumably measured at necropsy.
	Metric 18:	Sampling Adequacy	Low	Results for serum cholinesterase were qualitatively reported and the sample size was not specified either in the methods or in the results. Based on the "n's" provided text. It is unclear whether brain tissue was examined for animals from all groups. The results for brain were only reported for rats. Organ weight data for this organ were not reported.
	Metric 19:	Blinding of Assessors	High	Secondary histopathological analyses were conducted in a blind manner. Blinding is not necessary for organ weights or initial histopathology.

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Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Neurological/Behavioral
Reported Health Effect(s):	Serum cholinesterase, necropsy (including brain weight), brain histopathology
Duration:	Chronic (>91 days) 16 weeks - Mice
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
	Metric 20:	Negative Control Response	Low	The biological responses of the negative controls were not provided (qualitatively or quantitatively) so the adequacy cannot be determined.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	Some information to determine confounding (initial body weights) was not provided. The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP.
	Metric 22:	Health Outcomes Unrelated to Exposure	Low	The study text noted that during week 4, the two highest dose groups were prepared incorrectly, and for the first three days of that week, the animals were administered double the target levels. Animals in the 350 mg/kg group, were instead dosed with 700 mg/kg, and animals in the 700 mg/kg group were dosed with 1,400 mg/kg. No deaths occurred as a result of the dosing error, but two male mice had convulsions and labored breathing on the third day of overdosing. These animals were not dosed on the 4th day of the week to allow them to recover. Dosing resumed on the 5th day. Three males and two females died during the study due to gavage trauma. The males were from the 175, 350, and 700 mg/kg groups, and the females were from the 175 and 300 mg/kg groups, respectively.
	Metric 23:	Data Presentation and Analysis	Low	Statistical methods used to analyze brain lesion data were adequately described and significance was reported in the results. It is unclear, however, whether it was appropriate to include animals that died early due to gavage trauma in the statistical analysis. The methods used to analyze cholinesterase activity or organ weights weren't clearly specified, only that the significance level was set at $p < 0.05$. However, the statistical significance of brain weight changes was not specified and the data were not available for an independent review.
	Metric 24:	Reporting of Data	Low	Negative findings for serum cholinesterase activity were qualitatively reported in the text. Histopathology results were not reported in table form. No brain lesions were reported for mice. Other dose groups were not mentioned. No results for brain weight were reported so it is assumed there were no changes.

Overall Quality Determination Medium

Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Neurological/Behavioral
Reported Health Effect(s):	Serum cholinesterase, necropsy (including brain weight), brain histopathology
Duration:	Chronic (>91 days) 16 weeks - Rats
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was clearly identified as tris(2-chloroethyl)phosphate.
	Metric 2:	Test Substance Source	High	The test substance was purchased from Stauffer Chemical Company. The lot and batch number were provided.
	Metric 3:	Test Substance Purity	Low	The purity was not reported and could not be determined on the manufacturer's website.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	The study included a concurrent negative vehicle (corn oil) control group.
	Metric 5:	Positive Controls	N/A	Positive controls are not necessary for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	Animals were assigned to dose groups and to cages using a random number table. It was not specified whether animals were also normalized to starting body weights.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Medium	Fresh solutions were made every two weeks by dissolving the test material in 100% pure corn oil. Test solutions were stored at 5 degrees C until use. Details of mixing for homogeneity weren't provided. Testing for stability was not discussed.
	Metric 8:	Consistency of Exposure Administration	High	Sufficient exposure administration details were reported. A consistent gavage volume of 5 mL/kg was used. The time of day of dosing was not specified.
	Metric 9:	Reporting of Doses/Concentrations	Medium	Doses were clearly reported. Dosing solutions were analyzed (method and frequency not specified), and the text indicated that the actual concentrations administered remained within 10% of the target. Analytical values were not provided.
	Metric 10:	Exposure Frequency and Duration	Medium	The study did not mention adherence to a specific guideline, but the text indicated this was an NTP study. Animals were dosed 5 days per week, consistent with the "Specifications for the Conduct of Studies to Evaluate the Toxic and Carcinogenic Potential of Chemical, Biological and Physical Agents in Laboratory Animals for the National Toxicology Program (NTP). The study duration was 16 weeks. The authors did not provide justification for this duration. This is longer than a typical 90-day subchronic study, and shorter than an NTP chronic/carcinogenicity study.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	The study tested 5 dose groups plus a control. This is consistent with NTP guidelines. The spacing was sufficient to identify NOAEL and LOAEL values
	Metric 12:	Exposure Route and Method	High	Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				

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Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Neurological/Behavioral
Reported Health Effect(s):	Serum cholinesterase, necropsy (including brain weight), brain histopathology
Duration:	Chronic (>91 days) 16 weeks - Rats
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
	Metric 13:	Test Animal Characteristics	Medium	The study used male and female F344/N rats. The test animal source (Charles River Breeding Laboratories), and age purchase (5 weeks old), were reported. Initial body weights were not specified. A quarantine period was mentioned, but the duration was not reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	Animal husbandry (caging, food and water access, temperature, humidity, and light cycle) were reported. The relative humidity varied from 10% to 78%. This deviates from NTP guidelines that stat humidity should not be below 35% or above 65%. The temperature range in the study was 70 to 81 degrees. NTP indicates temperature should not be above 75 degrees, and that there should be minimal fluctuations. The number of animals per cage (n =5) was appropriate. It is unclear whether the deviations in animal husbandry conditions had an impact on the study results.
	Metric 15:	Number of Animals per Group	Medium	The number of animals per group (10/sex) was reported and consistent with NTP guidelines.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	Low	Brains were weighed. Initial histopathology was performed on the brain, followed by a more detailed histopathological analysis to quantitate the damage observed. What animals were microscopically examined and when is unclear. Some animals died early in the study due to overdose, and other animals died due to gavage trauma. It was not specified whether these animals were examined, but based in the incidences reported (which are all out of an n of 10/sex), it appears that they were. Additionally, animals in this study were dosed 5 days per week for 16 weeks, yet histopathology images shown in the study indicate they are from rats treated for 90 days. Five days per week for 16 weeks would be 80 days. The study also indicated that serum cholinesterase levels were measured and referenced: Ellman, G.L., Courtney, K.D., Andres, V., Jr., and Featherstone, R.M. (1961). A new and rapid colorimetric determination of acetylcholinesterase activity. Biochem. Phamacol. 7,88-95 for methods. Overall, the methods were sensitive for the outcomes of interest, but there were limitations in reporting the details.
	Metric 17:	Consistency of Outcome Assessment	Medium	Details regarding the execution of the study protocols for outcome assessment were partially reported. The time of serum draw for measuring cholinesterase activity wasn't specified. The timing of histopathological examinations is unclear (90 days vs. after 16 weeks). Ogan weights were presumably measured at necropsy.
	Metric 18:	Sampling Adequacy	Medium	Results for serum cholinesterase were qualitatively reported and the sample size was not specified either in the methods or in the results. Based on the "n.s" provided text, it appears that all animals from all dose groups were microscopically examined. The sample size for organ weight measurements was not reported.
	Metric 19:	Blinding of Assessors	High	Secondary histopathological analyses were conducted in a blind manner. Blinding is not necessary for organ weights or initial histopathology.

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Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Neurological/Behavioral
Reported Health Effect(s):	Serum cholinesterase, necropsy (including brain weight), brain histopathology
Duration:	Chronic (>91 days) 16 weeks - Rats
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
	Metric 20:	Negative Control Response	Low	The biological responses of the negative controls were not provided (qualitatively or quantitatively) so the adequacy cannot be determined.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	Some information to determine confounding (initial body weights) was not provided. The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP.
	Metric 22:	Health Outcomes Unrelated to Exposure	Low	The study text noted that during week 4, the two highest dose groups were prepared incorrectly, and for the first three days of that week, the animals were administered double the target levels. Animals in the 175 mg/kg-day group, were instead dosed with 350 mg/kg-day, and animals in the 350 mg/kg-day group were dosed with 700 mg/kg-day. As a result, 2 females in each group died, and others showed excessive signs of acute toxicity (e.g., ataxia, excessive salivation, gasping, and convulsions). The overdose caused no deaths in males, and they showed no signs of toxicity. The surviving animals were not dosed on the 4th day of the week to allow them to recover. Dosing resumed on the 5th day. In addition to these deaths, three animals died due to gavage error including 1 male and 1 female at 22 mg/kg-day and 1 female at 175 mg/kg-day.
	Metric 23:	Data Presentation and Analysis	Low	Statistical methods used to analyze brain lesion data were adequately described and significance was reported in the results. It is unclear, however, whether it was appropriate to include animals that died during week 4 due to the overdose, or animals that died early due to gavage trauma in the statistical analysis. The methods used to analyze cholinesterase activity or organ weights weren't clearly specified, only that the significance level was set at $p < 0.05$. However, the statistical significance of brain weight changes was not specified and the data were not available for an independent review.
	Metric 24:	Reporting of Data	Low	Serum cholinesterase data were qualitatively reported in the text. Histopathology results were not reported in table form. The incidences of brain lesions were reported for the two highest-dose groups in females, and for the high-dose group in males. Other dose groups were not mentioned; no lesions were observed in controls. An increase in severity with dose was mentioned. Representative images were shown, although the figure legends reporting the duration of dosing stated that the images were from animals dosed for 90 days. The study reported an 11% decrease in brain weight in high-dose females. It was not specified whether this was absolute or relative brain weight, and statistical significance was not specified.

Overall Quality Determination Medium

Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Mortality
Reported Health Effect(s):	Survival
Duration:	Chronic (>91 days) 16 weeks - Mice
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was clearly identified as tris(2-chloroethyl)phosphate.
	Metric 2:	Test Substance Source	High	The test substance was purchased from Stauffer Chemical Company. The lot and batch number were provided.
	Metric 3:	Test Substance Purity	Low	The purity was not reported and could not be determined on the manufacturer's website.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	The study included a concurrent negative vehicle (corn oil) control group.
	Metric 5:	Positive Controls	N/A	Positive controls are not necessary for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	Animals were assigned to dose groups and to cages using a random number table. It was not specified whether animals were also normalized to starting body weights.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Medium	Fresh solutions were made every two weeks by dissolving the test material in 100% pure corn oil. Test solutions were stored at 5 degrees C until use. Details of mixing for homogeneity weren't provided. Testing for stability was not discussed.
	Metric 8:	Consistency of Exposure Administration	High	Sufficient exposure administration details were reported. A consistent gavage volume of 5 mL/kg was used. The time of day of dosing was not specified.
	Metric 9:	Reporting of Doses/Concentrations	Medium	Doses were clearly reported. Dosing solutions were analyzed (method and frequency not specified), and the text indicated that the actual concentrations administered remained within 10% of the target. Analytical values were not provided.
	Metric 10:	Exposure Frequency and Duration	Medium	The study did not mention adherence to a specific guideline, but the text indicated this was an NTP study. Animals were dosed 5 days per week, consistent with the "Specifications for the Conduct of Studies to Evaluate the Toxic and Carcinogenic Potential of Chemical, Biological and Physical Agents in Laboratory Animals for the National Toxicology Program (NTP). The study duration was 16 weeks. The authors did not provide justification for this duration. This is longer than a typical 90-day subchronic study, and shorter than an NTP chronic/carcinogenicity study.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	The study tested 5 dose groups plus a control. This is consistent with NTP guidelines. The spacing was sufficient to identify NOAEL and LOAEL values
	Metric 12:	Exposure Route and Method	High	Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				

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Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Mortality
Reported Health Effect(s):	Survival
Duration:	Chronic (>91 days) 16 weeks - Mice
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
	Metric 13:	Test Animal Characteristics	Medium	The study used male and female B6C3F1 mice. The test animal source (Charles River Breeding Laboratories), and age purchase (5 weeks old), were reported. Initial body weights were not specified. A quarantine period was mentioned, but the duration was not reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	Animal husbandry (caging, food and water access, temperature, humidity, and light cycle) were reported. The relative humidity varied from 10% to 78%. This deviates from NTP guidelines that state humidity should not be below 35% or above 65%. The temperature range in the study was 70 to 81 degrees. NTP indicates temperature should not be above 75 degrees, and that there should be minimal fluctuations. The number of animals per cage (n =5) was reported. NTP guidelines specify that male mice should always be housed individually. It is unclear whether the deviations in animal husbandry conditions had an impact on the study results.
	Metric 15:	Number of Animals per Group	Medium	The number of animals per group (10/sex) was reported and consistent with NTP guidelines.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	Medium	The study clearly recorded any animal deaths, but the frequency of observations for the mortality endpoint was not specified in the study methods. This is not expected to have an impact on the study results.
	Metric 17:	Consistency of Outcome Assessment	High	A protocol for outcome assessment was not provided, but the survival of animals until termination was recorded for all groups. There is no indication that there were inconsistencies across groups for this outcome.
	Metric 18:	Sampling Adequacy	High	All animals were sampled and accounted for.
	Metric 19:	Blinding of Assessors	N/A	Blinding is not required for this outcome because it is not subjective in nature.
	Metric 20:	Negative Control Response	High	No control animals died.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	Some information to determine confounding (initial body weights) was not provided. The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP.

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Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Mortality
Reported Health Effect(s):	Survival
Duration:	Chronic (>91 days) 16 weeks - Mice
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
	Metric 22:	Health Outcomes Unrelated to Exposure	Low	The study text noted that during week 4, the two highest dose groups were prepared incorrectly, and for the first three days of that week, the animals were administered double the target levels. Animals in the 350 mg/kg group, were instead dosed with 700 mg/kg, and animals in the 700 mg/kg group were dosed with 1,400 mg/kg. No deaths occurred as a result of the dosing error, but two male mice had convulsions and labored breathing on the third day of overdosing. Overdosed females were uncoordinated. These animals were not dosed on the 4th day of the week to allow them to recover. Dosing resumed on the 5th day. Three males and two females died during the study due to gavage trauma. The males were from the 175, 350, and 700 mg/kg groups, and the females were from the 175 and 300 mg/kg groups, respectively.
	Metric 23:	Data Presentation and Analysis	N/A	All of the deaths were due to gavage-related deaths, statistical analysis was not necessary.
	Metric 24:	Reporting of Data	High	Mortality incidences were clearly reported and the cause of death was indicated.

Overall Quality Determination High

Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Mortality
Reported Health Effect(s):	Survival
Duration:	Chronic (>91 days) 16 weeks - Rats
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was clearly identified as tris(2-chloroethyl)phosphate.
	Metric 2:	Test Substance Source	High	The test substance was purchased from Stauffer Chemical Company. The lot and batch number were provided.
	Metric 3:	Test Substance Purity	Low	The purity was not reported and could not be determined on the manufacturer's website.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	The study included a concurrent negative vehicle (corn oil) control group.
	Metric 5:	Positive Controls	N/A	Positive controls are not necessary for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	Animals were assigned to dose groups and to cages using a random number table. It was not specified whether animals were also normalized to starting body weights.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Medium	Fresh solutions were made every two weeks by dissolving the test material in 100% pure corn oil. Test solutions were stored at 5 degrees C until use. Details of mixing for homogeneity weren't provided. Testing for stability was not discussed.
	Metric 8:	Consistency of Exposure Administration	High	Sufficient exposure administration details were reported. A consistent gavage volume of 5 mL/kg was used. The time of day of dosing was not specified.
	Metric 9:	Reporting of Doses/Concentrations	Medium	Doses were clearly reported. Dosing solutions were analyzed (method and frequency not specified), and the text indicated that the actual concentrations administered remained within 10% of the target. Analytical values were not provided.
	Metric 10:	Exposure Frequency and Duration	Medium	The study did not mention adherence to a specific guideline, but the text indicated this was an NTP study. Animals were dosed 5 days per week, consistent with the "Specifications for the Conduct of Studies to Evaluate the Toxic and Carcinogenic Potential of Chemical, Biological and Physical Agents in Laboratory Animals for the National Toxicology Program (NTP). The study duration was 16 weeks. The authors did not provide justification for this duration. This is longer than a typical 90-day subchronic study, and shorter than an NTP chronic/carcinogenicity study.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	The study tested 5 dose groups plus a control. This is consistent with NTP guidelines. The spacing was sufficient to identify NOAEL and LOAEL values
	Metric 12:	Exposure Route and Method	High	Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				

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Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Mortality
Reported Health Effect(s):	Survival
Duration:	Chronic (>91 days) 16 weeks - Rats
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
	Metric 13:	Test Animal Characteristics	Medium	The study used male and female F344/N rats. The test animal source (Charles River Breeding Laboratories), and age purchase (5 weeks old), were reported. Initial body weights were not specified. A quarantine period was mentioned, but the duration was not reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	Animal husbandry (caging, food and water access, temperature, humidity, and light cycle) were reported. The relative humidity varied from 10% to 78%. This deviates from NTP guidelines that stat humidity should not be below 35% or above 65%. The temperature range in the study was 70 to 81 degrees. NTP indicates temperature should not be above 75 degrees, and that there should be minimal fluctuations. The number of animals per cage (n =5) was appropriate. It is unclear whether the deviations in animal husbandry conditions had an impact on the study results.
	Metric 15:	Number of Animals per Group	Medium	The number of animals per group (10/sex) was reported and consistent with NTP guidelines.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	Medium	The study clearly recorded any animal deaths, but the frequency of observations for the mortality endpoint was not specified in the study methods. This is not expected to have an impact on the study results.
	Metric 17:	Consistency of Outcome Assessment	High	A protocol for outcome assessment was not provided, but the survival of animals until termination was recorded for all groups. There is no indication that there were inconsistencies across groups for this outcome.
	Metric 18:	Sampling Adequacy	High	All animals were sampled.
	Metric 19:	Blinding of Assessors	N/A	Blinding is not required for this outcome because it is not subjective in nature.
	Metric 20:	Negative Control Response	High	No control animals died.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	Some information to determine confounding (initial body weights) was not provided. The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP.

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Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Mortality
Reported Health Effect(s):	Survival
Duration:	Chronic (>91 days) 16 weeks - Rats
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
	Metric 22:	Health Outcomes Unrelated to Exposure	Low	The study text noted that during week 4, the two highest dose groups were prepared incorrectly, and for the first three days of that week, the animals were administered double the target levels. Animals in the 175 mg/kg-day group, were instead dosed with 350 mg/kg-day, and animals in the 350 mg/kg-day group were dosed with 700 mg/kg-day. As a result, 2 females in each group died, and others showed excessive signs of acute toxicity (e.g., ataxia, excessive salivation, gasping, and convulsions). The overdose caused no deaths in males, and they showed no signs of toxicity. The surviving animals were not dosed on the 4th day of the week to allow them to recover. Dosing resumed on the 5th day. In addition to these deaths, three animals died due to gavage error including 1 male and 1 female at 22 mg/kg-day and 1 female at 175 mg/kg-day.
	Metric 23:	Data Presentation and Analysis	High	Some data were clearly statistically analyzed, but the statistical methods used were not reported; only p-values were provided in the data tables. It does not appear that the mortality data were statistically analyzed, but the majority of deaths were related to an overdose or to gavage trauma. Incidences were provided to allow for an independent analysis.
	Metric 24:	Reporting of Data	Medium	Mortality incidences were clearly reported. For the few animals whose deaths were treatment-related, the timing and causes of death were not reported.

Overall Quality Determination — High

Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Lung/Respiratory; Gastrointestinal; Thyroid; Endocrine; Cardiovascular;
Reported Health Effect(s):	Lung/Respiratory: Histopathology lung; lungs may have been weighed; Gastrointestinal: Histopathology esophagus and salivary gland; relevant organs may have been weighed; Thyroid: Histopathology (thyroid); thyroid may have been weighed; Endocrine: Histopathology (adrenal glands); adrenal glands may have been weighed; Cardiovascular: Histopathology (heart); heart may have been weighed;
Duration:	Chronic (>91 days) 16 weeks - Rats
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	All Outcomes: The test substance was clearly identified as tris(2-chloroethyl)phosphate.
	Metric 2:	Test Substance Source	High	All Outcomes: The test substance was purchased from Stauffer Chemical Company. The lot and batch number were provided.
	Metric 3:	Test Substance Purity	Low	All Outcomes: The purity was not reported and could not be determined on the manufacturer's website.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	All Outcomes: The study included a concurrent negative vehicle (corn oil) control group.
	Metric 5:	Positive Controls	N/A	All Outcomes: Positive controls are not necessary for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	All Outcomes: Animals were assigned to dose groups and to cages using a random number table. It was not specified whether animals were also normalized to starting body weights.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Medium	All Outcomes: Fresh solutions were made every two weeks by dissolving the test material in 100% pure corn oil. Test solutions were stored at 5 degrees C until use. Details of mixing for homogeneity weren't provided. Testing for stability was not discussed.
	Metric 8:	Consistency of Exposure Administration	High	All Outcomes: Sufficient exposure administration details were reported. A consistent gavage volume of 5 mL/kg was used. The time of day of dosing was not specified.
	Metric 9:	Reporting of Doses/Concentrations	Medium	All Outcomes: Doses were clearly reported. Dosing solutions were analyzed (method and frequency not specified), and the text indicated that the actual concentrations administered remained within 10% of the target. Analytical values were not provided.
	Metric 10:	Exposure Frequency and Duration	Medium	All Outcomes: The study did not mention adherence to a specific guideline, but the text indicated this was an NTP study. Animals were dosed 5 days per week, consistent with the "Specifications for the Conduct of Studies to Evaluate the Toxic and Carcinogenic Potential of Chemical, Biological and Physical Agents in Laboratory Animals for the National Toxicology Program (NTP). The study duration was 16 weeks. The authors did not provide justification for this duration. This is longer than a typical 90-day subchronic study, and shorter than an NTP chronic/carcinogenicity study.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	All Outcomes: The study tested 5 dose groups plus a control. This is consistent with NTP guidelines. The spacing was sufficient to identify NOAEL and LOAEL values
	Metric 12:	Exposure Route and Method	High	All Outcomes: Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.

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Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Lung/Respiratory; Gastrointestinal; Thyroid; Endocrine; Cardiovascular;
Reported Health Effect(s):	Lung/Respiratory: Histopathology lung; lungs may have been weighed; Gastrointestinal: Histopathology esophagus and salivary gland; relevant organs may have been weighed; Thyroid: Histopathology (thyroid); thyroid may have been weighed; Endocrine: Histopathology (adrenal glands); adrenal glands may have been weighed; Cardiovascular: Histopathology (heart); heart may have been weighed;
Duration:	Chronic (>91 days) 16 weeks - Rats
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	Medium	Lung/Respiratory: The study used male and female F344/N rats. The test animal source (Charles River Breeding Laboratories), and age purchase (5 weeks old), were reported. Initial body weights were not specified. A quarantine period was mentioned, but the duration was not reported.; Gastrointestinal: The study used male and female F344/N rats. The test animal source (Charles River Breeding Laboratories), and age purchase (5 weeks old), were reported. Initial body weights were not specified. A quarantine period was mentioned, but the duration was not reported.; Thyroid: The study used male and female F344/N rats. The test animal source (Charles River Breeding Laboratories), and age purchase (5 weeks old), were reported. Initial body weights were not specified. A quarantine period was mentioned, but the duration was not reported.; Endocrine: The study used male and female F344/N rats. The test animal source (Charles River Breeding Laboratories), and age purchase (5 weeks old), were reported. Initial body weights were not specified. A quarantine period was mentioned, but the duration was not reported.; Cardiovascular: The study used male and female B6C3F1 mice. The test animal source (Charles River Breeding Laboratories), and age purchase (5 weeks old), were reported. Initial body weights were not specified. A quarantine period was mentioned, but the duration was not reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	All Outcomes: Animal husbandry (caging, food and water access, temperature, humidity, and light cycle) were reported. The relative humidity varied from 10% to 78%. This deviates from NTP guidelines that stat humidity should not be below 35% or above 65%. The temperature range in the study was 70 to 81 degrees. NTP indicates temperature should not be above 75 degrees, and that there should be minimal fluctuations. The number of animals per cage (n =5) was appropriate. It is unclear whether the deviations in animal husbandry conditions had an impact on the study results.
	Metric 15:	Number of Animals per Group	Medium	All Outcomes: The number of animals per group (10/sex) was reported and consistent with NTP guidelines.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	Medium	All Outcomes: The methods did not specify which organs were weighed. Histopathology was conducted which is considered to be a sensitive method for this outcome of interest.
	Metric 17:	Consistency of Outcome Assessment	High	All Outcomes: There is no indication that there were inconsistencies in the outcome assessment across groups. Histopathology was performed at the end of the study.
	Metric 18:	Sampling Adequacy	High	All Outcomes: Histopathology was conducted in controls and animals from the 175 and 350 mg/kg-day groups. This is acceptable particularly because no treatment-related lesions were observed.

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Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Lung/Respiratory; Gastrointestinal; Thyroid; Endocrine; Cardiovascular;
Reported Health Effect(s):	Lung/Respiratory: Histopathology lung; lungs may have been weighed; Gastrointestinal: Histopathology esophagus and salivary gland; relevant organs may have been weighed; Thyroid: Histopathology (thyroid); thyroid may have been weighed; Endocrine: Histopathology (adrenal glands); adrenal glands may have been weighed; Cardiovascular: Histopathology (heart); heart may have been weighed;
Duration:	Chronic (>91 days) 16 weeks - Rats
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
	Metric 19:	Blinding of Assessors	N/A	All Outcomes: Blinding is not necessary for initial histopathology.
	Metric 20:	Negative Control Response	Medium	All Outcomes: The biological responses of negative controls were not explicitly reported; negative findings were qualitatively reported in the text.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	All Outcomes: Some information to determine confounding (initial body weights) was not provided. The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP.

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Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Lung/Respiratory; Gastrointestinal; Thyroid; Endocrine; Cardiovascular;
Reported Health Effect(s):	Lung/Respiratory: Histopathology lung; lungs may have been weighed; Gastrointestinal: Histopathology esophagus and salivary gland; relevant organs may have been weighed; Thyroid: Histopathology (thyroid); thyroid may have been weighed; Endocrine: Histopathology (adrenal glands); adrenal glands may have been weighed; Cardiovascular: Histopathology (heart); heart may have been weighed;
Duration:	Chronic (>91 days) 16 weeks - Rats
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
	Metric 22:	Health Outcomes Unrelated to Exposure	Low	Lung/Respiratory: The study text noted that during week 4, the two highest dose groups were prepared incorrectly, and for the first three days of that week, the animals were administered double the target levels. Animals in the 175 mg/kg-day group, were instead dosed with 350 mg/kg-day, and animals in the 350 mg/kg-day group were dosed with 700 mg/kg-day. As a result, 2 females in each group died, and others showed excessive signs of acute toxicity (e.g., ataxia, excessive salivation, gasping, and convulsions). The overdose caused no deaths in males, and they showed no signs of toxicity. The surviving animals were not dosed on the 4th day of the week to allow them to recover. Dosing resumed on the 5th day. In addition to these deaths, three animals died due to gavage error including 1 male and 1 female at 22 mg/kg-day and 1 female at 175 mg/kg-day.; Gastrointestinal: The study text noted that during week 4, the two highest dose groups were prepared incorrectly, and for the first three days of that week, the animals were administered double the target levels. Animals in the 175 mg/kg-day group, were instead dosed with 350 mg/kg-day, and animals in the 350 mg/kg-day group were dosed with 700 mg/kg-day. As a result, 2 females in each group died, and others showed excessive signs of acute toxicity (e.g., ataxia, excessive salivation, gasping, and convulsions). The overdose caused no deaths in males, and they showed no signs of toxicity. The surviving animals were not dosed on the 4th day of the week to allow them to recover. Dosing resumed on the 5th day. In addition to these deaths, three animals died due to gavage error including 1 male and 1 female at 22 mg/kg-day and 1 female at 175 mg/kg-day.; Thyroid: The study text noted that during week 4, the two highest dose groups were prepared incorrectly, and for the first three days of that week, the animals were administered double the target levels. Animals in the 175 mg/kg-day group, were instead dosed with 350 mg/kg-day, and animals in the 350 mg/kg-day group were dosed with 700 mg/kg-day. As a result, 2 females in each group died, and others showed excessive signs of acute toxicity (e.g., ataxia, excessive salivation, gasping, and convulsions). The overdose caused no deaths in males, and they showed no signs of toxicity. The surviving animals were not dosed on the 4th day of the week to allow them to recover. Dosing resumed on the 5th day. In addition to these deaths, three animals died due to gavage error including 1 male and 1 female at 22 mg/kg-day and 1 female at 175 mg/kg-day.; Endocrine: The study text noted that during week 4, the two highest dose groups were prepared incorrectly, and for the first three days of that week, the animals were administered double the target levels. Animals in the 175 mg/kg-day group, were instead dosed with 350 mg/kg-day, and animals in the 350 mg/kg-day group were dosed with 700 mg/kg-day. As a result, 2 females in each group died, and others showed excessive signs of acute toxicity (e.g., ataxia, excessive salivation, gasping, and convulsions). The overdose caused no deaths in males, and they showed no signs of toxicity. The surviving animals were not dosed on the 4th day of the week to allow them to recover. Dosing resumed on the 5th day. In addition to these deaths, three animals died due to gavage error including 1 male and 1 female at 22 mg/kg-day and 1 female at 175 mg/kg-day.; Cardiovascular: The study text noted that during week 4, the two highest dose groups were prepared incorrectly, and for the first three days of that week, the animals were administered double the target levels. Animals in the 350 mg/kg group, were instead dosed with 700 mg/kg, and animals in the 700 mg/kg group were dosed with 1,400 mg/kg

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Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Lung/Respiratory; Gastrointestinal; Thyroid; Endocrine; Cardiovascular;
Reported Health Effect(s):	Lung/Respiratory: Histopathology lung; lungs may have been weighed; Gastrointestinal: Histopathology esophagus and salivary gland; relevant organs may have been weighed; Thyroid: Histopathology (thyroid); thyroid may have been weighed; Endocrine: Histopathology (adrenal glands); adrenal glands may have been weighed; Cardiovascular: Histopathology (heart); heart may have been weighed;
Duration:	Chronic (>91 days) 16 weeks - Rats
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
	Metric 23:	Data Presentation and Analysis	Low	All Outcomes: Statistical analysis was performed, but the methods used to analyze initial histopathology data weren't clearly specified, only that the significance level was set at $p < 0.05$.
	Metric 24:	Reporting of Data	High	All Outcomes: Negative findings for initial histopathology were reported qualitatively in the text.

Overall Quality Determination High

Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Cardiovascular; Endocrine; Gastrointestinal; Lung/Respiratory; Gastrointestinal; Thyroid; Immune/Hematological;
Reported Health Effect(s):	Cardiovascular: Histopathology (heart); heart may have been weighed; Endocrine: Histopathology (adrenal glands); adrenal glands may have been weighed; Gastrointestinal: Histopathology esophagus and salivary gland; relevant organs may have been weighed; Lung/Respiratory: Histopathology lung; lungs may have been weighed; Gastrointestinal: Histopathology esophagus and salivary gland; relevant organs may have been weighed; Thyroid: Histopathology (thyroid); thyroid may have been weighed; Immune/Hematological: Histopathology (spleen, thymus, mesenteric lymph nodes, bone marrow); organs may have been weighed;
Duration:	Chronic (>91 days) 16 weeks - Rats
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	All Outcomes: The test substance was clearly identified as tris(2-chloroethyl)phosphate.
	Metric 2:	Test Substance Source	High	All Outcomes: The test substance was purchased from Stauffer Chemical Company. The lot and batch number were provided.
	Metric 3:	Test Substance Purity	Low	All Outcomes: The purity was not reported and could not be determined on the manufacturer's website.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	All Outcomes: The study included a concurrent negative vehicle (corn oil) control group.
	Metric 5:	Positive Controls	N/A	All Outcomes: Positive controls are not necessary for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	All Outcomes: Animals were assigned to dose groups and to cages using a random number table. It was not specified whether animals were also normalized to starting body weights.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Medium	All Outcomes: Fresh solutions were made every two weeks by dissolving the test material in 100% pure corn oil. Test solutions were stored at 5 degrees C until use. Details of mixing for homogeneity weren't provided. Testing for stability was not discussed.
	Metric 8:	Consistency of Exposure Administration	High	All Outcomes: Sufficient exposure administration details were reported. A consistent gavage volume of 5 mL/kg was used. The time of day of dosing was not specified.
	Metric 9:	Reporting of Doses/Concentrations	Medium	All Outcomes: Doses were clearly reported. Dosing solutions were analyzed (method and frequency not specified), and the text indicated that the actual concentrations administered remained within 10% of the target. Analytical values were not provided.

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Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Cardiovascular; Endocrine; Gastrointestinal; Lung/Respiratory; Gastrointestinal; Thyroid; Immune/Hematological;
Reported Health Effect(s):	Cardiovascular: Histopathology (heart); heart may have been weighed; Endocrine: Histopathology (adrenal glands); adrenal glands may have been weighed; Gastrointestinal: Histopathology esophagus and salivary gland; relevant organs may have been weighed; Lung/Respiratory: Histopathology lung; lungs may have been weighed; Gastrointestinal: Histopathology esophagus and salivary gland; relevant organs may have been weighed; Thyroid: Histopathology (thyroid); thyroid may have been weighed; Immune/Hematological: Histopathology (spleen, thymus, mesenteric lymph nodes, bone marrow); organs may have been weighed;
Duration:	Chronic (>91 days) 16 weeks - Rats
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
	Metric 10:	Exposure Frequency and Duration	Medium	Cardiovascular: The study did not mention adherence to a specific guideline, but the text indicated this was an NTP study. Animals were dosed 5 days per week, consistent with the "Specifications for the Conduct of Studies to Evaluate the Toxic and Carcinogenic Potential of Chemical, Biological and Physical Agents in Laboratory Animals for the National Toxicology Program (NTP). The study duration was 16 weeks. The authors did not provide justification for this duration. This is longer than a typical 90-day subchronic study, and shorter than an NTP chronic/carcinogenicity study.; Endocrine: The study did not mention adherence to a specific guideline, but the text indicated this was an NTP study. Animals were dosed 5 days per week, consistent with the "Specifications for the Conduct of Studies to Evaluate the Toxic and Carcinogenic Potential of Chemical, Biological and Physical Agents in Laboratory Animals for the National Toxicology Program (NTP). The study duration was 16 weeks. The authors did not provide justification for this duration. This is longer than a typical 90-day subchronic study, and shorter than an NTP chronic/carcinogenicity study.; Gastrointestinal: The study did not mention adherence to a specific guideline, but the text indicated this was an NTP study. Animals were dosed 5 days per week, consistent with the "Specifications for the Conduct of Studies to Evaluate the Toxic and Carcinogenic Potential of Chemical, Biological and Physical Agents in Laboratory Animals for the National Toxicology Program (NTP)." The study duration was 16 weeks. The authors did not provide justification for this duration. This is longer than a typical 90-day subchronic study, and shorter than an NTP chronic/carcinogenicity study.; Lung/Respiratory: The study did not mention adherence to a specific guideline, but the text indicated this was an NTP study. Animals were dosed 5 days per week, consistent with the "Specifications for the Conduct of Studies to Evaluate the Toxic and Carcinogenic Potential of Chemical, Biological and Physical Agents in Laboratory Animals for the National Toxicology Program (NTP). The study duration was 16 weeks. The authors did not provide justification for this duration. This is longer than a typical 90-day subchronic study, and shorter than an NTP chronic/carcinogenicity study.; Gastrointestinal: The study did not mention adherence to a specific guideline, but the text indicated this was an NTP study. Animals were dosed 5 days per week, consistent with the "Specifications for the Conduct of Studies to Evaluate the Toxic and Carcinogenic Potential of Chemical, Biological and Physical Agents in Laboratory Animals for the National Toxicology Program (NTP). The study duration was 16 weeks. The authors did not provide justification for this duration. This is longer than a typical 90-day subchronic study, and shorter than an NTP chronic/carcinogenicity study.; Thyroid: The study did not mention adherence to a specific guideline, but the text indicated this was an NTP study. Animals were dosed 5 days per week, consistent with the "Specifications for the Conduct of Studies to Evaluate the Toxic and Carcinogenic Potential of Chemical, Biological and Physical Agents in Laboratory Animals for the National Toxicology Program (NTP). The study duration was 16 weeks. The authors did not provide justification for this duration. This is longer than a typical 90-day subchronic study, and shorter than an NTP chronic/carcinogenicity study.; Immune/Hematological: The study

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Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Cardiovascular; Endocrine; Gastrointestinal; Lung/Respiratory; Gastrointestinal; Thyroid; Immune/Hematological;
Reported Health Effect(s):	Cardiovascular: Histopathology (heart); heart may have been weighed; Endocrine: Histopathology (adrenal glands); adrenal glands may have been weighed; Gastrointestinal: Histopathology esophagus and salivary gland; relevant organs may have been weighed; Lung/Respiratory: Histopathology lung; lungs may have been weighed; Gastrointestinal: Histopathology esophagus and salivary gland; relevant organs may have been weighed; Thyroid: Histopathology (thyroid); thyroid may have been weighed; Immune/Hematological: Histopathology (spleen, thymus, mesenteric lymph nodes, bone marrow); organs may have been weighed;
Duration:	Chronic (>91 days) 16 weeks - Rats
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	Cardiovascular: The study tested 5 dose groups plus a control. This is consistent with NTP guidelines. The spacing was sufficient to identify NOAEL and LOAEL values; Endocrine: The study tested 5 dose groups plus a control. This is consistent with NTP guidelines. The spacing was sufficient to identify NOAEL and LOAEL values; Gastrointestinal: The study tested 5 dose groups plus a control. This is consistent with NTP guidelines. The spacing was sufficient to identify NOAEL and LOAEL values.; Lung/Respiratory: The study tested 5 dose groups plus a control. This is consistent with NTP guidelines. The spacing was sufficient to identify NOAEL and LOAEL values; Gastrointestinal: The study tested 5 dose groups plus a control. This is consistent with NTP guidelines. The spacing was sufficient to identify NOAEL and LOAEL values.; Thyroid: The study tested 5 dose groups plus a control. This is consistent with NTP guidelines. The spacing was sufficient to identify NOAEL and LOAEL values; Immune/Hematological: The study tested 5 dose groups plus a control. This is consistent with NTP guidelines. The spacing was sufficient to identify NOAEL and LOAEL values.
	Metric 12:	Exposure Route and Method	High	All Outcomes: Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.

Domain 4: Test Animals

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Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Cardiovascular; Endocrine; Gastrointestinal; Lung/Respiratory; Gastrointestinal; Thyroid; Immune/Hematological;
Reported Health Effect(s):	Cardiovascular: Histopathology (heart); heart may have been weighed; Endocrine: Histopathology (adrenal glands); adrenal glands may have been weighed; Gastrointestinal: Histopathology esophagus and salivary gland; relevant organs may have been weighed; Lung/Respiratory: Histopathology lung; lungs may have been weighed; Gastrointestinal: Histopathology esophagus and salivary gland; relevant organs may have been weighed; Thyroid: Histopathology (thyroid); thyroid may have been weighed; Immune/Hematological: Histopathology (spleen, thymus, mesenteric lymph nodes, bone marrow); organs may have been weighed;
Duration:	Chronic (>91 days) 16 weeks - Rats
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
	Metric 13:	Test Animal Characteristics	Medium	Cardiovascular: The study used male and female F344/N rats. The test animal source (Charles River Breeding Laboratories), and age purchase (5 weeks old), were reported. Initial body weights were not specified. A quarantine period was mentioned, but the duration was not reported.; Endocrine: The study used male and female B6C3F1 mice. The test animal source (Charles River Breeding Laboratories), and age purchase (5 weeks old), were reported. Initial body weights were not specified. A quarantine period was mentioned, but the duration was not reported.; Gastrointestinal: The study used male and female B6C3F1 mice. The test animal source (Charles River Breeding Laboratories), and age purchase (5 weeks old), were reported. Initial body weights were not specified. A quarantine period was mentioned, but the duration was not reported.; Lung/Respiratory: The study used male and female B6C3F1 mice. The test animal source (Charles River Breeding Laboratories), and age purchase (5 weeks old), were reported. Initial body weights were not specified. A quarantine period was mentioned, but the duration was not reported.; Gastrointestinal: The study used male and female B6C3F1 mice. The test animal source (Charles River Breeding Laboratories), and age purchase (5 weeks old), were reported. Initial body weights were not specified. A quarantine period was mentioned, but the duration was not reported.; Thyroid: The study used male and female B6C3F1 mice. The test animal source (Charles River Breeding Laboratories), and age purchase (5 weeks old), were reported. Initial body weights were not specified. A quarantine period was mentioned, but the duration was not reported.; Immune/Hematological: The study used male and female B6C3F1 mice. The test animal source (Charles River Breeding Laboratories), and age purchase (5 weeks old), were reported. Initial body weights were not specified. A quarantine period was mentioned, but the duration was not reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	All Outcomes: Animal husbandry (caging, food and water access, temperature, humidity, and light cycle) were reported. The relative humidity varied from 10% to 78%. This deviates from NTP guidelines that state humidity should not be below 35% or above 65%. The temperature range in the study was 70 to 81 degrees. NTP indicates temperature should not be above 75 degrees, and that there should be minimal fluctuations. The number of animals per cage (n =5) was reported. NTP guidelines specify that male mice should always be housed individually. It is unclear whether the deviations in animal husbandry conditions had an impact on the study results.
	Metric 15:	Number of Animals per Group	Medium	All Outcomes: The number of animals per group (10/sex) was reported and consistent with NTP guidelines.

Domain 5: Outcome Assessment

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Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Cardiovascular; Endocrine; Gastrointestinal; Lung/Respiratory; Gastrointestinal; Thyroid; Immune/Hematological;
Reported Health Effect(s):	Cardiovascular: Histopathology (heart); heart may have been weighed; Endocrine: Histopathology (adrenal glands); adrenal glands may have been weighed; Gastrointestinal: Histopathology esophagus and salivary gland; relevant organs may have been weighed; Lung/Respiratory: Histopathology lung; lungs may have been weighed; Gastrointestinal: Histopathology esophagus and salivary gland; relevant organs may have been weighed; Thyroid: Histopathology (thyroid); thyroid may have been weighed; Immune/Hematological: Histopathology (spleen, thymus, mesenteric lymph nodes, bone marrow); organs may have been weighed;
Duration:	Chronic (>91 days) 16 weeks - Rats
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
	Metric 16:	Outcome Assessment Methodology	Medium	All Outcomes: The methods did not specify which organs were weighed. Histopathology was conducted which is considered to be a sensitive method for this outcome of interest.
	Metric 17:	Consistency of Outcome Assessment	High	All Outcomes: There is no indication that there were inconsistencies in the outcome assessment across groups. Histopathology was performed at the end of the study.
	Metric 18:	Sampling Adequacy	Medium	All Outcomes: Histopathology was conducted in controls and animals from the high-dose group. This is acceptable because no treatment-related lesions were observed.
	Metric 19:	Blinding of Assessors	N/A	All Outcomes: Blinding is not necessary for initial histopathology.
	Metric 20:	Negative Control Response	Medium	All Outcomes: The biological responses of negative controls were not explicitly reported; negative findings were qualitatively reported in the text.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	All Outcomes: Some information to determine confounding (initial body weights) was not provided. The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP.

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Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Cardiovascular; Endocrine; Gastrointestinal; Lung/Respiratory; Gastrointestinal; Thyroid; Immune/Hematological;
Reported Health Effect(s):	Cardiovascular: Histopathology (heart); heart may have been weighed; Endocrine: Histopathology (adrenal glands); adrenal glands may have been weighed; Gastrointestinal: Histopathology esophagus and salivary gland; relevant organs may have been weighed; Lung/Respiratory: Histopathology lung; lungs may have been weighed; Gastrointestinal: Histopathology esophagus and salivary gland; relevant organs may have been weighed; Thyroid: Histopathology (thyroid); thyroid may have been weighed; Immune/Hematological: Histopathology (spleen, thymus, mesenteric lymph nodes, bone marrow); organs may have been weighed;
Duration:	Chronic (>91 days) 16 weeks - Rats
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
	Metric 22:	Health Outcomes Unrelated to Exposure	Low	Cardiovascular: The study text noted that during week 4, the two highest dose groups were prepared incorrectly, and for the first three days of that week, the animals were administered double the target levels. Animals in the 175 mg/kg-day group, were instead dosed with 350 mg/kg-day, and animals in the 350 mg/kg-day group were dosed with 700 mg/kg-day. As a result, 2 females in each group died, and others showed excessive signs of acute toxicity (e.g., ataxia, excessive salivation, gasping, and convulsions). The overdose caused no deaths in males, and they showed no signs of toxicity. The surviving animals were not dosed on the 4th day of the week to allow them to recover. Dosing resumed on the 5th day. In addition to these deaths, three animals died due to gavage error including 1 male and 1 female at 22 mg/kg-day and 1 female at 175 mg/kg-day.; Endocrine: The study text noted that during week 4, the two highest dose groups were prepared incorrectly, and for the first three days of that week, the animals were administered double the target levels. Animals in the 350 mg/kg group, were instead dosed with 700 mg/kg, and animals in the 700 mg/kg group were dosed with 1,400 mg/kg. No deaths occurred as a result of the dosing error, but two male mice had convulsions and labored breathing on the third day of overdosing. Overdosed females were uncoordinated. These animals were not dosed on the 4th day of the week to allow them to recover. Dosing resumed on the 5th day. Three males and two females died during the study due to gavage trauma. The males were from the 175, 350, and 700 mg/kg groups, and the females were from the 175 and 300 mg/kg groups, respectively.; Gastrointestinal: The study text noted that during week 4, the two highest dose groups were prepared incorrectly, and for the first three days of that week, the animals were administered double the target levels. Animals in the 350 mg/kg group, were instead dosed with 700 mg/kg, and animals in the 700 mg/kg group were dosed with 1,400 mg/kg. No deaths occurred as a result of the dosing error, but two male mice had convulsions and labored breathing on the third day of overdosing. Overdosed females were uncoordinated. These animals were not dosed on the 4th day of the week to allow them to recover. Dosing resumed on the 5th day. Three males and two females died during the study due to gavage trauma. The males were from the 175, 350, and 700 mg/kg groups, and the females were from the 175 and 300 mg/kg groups, respectively.; Lung/Respiratory: The study text noted that during week 4, the two highest dose groups were prepared incorrectly, and for the first three days of that week, the animals were administered double the target levels. Animals in the 350 mg/kg group, were instead dosed with 700 mg/kg, and animals in the 700 mg/kg group were dosed with 1,400 mg/kg. No deaths occurred as a result of the dosing error, but two male mice had convulsions and labored breathing on the third day of overdosing. Overdosed females were uncoordinated. These animals were not dosed on the 4th day of the week to allow them to recover. Dosing resumed on the 5th day. Three males and two females died during the study due to gavage trauma. The males were from the 175, 350, and 700 mg/kg groups, and the females were from the 175 and 300 mg/kg groups, respectively.; Gastrointestinal: The study text noted that during week 4, the two highest dose groups were prepared incorrectly, and for the first

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Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Cardiovascular; Endocrine; Gastrointestinal; Lung/Respiratory; Gastrointestinal; Thyroid; Immune/Hematological;
Reported Health Effect(s):	Cardiovascular: Histopathology (heart); heart may have been weighed; Endocrine: Histopathology (adrenal glands); adrenal glands may have been weighed; Gastrointestinal: Histopathology esophagus and salivary gland; relevant organs may have been weighed; Lung/Respiratory: Histopathology lung; lungs may have been weighed; Gastrointestinal: Histopathology esophagus and salivary gland; relevant organs may have been weighed; Thyroid: Histopathology (thyroid); thyroid may have been weighed; Immune/Hematological: Histopathology (spleen, thymus, mesenteric lymph nodes, bone marrow); organs may have been weighed;
Duration:	Chronic (>91 days) 16 weeks - Rats
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
	Metric 23:	Data Presentation and Analysis	Low	All Outcomes: Statistical analysis was performed, but the methods used to analyze initial histopathology data weren't clearly specified, only that the significance level was set at $p < 0.05$.
	Metric 24:	Reporting of Data	High	All Outcomes: Negative findings for initial histopathology were reported qualitatively in the text.

Overall Quality Determination High

Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Reproductive/Developmental
Reported Health Effect(s):	Histopathology (epididymis, prostate), sperm morphology and vaginal cytology; reproductive organs may have been weighed
Duration:	Chronic (>91 days) 16 weeks - Rats
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was clearly identified as tris(2-chloroethyl)phosphate.
	Metric 2:	Test Substance Source	High	The test substance was purchased from Stauffer Chemical Company. The lot and batch number were provided.
	Metric 3:	Test Substance Purity	Low	The purity was not reported and could not be determined on the manufacturer's website.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	The study included a concurrent negative vehicle (corn oil) control group.
	Metric 5:	Positive Controls	N/A	Positive controls are not necessary for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	Animals were assigned to dose groups and to cages using a random number table. It was not specified whether animals were also normalized to starting body weights.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Medium	Fresh solutions were made every two weeks by dissolving the test material in 100% pure corn oil. Test solutions were stored at 5 degrees C until use. Details of mixing for homogeneity weren't provided. Testing for stability was not discussed.
	Metric 8:	Consistency of Exposure Administration	High	Sufficient exposure administration details were reported. A consistent gavage volume of 5 mL/kg was used. The time of day of dosing was not specified.
	Metric 9:	Reporting of Doses/Concentrations	Medium	Doses were clearly reported. Dosing solutions were analyzed (method and frequency not specified), and the text indicated that the actual concentrations administered remained within 10% of the target. Analytical values were not provided.
	Metric 10:	Exposure Frequency and Duration	Medium	The study did not mention adherence to a specific guideline, but the text indicated this was an NTP study. Animals were dosed 5 days per week, consistent with the "Specifications for the Conduct of Studies to Evaluate the Toxic and Carcinogenic Potential of Chemical, Biological and Physical Agents in Laboratory Animals for the National Toxicology Program (NTP). The study duration was 16 weeks. The authors did not provide justification for this duration. This is longer than a typical 90-day subchronic study, and shorter than an NTP chronic/carcinogenicity study.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	The study tested 5 dose groups plus a control. This is consistent with NTP guidelines. The spacing was sufficient to identify NOAEL and LOAEL values
	Metric 12:	Exposure Route and Method	High	Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				

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Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Reproductive/Developmental
Reported Health Effect(s):	Histopathology (epididymis, prostate), sperm morphology and vaginal cytology; reproductive organs may have been weighed
Duration:	Chronic (>91 days) 16 weeks - Rats
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
	Metric 13:	Test Animal Characteristics	Medium	The study used male and female F344/N rats. The test animal source (Charles River Breeding Laboratories), and age purchase (5 weeks old), were reported. Initial body weights were not specified. A quarantine period was mentioned, but the duration was not reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	Animal husbandry (caging, food and water access, temperature, humidity, and light cycle) were reported. The relative humidity varied from 10% to 78%. This deviates from NTP guidelines that stat humidity should not be below 35% or above 65%. The temperature range in the study was 70 to 81 degrees. NTP indicates temperature should not be above 75 degrees, and that there should be minimal fluctuations. The number of animals per cage (n =5) was appropriate. It is unclear whether the deviations in animal husbandry conditions had an impact on the study results.
	Metric 15:	Number of Animals per Group	Medium	The number of animals per group (10/sex) was reported and consistent with NTP guidelines.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	Medium	The methods did not indicate whether any reproductive organ weights were measured; only that organs (unspecified) were weighed. At necropsy, relevant tissues were histopathologically examined. The study referenced Dunnick et al. 1984 for methods on sperm morphology and vaginal cytology (reviewed for this evaluation). It is not clear whether sperm assessments were conducted on animals that died prior to the end of the study. Overall, the methods were sensitive for the outcomes of interest.
	Metric 17:	Consistency of Outcome Assessment	High	There is no indication that there were inconsistencies in the outcome assessment across groups. Histopathology was performed at the end of the study.
	Metric 18:	Sampling Adequacy	Medium	The methods did not specify whether sperm morphology and vaginal cytology analysis were conducted in all groups. Except for brain tissues, histopathology was conducted in controls and animals from the 175 and 350 mg/kg-day groups.
	Metric 19:	Blinding of Assessors	N/A	Blinding is not necessary for initial histopathology.
	Metric 20:	Negative Control Response	Medium	The biological responses of negative controls were not explicitly reported. Negative findings were qualitatively reported in the text.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	Some information to determine confounding (initial body weights) was not provided. The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP.The study text mentioned technical difficulties that prevented accurate analysis of sperm morphology in rats. No further details were provided.

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Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Reproductive/Developmental
Reported Health Effect(s):	Histopathology (epididymis, prostate), sperm morphology and vaginal cytology; reproductive organs may have been weighed
Duration:	Chronic (>91 days) 16 weeks - Rats
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
	Metric 22:	Health Outcomes Unrelated to Exposure	Low	The study text noted that during week 4, the two highest dose groups were prepared incorrectly, and for the first three days of that week, the animals were administered double the target levels. Animals in the 175 mg/kg-day group, were instead dosed with 350 mg/kg-day, and animals in the 350 mg/kg-day group were dosed with 700 mg/kg-day. As a result, 2 females in each group died, and others showed excessive signs of acute toxicity (e.g., ataxia, excessive salivation, gasping, and convulsions). The overdose caused no deaths in males, and they showed no signs of toxicity. The surviving animals were not dosed on the 4th day of the week to allow them to recover. Dosing resumed on the 5th day. In addition to these deaths, three animals died due to gavage error including 1 male and 1 female at 22 mg/kg-day and 1 female at 175 mg/kg-day.
	Metric 23:	Data Presentation and Analysis	Low	Statistical analysis was performed, but the methods used to analyze initial histopathology data weren't clearly specified, only that the significance level was set at $p < 0.05$.
	Metric 24:	Reporting of Data	Low	Negative findings for initial histopathology were reported qualitatively in the text. Sperm data were not generated due to technical difficulties. Vaginal cytology was purportedly conducted, but these data were not reported.

Overall Quality Determination Medium

Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Reproductive/Developmental
Reported Health Effect(s):	Histopathology (epididymis, prostate), sperm morphology and vaginal cytology; reproductive organs may have been weighed
Duration:	Chronic (>91 days) 16 weeks - Mice
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was clearly identified as tris(2-chloroethyl)phosphate.
	Metric 2:	Test Substance Source	High	The test substance was purchased from Stauffer Chemical Company. The lot and batch number were provided.
	Metric 3:	Test Substance Purity	Low	The purity was not reported and could not be determined on the manufacturer's website.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	The study included a concurrent negative vehicle (corn oil) control group.
	Metric 5:	Positive Controls	N/A	Positive controls are not necessary for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	Animals were assigned to dose groups and to cages using a random number table. It was not specified whether animals were also normalized to starting body weights.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Medium	Fresh solutions were made every two weeks by dissolving the test material in 100% pure corn oil. Test solutions were stored at 5 degrees C until use. Details of mixing for homogeneity weren't provided. Testing for stability was not discussed.
	Metric 8:	Consistency of Exposure Administration	High	Sufficient exposure administration details were reported. A consistent gavage volume of 5 mL/kg was used. The time of day of dosing was not specified.
	Metric 9:	Reporting of Doses/Concentrations	Medium	Doses were clearly reported. Dosing solutions were analyzed (method and frequency not specified), and the text indicated that the actual concentrations administered remained within 10% of the target. Analytical values were not provided.
	Metric 10:	Exposure Frequency and Duration	Medium	The study did not mention adherence to a specific guideline, but the text indicated this was an NTP study. Animals were dosed 5 days per week, consistent with the "Specifications for the Conduct of Studies to Evaluate the Toxic and Carcinogenic Potential of Chemical, Biological and Physical Agents in Laboratory Animals for the National Toxicology Program (NTP). The study duration was 16 weeks. The authors did not provide justification for this duration. This is longer than a typical 90-day subchronic study, and shorter than an NTP chronic/carcinogenicity study.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	The study tested 5 dose groups plus a control. This is consistent with NTP guidelines. The spacing was sufficient to identify NOAEL and LOAEL values.
	Metric 12:	Exposure Route and Method	High	Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				

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Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Reproductive/Developmental
Reported Health Effect(s):	Histopathology (epididymis, prostate), sperm morphology and vaginal cytology; reproductive organs may have been weighed
Duration:	Chronic (>91 days) 16 weeks - Mice
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
	Metric 13:	Test Animal Characteristics	Medium	The study used male and female B6C3F1 mice. The test animal source (Charles River Breeding Laboratories), and age purchase (5 weeks old), were reported. Initial body weights were not specified. A quarantine period was mentioned, but the duration was not reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	Animal husbandry (caging, food and water access, temperature, humidity, and light cycle) were reported. The relative humidity varied from 10% to 78%. This deviates from NTP guidelines that state humidity should not be below 35% or above 65%. The temperature range in the study was 70 to 81 degrees. NTP indicates temperature should not be above 75 degrees, and that there should be minimal fluctuations. The number of animals per cage (n =5) was reported. NTP guidelines specify that male mice should always be housed individually. It is unclear whether the deviations in animal husbandry conditions had an impact on the study results.
	Metric 15:	Number of Animals per Group	Medium	The number of animals per group (10/sex) was reported and consistent with NTP guidelines.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	Medium	The methods did not indicate whether any reproductive organ weights were measured; only that organs (unspecified) were weighed. At necropsy, relevant tissues were histopathologically examined. The study referenced Dunnick et al. 1984 for methods on sperm morphology and vaginal cytology (reviewed for this evaluation). It is not clear whether sperm assessments were conducted on animals that died prior to the end of the study. Overall, the methods were sensitive for the outcomes of interest.
	Metric 17:	Consistency of Outcome Assessment	High	There is no indication that there were inconsistencies in the outcome assessment across groups. Histopathology was performed at the end of the study.
	Metric 18:	Sampling Adequacy	Medium	Sperm morphology was determined in all male mice surviving to terminal sacrifice. The methods did not specify whether vaginal cytology analysis was conducted in all groups. Histopathology was conducted in control animals and animals from the high-dose group.
	Metric 19:	Blinding of Assessors	N/A	Blinding is not necessary for initial histopathology.
	Metric 20:	Negative Control Response	Medium	The biological responses of negative controls were not explicitly reported. Negative findings were qualitatively reported in the text.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	Some information to determine confounding (initial body weights) was not provided. The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP.The study text mentioned technical difficulties that prevented accurate analysis of sperm morphology in rats. No further details were provided.

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Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Reproductive/Developmental
Reported Health Effect(s):	Histopathology (epididymis, prostate), sperm morphology and vaginal cytology; reproductive organs may have been weighed
Duration:	Chronic (>91 days) 16 weeks - Mice
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
	Metric 22:	Health Outcomes Unrelated to Exposure	Low	The study text noted that during week 4, the two highest dose groups were prepared incorrectly, and for the first three days of that week, the animals were administered double the target levels. Animals in the 350 mg/kg group, were instead dosed with 700 mg/kg, and animals in the 700 mg/kg group were dosed with 1,400 mg/kg. No deaths occurred as a result of the dosing error, but two male mice had convulsions and labored breathing on the third day of overdosing. Overdosed females were uncoordinated. These animals were not dosed on the 4th day of the week to allow them to recover. Dosing resumed on the 5th day. Three males and two females died during the study due to gavage trauma. The males were from the 175, 350, and 700 mg/kg groups, and the females were from the 175 and 300 mg/kg groups, respectively.
	Metric 23:	Data Presentation and Analysis	Low	Statistical analysis was performed, but the methods used to analyze initial histopathology data weren't clearly specified, only that the significance level was set at $p < 0.05$.
	Metric 24:	Reporting of Data	Medium	Negative findings for initial histopathology were reported qualitatively in the text. Sperm counts were significantly decreased at the high dose. Vaginal cytology was purportedly conducted, but these data were not reported.

Overall Quality Determination Medium

Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Clinical observations
Reported Health Effect(s):	Unspecified clinical observations
Duration:	Chronic (>91 days) 16 weeks - Mice
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was clearly identified as tris(2-chloroethyl)phosphate.
	Metric 2:	Test Substance Source	High	The test substance was purchased from Stauffer Chemical Company. The lot and batch number were provided.
	Metric 3:	Test Substance Purity	Low	The purity was not reported and could not be determined on the manufacturer's website.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	The study included a concurrent negative vehicle (corn oil) control group.
	Metric 5:	Positive Controls	N/A	Positive controls are not necessary for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	Animals were assigned to dose groups and to cages using a random number table. It was not specified whether animals were also normalized to starting body weights.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Medium	Fresh solutions were made every two weeks by dissolving the test material in 100% pure corn oil. Test solutions were stored at 5 degrees C until use. Details of mixing for homogeneity weren't provided. Testing for stability was not discussed.
	Metric 8:	Consistency of Exposure Administration	High	Sufficient exposure administration details were reported. A consistent gavage volume of 5 mL/kg was used. The time of day of dosing was not specified.
	Metric 9:	Reporting of Doses/Concentrations	Medium	Doses were clearly reported. Dosing solutions were analyzed (method and frequency not specified), and the text indicated that the actual concentrations administered remained within 10% of the target. Analytical values were not provided.
	Metric 10:	Exposure Frequency and Duration	Medium	The study did not mention adherence to a specific guideline, but the text indicated this was an NTP study. Animals were dosed 5 days per week, consistent with the "Specifications for the Conduct of Studies to Evaluate the Toxic and Carcinogenic Potential of Chemical, Biological and Physical Agents in Laboratory Animals for the National Toxicology Program (NTP). The study duration was 16 weeks. The authors did not provide justification for this duration. This is longer than a typical 90-day subchronic study, and shorter than an NTP chronic/carcinogenicity study.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	The study tested 5 dose groups plus a control. This is consistent with NTP guidelines. The spacing was sufficient to identify NOAEL and LOAEL values
	Metric 12:	Exposure Route and Method	High	Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				

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Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Clinical observations
Reported Health Effect(s):	Unspecified clinical observations
Duration:	Chronic (>91 days) 16 weeks - Mice
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
	Metric 13:	Test Animal Characteristics	Medium	The study used male and female B6C3F1 mice. The test animal source (Charles River Breeding Laboratories), and age purchase (5 weeks old), were reported. Initial body weights were not specified. A quarantine period was mentioned, but the duration was not reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	Animal husbandry (caging, food and water access, temperature, humidity, and light cycle) were reported. The relative humidity varied from 10% to 78%. This deviates from NTP guidelines that state humidity should not be below 35% or above 65%. The temperature range in the study was 70 to 81 degrees. NTP indicates temperature should not be above 75 degrees, and that there should be minimal fluctuations. The number of animals per cage (n =5) was reported. NTP guidelines specify that male mice should always be housed individually. It is unclear whether the deviations in animal husbandry conditions had an impact on the study results.
	Metric 15:	Number of Animals per Group	Medium	The number of animals per group (10/sex) was reported and consistent with NTP guidelines.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	Medium	Animals were subjected to clinical examinations weekly in accordance with NTP guidelines. No methodological details were provided. The guideline also specifies that expanded clinical observations should be done by a pathologist at a minimum at least once every other week. It is unclear if this was done.
	Metric 17:	Consistency of Outcome Assessment	High	Based on the information provided, all animals were observed daily. Additional outcome assessment methods (e.g., the time of observations (time of day)) were not provided, but based on the available information, there is no indication that there were differences across groups (except for those associated with the overdose).
	Metric 18:	Sampling Adequacy	Medium	All animals were observed for clinical signs, but because negative findings were qualitatively reported, the sample size cannot be verified.
	Metric 19:	Blinding of Assessors	Medium	Blinding was not reported and clinical signs can be somewhat subjective in nature; however, lack of blinding is not expected to have a significant impact on results because no clinical signs of toxicity were observed.
	Metric 20:	Negative Control Response	Medium	The appropriateness of the negative control response cannot be definitively determined because incidence data were not reported. The text mentioned some clinical signs in treated animals but did not explicitly report that there were no clinical signs in controls.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	Some information to determine confounding (initial body weights) was not provided. The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP.

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Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Clinical observations
Reported Health Effect(s):	Unspecified clinical observations
Duration:	Chronic (>91 days) 16 weeks - Mice
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
	Metric 22:	Health Outcomes Unrelated to Exposure	Low	The study text noted that during week 4, the two highest dose groups were prepared incorrectly, and for the first three days of that week, the animals were administered double the target levels. Animals in the 350 mg/kg group, were instead dosed with 700 mg/kg, and animals in the 700 mg/kg group were dosed with 1,400 mg/kg. No deaths occurred as a result of the dosing error, but two male mice had convulsions and labored breathing on the third day of overdosing. These animals were not dosed on the 4th day of the week to allow them to recover. Dosing resumed on the 5th day. Three males and two females died during the study due to gavage trauma. The males were from the 175, 350, and 700 mg/kg groups, and the females were from the 175 and 300 mg/kg groups, respectively.
	Metric 23:	Data Presentation and Analysis	N/A	The only observed clinical signs were those unrelated to exposure. Statistical analysis was not necessary for clearly negative findings across groups.
	Metric 24:	Reporting of Data	Medium	Clinical signs related to the overdose were noted in two males and all females. No clinical signs unrelated to the overdose were described.

Overall Quality Determination Medium

Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Clinical observations
Reported Health Effect(s):	Unspecified clinical observations
Duration:	Chronic (>91 days) 16 weeks - Rats
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was clearly identified as tris(2-chloroethyl)phosphate.
	Metric 2:	Test Substance Source	High	The test substance was purchased from Stauffer Chemical Company. The lot and batch number were provided.
	Metric 3:	Test Substance Purity	Low	The purity was not reported and could not be determined on the manufacturer's website.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	The study included a concurrent negative vehicle (corn oil) control group.
	Metric 5:	Positive Controls	N/A	Positive controls are not necessary for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	Animals were assigned to dose groups and to cages using a random number table. It was not specified whether animals were also normalized to starting body weights.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Medium	Fresh solutions were made every two weeks by dissolving the test material in 100% pure corn oil. Test solutions were stored at 5 degrees C until use. Details of mixing for homogeneity weren't provided. Testing for stability was not discussed.
	Metric 8:	Consistency of Exposure Administration	High	Sufficient exposure administration details were reported. A consistent gavage volume of 5 mL/kg was used. The time of day of dosing was not specified.
	Metric 9:	Reporting of Doses/Concentrations	Medium	Doses were clearly reported. Dosing solutions were analyzed (method and frequency not specified), and the text indicated that the actual concentrations administered remained within 10% of the target. Analytical values were not provided.
	Metric 10:	Exposure Frequency and Duration	Medium	The study did not mention adherence to a specific guideline, but the text indicated this was an NTP study. Animals were dosed 5 days per week, consistent with the "Specifications for the Conduct of Studies to Evaluate the Toxic and Carcinogenic Potential of Chemical, Biological and Physical Agents in Laboratory Animals for the National Toxicology Program (NTP). The study duration was 16 weeks. The authors did not provide justification for this duration. This is longer than a typical 90-day subchronic study, and shorter than an NTP chronic/carcinogenicity study.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	The study tested 5 dose groups plus a control. This is consistent with NTP guidelines. The spacing was sufficient to identify NOAEL and LOAEL values.
	Metric 12:	Exposure Route and Method	High	Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				

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Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Clinical observations
Reported Health Effect(s):	Unspecified clinical observations
Duration:	Chronic (>91 days) 16 weeks - Rats
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
	Metric 13:	Test Animal Characteristics	Medium	The study used male and female F344/N rats. The test animal source (Charles River Breeding Laboratories), and age purchase (5 weeks old), were reported. Initial body weights were not specified. A quarantine period was mentioned, but the duration was not reported.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	Animal husbandry (caging, food and water access, temperature, humidity, and light cycle) were reported. The relative humidity varied from 10% to 78%. This deviates from NTP guidelines that stat humidity should not be below 35% or above 65%. The temperature range in the study was 70 to 81 degrees. NTP indicates temperature should not be above 75 degrees, and that there should be minimal fluctuations. The number of animals per cage (n =5) was appropriate. It is unclear whether the deviations in animal husbandry conditions had an impact on the study results.
	Metric 15:	Number of Animals per Group	Medium	The number of animals per group (10/sex) was reported and consistent with NTP guidelines.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	Medium	Animals were subjected to clinical examinations weekly in accordance with NTP guidelines. No methodological details were provided. The guideline also specifies that expanded clinical observations should be done by a pathologist at a minimum at least once every other week. It is unclear if this was done.
	Metric 17:	Consistency of Outcome Assessment	High	Based on the information provided, all animals were observed daily. Additional outcome assessment methods (e.g., the time of observations (time of day)) were not provided, but based on the available information, there is no indication that there were differences across groups (except for those associated with the overdose).
	Metric 18:	Sampling Adequacy	Medium	All animals were observed for clinical signs, but since negative findings were qualitatively reported, the sample size cannot be verified.
	Metric 19:	Blinding of Assessors	Medium	Blinding was not reported and clinical signs can be somewhat subjective in nature; however, lack of blinding is not expected to have a significant impact on results because no clinical signs of toxicity were observed.
	Metric 20:	Negative Control Response	Medium	The appropriateness of the negative control response cannot be definitively determined because incidence data were not reported, the text mentioned some clinical signs in treated animals but did not explicitly report that there were no clinical signs in controls.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	Some information to determine confounding (initial body weights) was not provided. The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP.

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Study Citation:	Matthews, H. B., Dixon, D., Herr, D. W., Tilson, H. (1990). Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. Toxicology and Industrial Health 6(1):1-15.
Health Outcome(s):	Clinical observations
Reported Health Effect(s):	Unspecified clinical observations
Duration:	Chronic (>91 days) 16 weeks - Rats
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469641

Domain	Metric		Rating	Comments
	Metric 22:	Health Outcomes Unrelated to Exposure	Low	The study text noted that during week 4, the two highest dose groups were prepared incorrectly, and for the first three days of that week, the animals were administered double the target levels. Animals in the 175 mg/kg-day group, were instead dosed with 350 mg/kg-day, and animals in the 350 mg/kg-day group were dosed with 700 mg/kg-day. As a result, 2 females in each group died, and others showed excessive signs of acute toxicity (e.g., ataxia, excessive salivation, gasping, and convulsions). The overdose caused no deaths in males, and they showed no signs of toxicity. The surviving animals were not dosed on the 4th day of the week to allow them to recover. Dosing resumed on the 5th day. In addition to these deaths, three animals died due to gavage error including 1 male and 1 female at 22 mg/kg-day and 1 female at 175 mg/kg-day.
	Metric 23:	Data Presentation and Analysis	Low	Some data were clearly statistically analyzed, but the statistical methods used were not reported; the study text only specifies that the "Significance level was set at $p < 0.05$)." It is unclear whether clinical observations were statistically analyzed, and incidence data were not provided for an independent review.
	Metric 24:	Reporting of Data	Medium	Clinical signs related to the overdose were noted and a qualitative statement indicated seizures were observed in high-dose female rats during week 12. Incidence and significance were not specified.

Overall Quality Determination Medium

Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Cancer/Carcinogenesis
Reported Health Effect(s):	Tumor incidence
Duration:	Chronic (>91 days) 2-yrs (104-weeks rats)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was identified definitively as tris(2-chloroethyl phosphate) CASRN 115-96-8. A structure was also provided.
	Metric 2:	Test Substance Source	High	The test substance was manufactured by Stauffer Chemical Company and obtained from the analytical chemistry laboratory, Midwest Research Institute. The lot number was provided.
	Metric 3:	Test Substance Purity	High	The test chemical purity was ~98%, and was both provided by the supplier and confirmed via analysis (NMR and elemental analysis) by the study laboratory.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	The study included concurrent negative vehicle (corn oil) controls and conditions were consistent with the animals that were treated.
	Metric 5:	Positive Controls	N/A	Positive controls are not required for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	Animals were distributed into weight classes, and assigned to cages using a random number table. Cages were then assigned to treatment and control groups using another random number table.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) were also stable for 21 days in the dark at room temperature or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks
	Metric 8:	Consistency of Exposure Administration	High	All animals were gavaged on the same schedule. Gavage volumes were reported and were consistent across groups.
	Metric 9:	Reporting of Doses/Concentrations	High	Animals were dosed with 0, 44, or 88 mg/kg/day, 5 days per week. Doses were selected based on a subchronic study. Dose formulations were analyzed at approximately 8-week intervals by gas chromatography, and remained within 10% of the target concentrations throughout the course of the study. The target and measured concentrations in the solutions (mg/mL) were reported.
	Metric 10:	Exposure Frequency and Duration	High	Animals were dosed 5 days per week for two years. The exposure frequency and duration are consistent with NTP guidelines.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Cancer/Carcinogenesis
Reported Health Effect(s):	Tumor incidence
Duration:	Chronic (>91 days) 2-yrs (104-weeks rats)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	Low	This 2-year study only included two treatment groups and a control. Although the authors justified the doses used, NTP guidelines specify using 3 treatment groups plus a control. Effects were observed at both doses and a NOAEL could not be determined.
	Metric 12:	Exposure Route and Method	High	Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	Low	The study used male and female F344/N rats. The test animal source (Harlan industries) and age at the start of the study (8-10 weeks old) were reported. Although initial animal body weights for the 16-day and 16-week studies were reported, the initial body weights for the 2-year study are not reported. Body weight data begin after 1 week of dosing.NTP no longer uses F344/N rats for chronic/carcinogenicity studies. It was determined that these rats have a high background in some tumors including testicular interstitial cell tumors and mononuclear cell leukemia. The high backgrounds could decrease the ability to detect exposure-related effects in these organs/systems.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Low	The number of animals per cage (5/cage) was reported. According to NTP guidelines for chronic/carcinogenicity studies, male rats should only be housed up to 3 per cage. Food and water were provided ad libiutm. Animal room environments (temperature, humidity, lighting were reported. The humidity ranged considerably from 15% to 84%. This deviates from NTP guidelines which state humidity should not be below 35% or above 65%. Similarly, the temperature range was reported to be between 60 and 86 degrees F. NTP guidelines state that the temperatures shall not be below 69 or above 75 degrees F, with minimal fluctuations. It is unclear whether these deviations had a significant impact on the study results.
	Metric 15:	Number of Animals per Group	Medium	The study methods specify 50/sex/group which is consistent with NTP guidelines for a chronic/carcinogenicity study. An extra 10/sex/group were added for an interim sacrifice at 66 weeks.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	A detailed description of histopathology and tumor assessment methods at terminal sacrifice was provided. The methods were sensitive to the outcomes of interest and adhered to NTP guidelines.
	Metric 17:	Consistency of Outcome Assessment	High	The same protocol was applied to animals from all groups, and animals were consistently assessed for the outcomes of interest.
	Metric 18:	Sampling Adequacy	Low	The sampling was adequate. All animals from all groups were assessed for carcinogenicity.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Cancer/Carcinogenesis
Reported Health Effect(s):	Tumor incidence
Duration:	Chronic (>91 days) 2-yrs (104-weeks rats)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 19:	Blinding of Assessors	High	The study indicated that all histopathology data were sent to an independent quality assessment laboratory and slides, tissue counts, and histo-technique were evaluated. Additionally, all tumor diagnoses, all tissue sections of the brain, kidney, liver, spleen, and thyroid, and tissues randomly selected from 10% of the animals were re-examined by a pathologist. It was not specified whether these examinations were done blinded; however, in any instances where there was a disagreement in diagnosis, a Pathology Working Group chairperson, reviewed the slides blinded without prior knowledge of the dose group, or the previous diagnoses.
	Metric 20:	Negative Control Response	Medium	Incidences in control animals were generally low, but there were a few exceptions. There was a high incidence of testes adenomas in the controls (38/50 overall, and 33/36 at terminal sacrifice). The incidences of pituitary gland adenomas (39%) and adenomas or carcinomas (43%) were higher in control rats than in treated rats (29% in the high-dose group), and the incidence of thyroid gland adenomas or adenomas and carcinomas in control rats was higher than in the treated rats (28% overall, and 33% of controls at terminal sacrifice had tumors). Based on NTP historical control data for rats of this strain, these percentages fall within historical ranges, and therefore are not unexpected.Citation: Haseman JK, Hailey JR, Morris RW. Spontaneous Neoplasm Incidences in Fischer 344 Rats and B6C3F1 Mice in Two-Year Carcinogenicity Studies: A National Toxicology Program Update. Toxicologic Pathology. 1998;26(3):428-441. doi:10.1177/019262339802600318
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	High	No confounding variables in the test design and procedures were identified. The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP. There were no significant body weight changes that were suggestive of palatability issues.
	Metric 22:	Health Outcomes Unrelated to Exposure	Medium	Gavage-related deaths were noted in 4 controls (all males), 4 animals at 44 mg/kg-day (1 male, 3 females), and 4 at 88 mg/kg-day (all females). There were also 3 accidental deaths; details were only provided for one high-dose male that was inadvertently killed at the 66-week interim sacrifice. The small number of deaths not related to exposure is not expected to have a significant impact on the study results.
	Metric 23:	Data Presentation and Analysis	High	A detailed description of statistical methods used to analyze tumor data was provided and was appropriate.
	Metric 24:	Reporting of Data	High	Tumor data were reported in detail and included summary tables with statistical results, and tables showing individual animal tumor pathology.

Overall Quality Determination High

Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Mortality (Clinical signs)
Reported Health Effect(s):	Survival
Duration:	Chronic (>91 days) 2-yrs (104-weeks rats)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was identified definitively as tris(2-chloroethyl phosphate) CASRN 115-96-8. A structure was also provided.
	Metric 2:	Test Substance Source	High	The test substance was manufactured by Stauffer Chemical Company and obtained from the analytical chemistry laboratory, Midwest Research Institute. The lot number was provided.
	Metric 3:	Test Substance Purity	High	The test chemical purity was ~98%, and was both provided by the supplier and confirmed via analysis (NMR and elemental analysis) by the study laboratory.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	The study included concurrent negative vehicle (corn oil) controls and conditions were consistent with the animals that were treated.
	Metric 5:	Positive Controls	N/A	Positive controls are not required for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	Animals were distributed into weight classes, and assigned to cages using a random number table. Cages were then assigned to treatment and control groups using another random number table.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) were also stable for 21 days in the dark at room temperature or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks.
	Metric 8:	Consistency of Exposure Administration	High	All animals were gavaged on the same schedule. Gavage volumes were reported and were consistent across groups.
	Metric 9:	Reporting of Doses/Concentrations	High	Animals were dosed with 0, 44, or 88 mg/kg/day, 5 days per week. Doses were selected based on a subchronic study. Dose formulations were analyzed at approximately 8-week intervals by gas chromatography, and remained within 10% of the target concentrations throughout the course of the study. The target and measured concentrations in the solutions (mg/mL) were reported.
	Metric 10:	Exposure Frequency and Duration	High	Animals were dosed 5 days per week for two years. The exposure frequency and duration are consistent with NTP guidelines.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	Low	This 2-year study only included two treatment groups and a control. Although the authors justified the doses used, NTP guidelines specify using 3 treatment groups plus a control. Effects were observed at both doses and a NOAEL could not be determined.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Mortality (Clinical signs)
Reported Health Effect(s):	Survival
Duration:	Chronic (>91 days) 2-yrs (104-weeks rats)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 12:	Exposure Route and Method	High	Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	Medium	The study used male and female F344/N rats. The test animal source (Harlan industries) and age at the start of the study (8-10 weeks old) were reported. Although initial animal body weights for the 16-day and 16-week studies were reported, the initial body weights for the 2-year study are not reported. Body weight data begin after 1 week of dosing.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Low	The number of animals per cage (5/cage) was reported. According to NTP guidelines for chronic/carcinogenicity studies, male rats should only be housed up to 3 per cage. Food and water were provided ad libiutm. Animal room environments (temperature, humidity, lighting were reported. The humidity ranged considerably from 15% to 84%. This deviates from NTP guidelines which state humidity should not be below 35% or above 65%. Similarly, the temperature range was reported to be between 60 and 86 degrees F. NTP guidelines state that the temperatures shall not be below 69 or above 75 degrees F, with minimal fluctuations. It is unclear whether these deviations had a significant impact on the study results.
	Metric 15:	Number of Animals per Group	Medium	The study methods specify 50/sex/group which is consistent with NTP guidelines for a chronic/carcinogenicity study, plus an extra 10/sex/group for an interim sacrifice.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	Animals were observed twice daily for morbidity and mortality. The outcome assessment was sensitive and appropriate for the outcome of interest.
	Metric 17:	Consistency of Outcome Assessment	High	The same protocol was applied to animals from all groups, and animals were consistently assessed for the outcomes of interest.
	Metric 18:	Sampling Adequacy	High	All animals were assessed for mortality.
	Metric 19:	Blinding of Assessors	N/A	Blinding is not necessary because this outcome of interest is either not subjective in nature, or blinding is not required (e.g., initial histopathology).
	Metric 20:	Negative Control Response	High	The negative control responses were reported and were adequate.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	High	No confounding variables in the test design and procedures were identified. The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP. There were no significant body weight changes that were suggestive of palatability issues.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Mortality (Clinical signs)
Reported Health Effect(s):	Survival
Duration:	Chronic (>91 days) 2-yrs (104-weeks rats)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 22:	Health Outcomes Unrelated to Exposure	Medium	Gavage-related deaths were noted in 4 controls (all males), 4 animals at 44 mg/kg-day (1 male, 3 females), and 4 at 88 mg/kg-day (all females). There were also 3 accidental deaths; details were only provided for one high-dose male that was inadvertently killed at the 66-week interim sacrifice. The small number of deaths not related to exposure is not expected to have a significant impact on the study results.
	Metric 23:	Data Presentation and Analysis	High	Survival data were statistically analyzed and the methods were reported and appropriate for the data set.
	Metric 24:	Reporting of Data	High	Survival curves were provided. A table also reports the total number of natural deaths, moribund kills, gavage deaths, accidental deaths, animals at interim sacrifices, and the number surviving to study termination. Survival data were statistically analyzed.

Overall Quality Determination High

Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Unspecified clinical observations (Clinical signs)
Reported Health Effect(s):	Clinical signs (clinical observations)
Duration:	Chronic (>91 days) 2-yrs (104 weeks- mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was identified definitively as tris(2-chloroethyl phosphate) CASRN 115-96-8. A structure was also provided.
	Metric 2:	Test Substance Source	High	The test substance was manufactured by Stauffer Chemical Company and obtained from the analytical chemistry laboratory, Midwest Research Institute. The lot number was provided.
	Metric 3:	Test Substance Purity	High	The test chemical purity was ~98%, and was both provided by the supplier and confirmed via analysis (NMR and elemental analysis) by the study laboratory.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	The study included concurrent negative vehicle (corn oil) controls and conditions were consistent with the animals that were treated.
	Metric 5:	Positive Controls	N/A	Positive controls are not required for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	Animals were distributed into weight classes, and assigned to cages using a random number table. Cages were then assigned to treatment and control groups using another random number table.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) were also stable for 21 days in the dark at room temperature or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks
	Metric 8:	Consistency of Exposure Administration	High	All animals were gavaged on the same schedule. Gavage volumes were reported and were consistent across groups.
	Metric 9:	Reporting of Doses/Concentrations	High	The doses were clearly reported. Animals were exposed to 0, 175, or 350 mg/kg, 5 days per week. Adjusted or time-weighted average doses in mg/kg-day were not provided, but can be determined using the data provided. Dose formulations were analyzed at approximately 8-week intervals by gas chromatography, and remained within 10% of the target concentrations throughout the course of the study. The target and measured concentrations in the solutions (mg/mL) were reported.
	Metric 10:	Exposure Frequency and Duration	High	Animals were dosed 5 days per week for two years. The exposure frequency and duration are consistent with NTP guidelines.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	Low	This 2-year study only included two treatment groups and a control. Although the authors justified the doses used, NTP guidelines specify using 3 treatment groups plus a control. Effects were observed at both doses and a NOAEL could not be determined.

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Health Outcome(s):	Unspecified clinical observations (Clinical signs)
Reported Health Effect(s):	Clinical signs (clinical observations)
Duration:	Chronic (>91 days) 2-yrs (104 weeks- mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 12:	Exposure Route and Method	High	Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	Medium	The study used male and female B6C3F1 mice. The test animal source (Harlan industries), age at the start of the study (8-9 weeks old) were reported. Although initial animal body weights for the 16-day and 16-week studies were reported, the initial body weights for the 2-year study are not reported. Body weight data begin after 1 week of dosing.This strain of mouse is known to have a high background incidence of hepatocellular adenomas in males. This strain may not be appropriate for identifying treatment-induced tumors of this type.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Low	The number of animals per cage (5/cage) was reported. According to NTP guidelines for chronic/carcinogenicity studies, male mice should be housed individually. Food and water were provided ad libiutm. Animal room environments (temperature, humidity, lighting were reported. The humidity ranged considerably from 15% to 84%. This deviates from NTP guidelines which state humidity should not be below 35% or above 65%.Similarly, the temperature range was reported to be between 60 and 86 degrees F. NTP guidelines state that the temperatures shall not be below 69 or above 75 degrees F, with minimal fluctuations. It is unclear whether these deviations had an impact on the study results.
	Metric 15:	Number of Animals per Group	Medium	The study methods specify 50/sex/group which is consistent with NTP guidelines for a chronic/carcinogenicity study. An extra 10/sex/group were added for an interim sacrifice at 66 weeks.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	A detailed description of histopathology and tumor assessment methods at terminal sacrifice was provided. The methods were sensitive to the outcomes of interest and adhered to NTP guidelines.
	Metric 17:	Consistency of Outcome Assessment	High	The same protocol was applied to animals from all groups, and animals were consistently assessed for the outcomes of interest.
	Metric 18:	Sampling Adequacy	High	A sufficient number of animals were sampled to assess carcinogenicity.

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Health Outcome(s):	Unspecified clinical observations (Clinical signs)
Reported Health Effect(s):	Clinical signs (clinical observations)
Duration:	Chronic (>91 days) 2-yrs (104 weeks- mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 19:	Blinding of Assessors	High	The study indicated that all histopathology data were sent to an independent quality assessment laboratory and slides, tissue counts, and histotechnique were evaluated. Additionally, all tumor diagnoses, all tissue sections of the brain, kidney, liver, spleen, and thyroid, and tissues randomly selected from 10% of the animals were re-examined by a pathologist. It was not specified whether these examinations were done blinded; however, in any instances where there was a disagreement in diagnosis, a Pathology Working Group chairperson, reviewed the slides without prior knowledge of the dose group, or the previous diagnoses.
	Metric 20:	Negative Control Response	Medium	52% of control male mice overall had hepatocellular adenomas or carcinomas. Due to the high background, the increased incidences in the treatment groups were not statistically significant. However, based on NTP historical control data for this strain (available on the NTP website), the background level is expected for this strain of mouse. Neoplastic incidences of control mice in other tissues were appropriate.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	High	No confounding variables in the test design and procedures were identified. The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP. There were no significant body weight changes that were suggestive of palatability issues.
	Metric 22:	Health Outcomes Unrelated to Exposure	Medium	Two control and two high-dose male mice, and one control female mouse, all predesignated for the interim sacrifice died before week 66. The causes of death were not specified. Overall, several gavage deaths of both sexes were also noted across groups. These deaths are not expected to have a significant impact on the study results.
	Metric 23:	Data Presentation and Analysis	High	Statistical methods for analyzing tumor data were described in detail and were appropriate. Statistical significance was shown where appropriate.
	Metric 24:	Reporting of Data	High	Cancer data were adequately reported including summary tables, and individual animal data.

Overall Quality Determination — High

Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Mortality
Reported Health Effect(s):	Survival
Duration:	Chronic (>91 days) 2-yrs (104 weeks- mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was identified definitively as tris(2-chloroethyl phosphate) CASRN 115-96-8. A structure was also provided.
	Metric 2:	Test Substance Source	High	The test substance was manufactured by Stauffer Chemical Company and obtained from the analytical chemistry laboratory, Midwest Research Institute. The lot number was provided.
	Metric 3:	Test Substance Purity	High	The test chemical purity was ~98%, and was both provided by the supplier and confirmed via analysis (NMR and elemental analysis) by the study laboratory.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	The study included concurrent negative vehicle (corn oil) controls and conditions were consistent with the animals that were treated.
	Metric 5:	Positive Controls	N/A	Positive controls are not required for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	Animals were distributed into weight classes, and assigned to cages using a random number table. Cages were then assigned to treatment and control groups using another random number table.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) were also stable for 21 days in the dark at room temperature or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks.
	Metric 8:	Consistency of Exposure Administration	High	All animals were gavaged on the same schedule. Gavage volumes were reported and were consistent across groups.
	Metric 9:	Reporting of Doses/Concentrations	High	The doses were clearly reported. Animals were exposed to 0, 175, or 350 mg/kg, 5 days per week. Adjusted or time-weighted average doses in mg/kg-day were not provided, but can be determined using the data provided. Dose formulations were analyzed at approximately 8-week intervals by gas chromatography, and remained within 10% of the target concentrations throughout the course of the study. The target and measured concentrations in the solutions (mg/mL) were reported.
	Metric 10:	Exposure Frequency and Duration	High	Animals were dosed 5 days per week for two years. The exposure frequency and duration are consistent with NTP guidelines.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	Low	This 2-year study only included two treatment groups and a control. Although the authors justified the doses used, NTP guidelines specify using 3 treatment groups plus a control. Effects were observed at both doses and a NOAEL could not be determined.

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Health Outcome(s):	Mortality
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Duration:	Chronic (>91 days) 2-yrs (104 weeks- mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 12:	Exposure Route and Method	High	Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	Medium	The study used male and female B6C3F1 mice. The test animal source (Harlan industries), age at the start of the study (8-9 weeks old) were reported. Although initial animal body weights for the 16-day and 16-week studies were reported, the initial body weights for the 2-year study are not reported. Body weight data begin after 1 week of dosing.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Low	The number of animals per cage (5/cage) was reported. According to NTP guidelines for chronic/carcinogenicity studies, male mice should be housed individually. Food and water were provided ad libitum. Animal room environments (temperature, humidity, lighting) were reported. The humidity ranged considerably from 15% to 84%. This deviates from NTP guidelines which state humidity should not be below 35% or above 65%.Similarly, the temperature range was reported to be between 60 and 86 degrees F. NTP guidelines state that the temperatures shall not be below 69 or above 75 degrees F, with minimal fluctuations. It is unclear whether these deviations had an impact on the study results.
	Metric 15:	Number of Animals per Group	Medium	The study methods specify 50/sex/group which is consistent with NTP guidelines for a chronic/carcinogenicity study. An extra 10/sex/group were added for an interim sacrifice at 66 weeks.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	Animals were observed twice daily for morbidity and mortality. The outcome assessment was sensitive and appropriate for the outcome of interest.
	Metric 17:	Consistency of Outcome Assessment	High	The same protocol was applied to animals from all groups, and animals were consistently assessed for the outcomes of interest.
	Metric 18:	Sampling Adequacy	High	All animals were assessed for mortality.
	Metric 19:	Blinding of Assessors	Medium	Blinding was not reported, but blinding is not necessary because this outcome of interest is either not subjective in nature, or blinding is not required for this endpoint (e.g., initial histopathology).
	Metric 20:	Negative Control Response	High	The survival of control animals was appropriate.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	High	No confounding variables in the test design and procedures were identified. The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP. There were no significant body weight changes that were suggestive of palatability issues.

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Health Outcome(s):	Mortality
Reported Health Effect(s):	Survival
Duration:	Chronic (>91 days) 2-yrs (104 weeks- mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 22:	Health Outcomes Unrelated to Exposure	Medium	Two control and two high-dose male mice, and one control female mouse, all predesignated for the interim sacrifice died before week 66. The causes of death were not specified. Overall, several gavage deaths of both sexes were also noted across groups. These deaths are not expected to have a significant impact on the study results.
	Metric 23:	Data Presentation and Analysis	High	Survival data were statistically analyzed and the methods were reported and appropriate for the data set.
	Metric 24:	Reporting of Data	High	Survival curves were provided. A table also reports the total number of natural deaths, moribund kills, gavage deaths, accidental deaths, animals at interim sacrifices, and the number surviving to study termination. Survival data were statistically analyzed.

Overall Quality Determination High

Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Gastrointestinal; Ocular/Sensory; Lung/Respiratory;
Reported Health Effect(s):	Gastrointestinal: Gross necropsy and histopathology (esophagus, gall bladder (mice only), large intestines (cecum, colon, rectum), salivary gland, small intestines (duodenum, ileum, jejunum), stomach, mesentery, tooth); Ocular/Sensory: Gross necropsy, histopathology (harderian gland); Lung/Respiratory: Gross necropsy, histopathology (lung, nose, trachea);
Duration:	Chronic (>91 days) 2-yrs (104 weeks- mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	All Outcomes: The test substance was identified definitively as tris(2-chloroethyl phosphate) CASRN 115-96-8. A structure was also provided.
	Metric 2:	Test Substance Source	High	All Outcomes: The test substance was manufactured by Stauffer Chemical Company and obtained from the analytical chemistry laboratory, Midwest Research Institute. The lot number was provided.
	Metric 3:	Test Substance Purity	High	All Outcomes: The test chemical purity was ~98%, and was both provided by the supplier and confirmed via analysis (NMR and elemental analysis) by the study laboratory.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	All Outcomes: The study included concurrent negative vehicle (corn oil) controls and conditions were consistent with the animals that were treated.
	Metric 5:	Positive Controls	N/A	All Outcomes: Positive controls are not required for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	All Outcomes: Animals were distributed into weight classes, and assigned to cages using a random number table. Cages were then assigned to treatment and control groups using another random number table.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	All Outcomes: Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) were also stable for 21 days in the dark at room temperature or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks
	Metric 8:	Consistency of Exposure Administration	High	All Outcomes: All animals were gavaged on the same schedule. Gavage volumes were reported and were consistent across groups.
	Metric 9:	Reporting of Doses/Concentrations	High	All Outcomes: The doses were clearly reported. Animals were exposed to 0, 175, or 350 mg/kg, 5 days per week. Adjusted or time-weighted average doses in mg/kg-day were not provided, but can be determined using the data provided. Dose formulations were analyzed at approximately 8-week intervals by gas chromatography, and remained within 10% of the target concentrations throughout the course of the study. The target and measured concentrations in the solutions (mg/mL) were reported.
	Metric 10:	Exposure Frequency and Duration	High	All Outcomes: Animals were dosed 5 days per week for two years. The exposure frequency and duration are consistent with NTP guidelines.

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Health Outcome(s):	Gastrointestinal; Ocular/Sensory; Lung/Respiratory;
Reported Health Effect(s):	Gastrointestinal: Gross necropsy and histopathology (esophagus, gall bladder (mice only), large intestines (cecum, colon, rectum), salivary gland, small intestines (duodenum, ileum, jejunum), stomach, mesentery, tooth); Ocular/Sensory: Gross necropsy, histopathology (harderian gland); Lung/Respiratory: Gross necropsy, histopathology (lung, nose, trachea);
Duration:	Chronic (>91 days) 2-yrs (104 weeks- mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	Low	All Outcomes: This 2-year study only included two treatment groups and a control. Although the authors justified the doses used, NTP guidelines specify using 3 treatment groups plus a control. Effects were observed at both doses and a NOAEL could not be determined.
	Metric 12:	Exposure Route and Method	High	All Outcomes: Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	Medium	All Outcomes: The study used male and female B6C3F1 mice. The test animal source (Harlan industries), age at the start of the study (8-9 weeks old) were reported. Although initial animal body weights for the 16-day and 16-week studies were reported, the initial body weights for the 2-year study are not reported. Body weight data begin after 1 week of dosing.

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Health Outcome(s):	Gastrointestinal; Ocular/Sensory; Lung/Respiratory;
Reported Health Effect(s):	Gastrointestinal: Gross necropsy and histopathology (esophagus, gall bladder (mice only), large intestines (cecum, colon, rectum), salivary gland, small intestines (duodenum, ileum, jejunum), stomach, mesentery, tooth); Ocular/Sensory: Gross necropsy, histopathology (harderian gland); Lung/Respiratory: Gross necropsy, histopathology (lung, nose, trachea);
Duration:	Chronic (>91 days) 2-yrs (104 weeks- mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Low	Gastrointestinal: The number of animals per cage (5/cage) was reported. According to NTP guidelines for chronic/carcinogenicity studies, male mice should be housed individually. Food and water were provided ad libiutm. Animal room environments (temperature, humidity, lighting were reported. The humidity ranged considerably from 15% to 84%. This deviates from NTP guidelines which state humidity should not be below 35% or above 65%.Similarly, the temperature range was reported to be between 60 and 86 degrees F. NTP guidelines state that the temperatures shall not be below 69 or above 75 degrees F, with minimal fluctuations. It is unclear whether these deviations had an impact on the study results.; Ocular/Sensory: The number of animals per cage (5/cage) was reported. According to NTP guidelines for chronic/carcinogenicity studies, male mice should be housed individually. Food and water were provided ad libitum. Animal room environments (temperature, humidity, lighting) were reported. The humidity ranged considerably from 15% to 84%. This deviates from NTP guidelines which state humidity should not be below 35% or above 65%.Similarly, the temperature range was reported to be between 60 and 86 degrees F. NTP guidelines state that the temperatures shall not be below 69 or above 75 degrees F, with minimal fluctuations. It is unclear whether these deviations had an impact on the study results.; Lung/Respiratory: The number of animals per cage (5/cage) was reported. According to NTP guidelines for chronic/carcinogenicity studies, male mice should be housed individually. Food and water were provided ad libiutm. Animal room environments (temperature, humidity, lighting were reported. The humidity ranged considerably from 15% to 84%. This deviates from NTP guidelines which state humidity should not be below 35% or above 65%.Similarly, the temperature range was reported to be between 60 and 86 degrees F. NTP guidelines state that the temperatures shall not be below 69 or above 75 degrees F, with minimal fluctuations. It is unclear whether these deviations had an impact on the study results.
	Metric 15:	Number of Animals per Group	Medium	All Outcomes: The study methods specify 50/sex/group which is consistent with NTP guidelines for a chronic/carcinogenicity study. An extra 10/sex/group were added for an interim sacrifice at 66 weeks.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	All Outcomes: The study included interim sacrifices (10/sex/group) at 66-weeks. These animals were subjected to gross necropsy and histopathology. Histopathological examination of non-neoplastic lesions was also conducted in the main group of animals at the terminal sacrifice. A detailed description of histopathological procedures was provided and the methods were sensitive to the outcomes of interest.
	Metric 17:	Consistency of Outcome Assessment	High	All Outcomes: Details of the outcome assessment protocol were reported and the outcomes were consistently assessed for the groups that were examined.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Gastrointestinal; Ocular/Sensory; Lung/Respiratory;
Reported Health Effect(s):	Gastrointestinal: Gross necropsy and histopathology (esophagus, gall bladder (mice only), large intestines (cecum, colon, rectum), salivary gland, small intestines (duodenum, ileum, jejunum), stomach, mesentery, tooth); Ocular/Sensory: Gross necropsy, histopathology (harderian gland); Lung/Respiratory: Gross necropsy, histopathology (lung, nose, trachea);
Duration:	Chronic (>91 days) 2-yrs (104 weeks- mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 18:	Sampling Adequacy	High	Gastrointestinal: At both the 66-week and 104-week terminal sacrifices, histopathological analysis was conducted on tissues from the control and high-dose animals, except for tissues from the harderian gland, kidney, liver, lung, and stomach (this outcome), which were also examined from low-dose animals.; Ocular/Sensory: At both the 66-week and 104-week terminal sacrifices, histopathological analysis was conducted on tissues from the control and high-dose animals, except for tissues from the harderian gland, kidney, liver, lung, and stomach, which were also examined from low-dose animals.; Lung/Respiratory: At both the 66-week and 104-week terminal sacrifices, histopathological analysis was conducted on tissues from the control and high-dose animals, except for tissues from the harderian gland, kidney, liver, lung, and stomach, which were also examined from low-dose animals.
	Metric 19:	Blinding of Assessors	Medium	All Outcomes: The study indicated that all histopathology data were sent to an independent quality assessment laboratory and slides, tissue counts, and histotechnique were evaluated. Blinding was not reported but is not required for initial histopathology.
	Metric 20:	Negative Control Response	Medium	All Outcomes: Non-neoplastic control data from the main group animals were reported and the incidences were appropriate. Histopathology results from the 66-interim sacrifice were not reported. Gross pathological control responses were not reported.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	High	All Outcomes: No confounding variables in the test design and procedures were identified. The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP. There were no significant body weight changes that were suggestive of palatability issues.
	Metric 22:	Health Outcomes Unrelated to Exposure	Medium	All Outcomes: Two control and two high-dose male mice, and one control female mouse, all predesignated for the interim sacrifice died before week 66. The causes of death were not specified. Overall, several gavage deaths of both sexes were also noted across groups. These deaths are not expected to have a significant impact on the study results.
	Metric 23:	Data Presentation and Analysis	High	All Outcomes: Statistical methods were adequately described and were appropriate for the datasets. Statistical significance was shown where appropriate.
	Metric 24:	Reporting of Data	Low	All Outcomes: Incidence data of non-neoplastic lesions from the main group animals were adequately reported, although measures of severity were not included. Histopathology results from the 66-week interim sacrifice were not reported, and no results for gross examinations were reported.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Gastrointestinal; Ocular/Sensory; Lung/Respiratory;
Reported Health Effect(s):	Gastrointestinal: Gross necropsy and histopathology (esophagus, gall bladder (mice only), large intestines (cecum, colon, rectum), salivary gland, small intestines (duodenum, ileum, jejunum), stomach, mesentery, tooth); Ocular/Sensory: Gross necropsy, histopathology (harderian gland); Lung/Respiratory: Gross necropsy, histopathology (lung, nose, trachea);
Duration:	Chronic (>91 days) 2-yrs (104 weeks- mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric	Rating	Comments
Overall Quality Determination		**High**	

Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Nutritional/Metabolic (Clinical signs); Neurological/Behavioral (Clinical signs);
Reported Health Effect(s):	Nutritional/Metabolic (Clinical signs): Body weights; Neurological/Behavioral (Clinical signs): Serum cholinesterase activity (special study 16-day and 16-week studies, and as part of serum chemistry in 2-yr study), brain weights, gross necropsy, histopathology (brain);
Duration:	Chronic (>91 days) 2-yrs (104-weeks rats)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	All Outcomes: The test substance was identified definitively as tris(2-chloroethyl phosphate) CASRN 115-96-8. A structure was also provided.
	Metric 2:	Test Substance Source	High	All Outcomes: The test substance was manufactured by Stauffer Chemical Company and obtained from the analytical chemistry laboratory, Midwest Research Institute. The lot number was provided.
	Metric 3:	Test Substance Purity	High	All Outcomes: The test chemical purity was ~98%, and was both provided by the supplier and confirmed via analysis (NMR and elemental analysis) by the study laboratory.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	All Outcomes: The study included concurrent negative vehicle (corn oil) controls and conditions were consistent with the animals that were treated.
	Metric 5:	Positive Controls	N/A	All Outcomes: Positive controls are not required for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	All Outcomes: Animals were distributed into weight classes, and assigned to cages using a random number table. Cages were then assigned to treatment and control groups using another random number table.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	All Outcomes: Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) were also stable for 21 days in the dark at room temperature or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks
	Metric 8:	Consistency of Exposure Administration	High	All Outcomes: All animals were gavaged on the same schedule. Gavage volumes were reported and were consistent across groups.
	Metric 9:	Reporting of Doses/Concentrations	High	All Outcomes: Animals were dosed with 0, 44, or 88 mg/kg/day, 5 days per week. Doses were selected based on a subchronic study. Dose formulations were analyzed at approximately 8-week intervals by gas chromatography, and remained within 10% of the target concentrations throughout the course of the study. The target and measured concentrations in the solutions (mg/mL) were reported.
	Metric 10:	Exposure Frequency and Duration	High	All Outcomes: Animals were dosed 5 days per week for two years. The exposure frequency and duration are consistent with NTP guidelines.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	Low	All Outcomes: This 2-year study only included two treatment groups and a control. Although the authors justified the doses used, NTP guidelines specify using 3 treatment groups plus a control. Effects were observed at both doses and a NOAEL could not be determined.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Nutritional/Metabolic (Clinical signs); Neurological/Behavioral (Clinical signs);
Reported Health Effect(s):	Nutritional/Metabolic (Clinical signs): Body weights; Neurological/Behavioral (Clinical signs): Serum cholinesterase activity (special study 16-day and 16-week studies, and as part of serum chemistry in 2-yr study), brain weights, gross necropsy, histopathology (brain);
Duration:	Chronic (>91 days) 2-yrs (104-weeks rats)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 12:	Exposure Route and Method	High	All Outcomes: Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	Medium	All Outcomes: The study used male and female F344/N rats. The test animal source (Harlan industries) and age at the start of the study (8-10 weeks old) were reported. Although initial animal body weights for the 16-day and 16-week studies were reported, the initial body weights for the 2-year study are not reported. Body weight data begin after 1 week of dosing.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Low	All Outcomes: The number of animals per cage (5/cage) was reported. According to NTP guidelines for chronic/carcinogenicity studies, male rats should only be housed up to 3 per cage. Food and water were provided ad libiutm. Animal room environments (temperature, humidity, lighting were reported. The humidity ranged considerably from 15% to 84%. This deviates from NTP guidelines which state humidity should not be below 35% or above 65%. Similarly, the temperature range was reported to be between 60 and 86 degrees F. NTP guidelines state that the temperatures shall not be below 69 or above 75 degrees F, with minimal fluctuations. It is unclear whether these deviations had a significant impact on the study results.
	Metric 15:	Number of Animals per Group	Medium	Nutritional/Metabolic (Clinical signs): The study methods specify 50/sex/group which is consistent with NTP guidelines for a chronic/carcinogenicity study, plus an extra 10/sex/group for an interim sacrifice.; Neurological/Behavioral (Clinical signs): The study methods specify 50/sex/group which is consistent with NTP guidelines for a chronic/carcinogenicity study. An extra 10/sex/group were added for an interim sacrifice at 66 weeks.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	Nutritional/Metabolic (Clinical signs): The outcome assessment methodology was described and was sensitive to the outcome of interest. Body weights were measured initially, then weekly through week 13, and monthly after week 13. Weights were recorded at 3-4 week intervals for the last 3 months.; Neurological/Behavioral (Clinical signs): A limited number of organs were weighed (including the brain) at the 66-week interim sacrifice, and animals were subjected to gross necropsy and detailed histopathology. Only histopathology was conducted at the 2-yr terminal sacrifice. The methods for these endpoints were described and were sensitive to the outcomes of interest.
	Metric 17:	Consistency of Outcome Assessment	High	All Outcomes: The same protocol was applied to animals from all groups, and animals were consistently assessed for the outcomes of interest.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Nutritional/Metabolic (Clinical signs); Neurological/Behavioral (Clinical signs);
Reported Health Effect(s):	Nutritional/Metabolic (Clinical signs): Body weights; Neurological/Behavioral (Clinical signs): Serum cholinesterase activity (special study 16-day and 16-week studies, and as part of serum chemistry in 2-yr study), brain weights, gross necropsy, histopathology (brain);
Duration:	Chronic (>91 days) 2-yrs (104-weeks rats)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 18:	Sampling Adequacy	Medium	Nutritional/Metabolic (Clinical signs): The number of animals sampled (n) is not explicitly shown on the growth curve figures or body weight tables. The table does report the number of surviving animals at each timepoint. It is assumed the body weights were measured for all of the surviving animals shown.; Neurological/Behavioral (Clinical signs): Sampling was adequate for all outcomes. Organs were weighed from all surviving animals at the interim sacrifice, and histopathology was purportedly conducted on all animals from all groups both at the interim and terminal sacrifices, but interim histopathology data were not reported, so sampling cannot be verified.
	Metric 19:	Blinding of Assessors	N/A	All Outcomes: Blinding is not necessary because this outcome of interest is either not subjective in nature, or blinding is not required (e.g., initial histopathology).
	Metric 20:	Negative Control Response	High	Nutritional/Metabolic (Clinical signs): The negative control responses were reported and were adequate.; Neurological/Behavioral (Clinical signs): The organ weights and non-neoplastic lesions incidences of negative controls (main group animals) were reported and were adequate.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	High	All Outcomes: No confounding variables in the test design and procedures were identified. The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP. There were no significant body weight changes that were suggestive of palatability issues.
	Metric 22:	Health Outcomes Unrelated to Exposure	Medium	All Outcomes: Gavage-related deaths were noted in 4 controls (all males), 4 animals at 44 mg/kg-day (1 male, 3 females), and 4 at 88 mg/kg-day (all females). There were also 3 accidental deaths; details were only provided for one high-dose male that was inadvertently killed at the 66-week interim sacrifice. The small number of deaths not related to exposure is not expected to have a significant impact on the study results.
	Metric 23:	Data Presentation and Analysis	High	Nutritional/Metabolic (Clinical signs): Statistical methods were adequately described and were appropriate for the datasets. Statistical significance was shown where appropriate.; Neurological/Behavioral (Clinical signs): Statistical methods were adequately described and were appropriate for the datasets. Statistical significance was shown where appropriate and quantitative data/incidences were provided for the main group animals allowing for independent statistical analysis.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Nutritional/Metabolic (Clinical signs); Neurological/Behavioral (Clinical signs);
Reported Health Effect(s):	Nutritional/Metabolic (Clinical signs): Body weights; Neurological/Behavioral (Clinical signs): Serum cholinesterase activity (special study 16-day and 16-week studies, and as part of serum chemistry in 2-yr study), brain weights, gross necropsy, histopathology (brain);
Duration:	Chronic (>91 days) 2-yrs (104-weeks rats)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric	Rating	Comments
	Metric 24: Reporting of Data	Low	Nutritional/Metabolic (Clinical signs): Groth curves and body weight tables were provided. The data were presented as means in the absence of measures of variance. The study indicates that initial body weights were measured, but the body weight data tables start after 1 week of exposure.; Neurological/Behavioral (Clinical signs): Organ weight data from the 66-week interim sacrifice were presented quantitatively and reported as means ± SEM. Incidence data of non-neoplastic lesions from the main group animals at terminal sacrifice were adequately reported, although measures of severity were not included. The methods suggest that histopathology was also conducted on animals sacrificed at 66 weeks, but no quantitative data were provided. A brief description of lesions in the brain was provided in the text but did not distinguish by group and significance was not reported.

Overall Quality Determination High

Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Hepatic/Liver (Clinical signs); Renal/Kidney (Clinical signs);
Reported Health Effect(s):	Hepatic/Liver (Clinical signs): Liver weights, gross necropsy, histopathology, clinical chemistry (serum glucose, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, sorbitol dehydrogenase, cholesterol); Renal/Kidney (Clinical signs): Serum chemistry (BUN, creatinine), organ weights, gross necropsy, histopathology (kidney, bladder);
Duration:	Chronic (>91 days) 2-yrs (104-weeks rats)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	All Outcomes: The test substance was identified definitively as tris(2-chloroethyl phosphate) CASRN 115-96-8. A structure was also provided.
	Metric 2:	Test Substance Source	High	All Outcomes: The test substance was manufactured by Stauffer Chemical Company and obtained from the analytical chemistry laboratory, Midwest Research Institute. The lot number was provided.
	Metric 3:	Test Substance Purity	High	All Outcomes: The test chemical purity was ~98%, and was both provided by the supplier and confirmed via analysis (NMR and elemental analysis) by the study laboratory.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	All Outcomes: The study included concurrent negative vehicle (corn oil) controls and conditions were consistent with the animals that were treated.
	Metric 5:	Positive Controls	N/A	All Outcomes: Positive controls are not required for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	All Outcomes: Animals were distributed into weight classes, and assigned to cages using a random number table. Cages were then assigned to treatment and control groups using another random number table.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	All Outcomes: Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) were also stable for 21 days in the dark at room temperature or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks
	Metric 8:	Consistency of Exposure Administration	High	All Outcomes: All animals were gavaged on the same schedule. Gavage volumes were reported and were consistent across groups.
	Metric 9:	Reporting of Doses/Concentrations	High	All Outcomes: Animals were dosed with 0, 44, or 88 mg/kg/day, 5 days per week. Doses were selected based on a subchronic study. Dose formulations were analyzed at approximately 8-week intervals by gas chromatography, and remained within 10% of the target concentrations throughout the course of the study. The target and measured concentrations in the solutions (mg/mL) were reported.
	Metric 10:	Exposure Frequency and Duration	High	All Outcomes: Animals were dosed 5 days per week for two years. The exposure frequency and duration are consistent with NTP guidelines.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Hepatic/Liver (Clinical signs); Renal/Kidney (Clinical signs);
Reported Health Effect(s):	Hepatic/Liver (Clinical signs): Liver weights, gross necropsy, histopathology, clinical chemistry (serum glucose, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, sorbitol dehydrogenase, cholesterol); Renal/Kidney (Clinical signs): Serum chemistry (BUN, creatinine), organ weights, gross necropsy, histopathology (kidney, bladder);
Duration:	Chronic (>91 days) 2-yrs (104-weeks rats)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	Low	All Outcomes: This 2-year study only included two treatment groups and a control. Although the authors justified the doses used, NTP guidelines specify using 3 treatment groups plus a control. Effects were observed at both doses and a NOAEL could not be determined.
	Metric 12:	Exposure Route and Method	High	All Outcomes: Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	Medium	All Outcomes: The study used male and female F344/N rats. The test animal source (Harlan industries) and age at the start of the study (8-10 weeks old) were reported. Although initial animal body weights for the 16-day and 16-week studies were reported, the initial body weights for the 2-year study are not reported. Body weight data begin after 1 week of dosing.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Low	All Outcomes: The number of animals per cage (5/cage) was reported. According to NTP guidelines for chronic/carcinogenicity studies, male rats should only be housed up to 3 per cage. Food and water were provided ad libiutm. Animal room environments (temperature, humidity, lighting were reported. The humidity ranged considerably from 15% to 84%. This deviates from NTP guidelines which state humidity should not be below 35% or above 65%. Similarly, the temperature range was reported to be between 60 and 86 degrees F. NTP guidelines state that the temperatures shall not be below 69 or above 75 degrees F, with minimal fluctuations. It is unclear whether these deviations had a significant impact on the study results.
	Metric 15:	Number of Animals per Group	Medium	All Outcomes: The study methods specify 50/sex/group which is consistent with NTP guidelines for a chronic/carcinogenicity study. An extra 10/sex/group were added for an interim sacrifice at 66 weeks.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	Hepatic/Liver (Clinical signs): Serum chemistry measurements and a limited number of organs were weighed at the 66-week interim sacrifice, and animals were subjected to gross necropsy and detailed histopathology. Only histopathology was conducted at the 2-yr terminal sacrifice. The methods for these endpoints were described and were sensitive to the outcomes of interest.; Renal/Kidney (Clinical signs): Serum chemistry measurements and a limited number of organs were weighed at the 66-week interim sacrifice, and these animals were subjected to gross necropsy and detailed histopathology. Only histopathology was conducted at the 2-yr terminal sacrifice. The methods for these endpoints were described and were sensitive to the outcomes of interest.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Hepatic/Liver (Clinical signs); Renal/Kidney (Clinical signs);
Reported Health Effect(s):	Hepatic/Liver (Clinical signs): Liver weights, gross necropsy, histopathology, clinical chemistry (serum glucose, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, sorbitol dehydrogenase, cholesterol); Renal/Kidney (Clinical signs): Serum chemistry (BUN, creatinine), organ weights, gross necropsy, histopathology (kidney, bladder);
Duration:	Chronic (>91 days) 2-yrs (104-weeks rats)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 17:	Consistency of Outcome Assessment	High	All Outcomes: The same protocol was applied to animals from all groups, and animals were consistently assessed for the outcomes of interest.
	Metric 18:	Sampling Adequacy	Medium	Hepatic/Liver (Clinical signs): Sampling was adequate for most outcomes. Organs were weighed from all surviving animals at the interim sacrifice, and histopathology was purportedly conducted on all animals from all groups both at the interim and terminal sacrifices, but interim serum chemistry and histopathology data were not reported, so sampling cannot be verified.; Renal/Kidney (Clinical signs): Sampling was adequate for all outcomes. Organs were weighed from all surviving animals at the interim sacrifice, and histopathology was purportedly conducted on all animals from all groups both at the interim and terminal sacrifices. Serum chemistry and interim histopathology data were not reported, so sampling cannot be verified.
	Metric 19:	Blinding of Assessors	N/A	All Outcomes: Blinding is not necessary because this outcome of interest is either not subjective in nature, or blinding is not required (e.g., initial histopathology).
	Metric 20:	Negative Control Response	Medium	Hepatic/Liver (Clinical signs): The organ weights and non-neoplastic lesions incidences of negative controls (main group animals) were reported and were adequate. The negative control responses for serum chemistry and for histopathology at the 66-week interim sacrifice were not provided.; Renal/Kidney (Clinical signs): The organ weights and non-neoplastic lesions incidences of negative controls (main group animals) were reported and were adequate. The adequacy of biological responses of the negative controls for serum chemistry endpoints or for histopathology at the 66-week interim sacrifice cannot be determined because quantitative data were not provided.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	High	All Outcomes: No confounding variables in the test design and procedures were identified. The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP. There were no significant body weight changes that were suggestive of palatability issues.
	Metric 22:	Health Outcomes Unrelated to Exposure	Medium	All Outcomes: Gavage-related deaths were noted in 4 controls (all males), 4 animals at 44 mg/kg-day (1 male, 3 females), and 4 at 88 mg/kg-day (all females). There were also 3 accidental deaths; details were only provided for one high-dose male that was inadvertently killed at the 66-week interim sacrifice. The small number of deaths not related to exposure is not expected to have a significant impact on the study results.
	Metric 23:	Data Presentation and Analysis	High	All Outcomes: Statistical methods were adequately described and were appropriate for the datasets. Statistical significance was shown where appropriate and quantitative data/incidences were provided for the main group animals allowing for independent statistical analysis.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Hepatic/Liver (Clinical signs); Renal/Kidney (Clinical signs);
Reported Health Effect(s):	Hepatic/Liver (Clinical signs): Liver weights, gross necropsy, histopathology, clinical chemistry (serum glucose, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, sorbitol dehydrogenase, cholesterol); Renal/Kidney (Clinical signs): Serum chemistry (BUN, creatinine), organ weights, gross necropsy, histopathology (kidney, bladder);
Duration:	Chronic (>91 days) 2-yrs (104-weeks rats)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric	Rating	Comments
	Metric 24: Reporting of Data	Low	Hepatic/Liver (Clinical signs): Organ weight data from the 66-week interim sacrifice were presented quantitatively and reported as means ± SEM. Incidence data of non-neoplastic lesions from the main group animals at terminal sacrifice were adequately reported, although measures of severity were not included. The methods suggest that histopathology was also conducted on animals sacrificed at 66 weeks, but no quantitative data were provided. The text only indicated that observed lesions (other than those in the brain) were considered incidental and unrelated to treatment. Exposure-related serum chemistry results were described in the text; significance was noted.; Renal/Kidney (Clinical signs): Organ weight data from the 66-week interim sacrifice were presented quantitatively and reported as means ± SEM. Incidence data of non-neoplastic lesions from the main group animals at terminal sacrifice were adequately reported, although measures of severity were not included. The methods suggest that histopathology was also conducted on animals sacrificed at 66 weeks, but no quantitative data were provided. The text only indicated that observed lesions (other than those in the brain) were considered incidental and unrelated to treatment. Results for all serum chemistry endpoints were not reported, only a single change for a liver enzyme was mentioned in the text.

Overall Quality Determination High

Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Immune/Hematological; Reproductive/Developmental; Cardiovascular; Gastrointestinal; Thyroid; Skin/Connective Tissue; Musculoskeletal; Ocular/Sensory; Lung/Respiratory; Endocrine (Endocrine);
Reported Health Effect(s):	Immune/Hematological: Hematology (hematocrit, hemoglobin, erythrocytes, leukocytes with differential, MCV, MCH, MCHC, and reticulocyte count), thymus weights, gross pathology, histopathology (spleen, thymus, lymph nodes (mandibular and mesenteric), bone marrow); Reproductive/Developmental: Gross necropsy and histopathology (clitoral gland, epididymis, mammary glands, ovary, preputial gland, prostate, seminal vesicle, testis, uterus); Cardiovascular: Heart organ weights, gross necropsy, histopathology (heart); Gastrointestinal: Gross necropsy and histopathology (esophagus, gall bladder (mice only), large intestines (cecum, colon, rectum), salivary gland, small intestines (duodenum, ileum, jejunum), stomach, mesentery, tooth); Thyroid: Gross necropsy and histopathology (thyroid); Skin/Connective Tissue: Gross necropsy, histopathology (skin); Musculoskeletal: Gross necropsy, histopathology (skeletal muscle, bone); Ocular/Sensory: Gross necropsy, histopathology (harderian gland); Lung/Respiratory: Gross necropsy, histopathology (lung, nose, trachea); Endocrine (Endocrine): Gross necropsy and histopathology (pancreas, adrenal glands, pituitary glands, parathyroid);
Duration:	Chronic (>91 days) 2-yrs (104-weeks rats)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	All Outcomes: The test substance was identified definitively as tris(2-chloroethyl phosphate) CASRN 115-96-8. A structure was also provided.
	Metric 2:	Test Substance Source	High	All Outcomes: The test substance was manufactured by Stauffer Chemical Company and obtained from the analytical chemistry laboratory, Midwest Research Institute. The lot number was provided.
	Metric 3:	Test Substance Purity	High	All Outcomes: The test chemical purity was ~98%, and was both provided by the supplier and confirmed via analysis (NMR and elemental analysis) by the study laboratory.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	All Outcomes: The study included concurrent negative vehicle (corn oil) controls and conditions were consistent with the animals that were treated.
	Metric 5:	Positive Controls	N/A	All Outcomes: Positive controls are not required for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	All Outcomes: Animals were distributed into weight classes, and assigned to cages using a random number table. Cages were then assigned to treatment and control groups using another random number table.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	All Outcomes: Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) were also stable for 21 days in the dark at room temperature or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks
	Metric 8:	Consistency of Exposure Administration	High	All Outcomes: All animals were gavaged on the same schedule. Gavage volumes were reported and were consistent across groups.
	Metric 9:	Reporting of Doses/Concentrations	High	All Outcomes: Animals were dosed with 0, 44, or 88 mg/kg/day, 5 days per week. Doses were selected based on a subchronic study. Dose formulations were analyzed at approximately 8-week intervals by gas chromatography, and remained within 10% of the target concentrations throughout the course of the study. The target and measured concentrations in the solutions (mg/mL) were reported.

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Reported Health Effect(s):	Immune/Hematological: Hematology (hematocrit, hemoglobin, erythrocytes, leukocytes with differential, MCV, MCH, MCHC, and reticulocyte count), thymus weights, gross pathology, histopathology (spleen, thymus, lymph nodes (mandibular and mesenteric), bone marrow); Reproductive/Developmental: Gross necropsy and histopathology (clitoral gland, epididymis, mammary glands, ovary, preputial gland, prostate, seminal vesicle, testis, uterus); Cardiovascular: Heart organ weights, gross necropsy, histopathology (heart); Gastrointestinal: Gross necropsy and histopathology (esophagus, gall bladder (mice only), large intestines (cecum, colon, rectum), salivary gland, small intestines (duodenum, ileum, jejunum), stomach, mesentery, tooth); Thyroid: Gross necropsy and histopathology (thyroid); Skin/Connective Tissue: Gross necropsy, histopathology (skin); Musculoskeletal: Gross necropsy, histopathology (skeletal muscle, bone); Ocular/Sensory: Gross necropsy, histopathology (harderian gland); Lung/Respiratory: Gross necropsy, histopathology (lung, nose, trachea); Endocrine (Endocrine): Gross necropsy and histopathology (pancreas, adrenal glands, pituitary glands, parathyroid);
Duration:	Chronic (>91 days) 2-yrs (104-weeks rats)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 10:	Exposure Frequency and Duration	High	All Outcomes: Animals were dosed 5 days per week for two years. The exposure frequency and duration are consistent with NTP guidelines.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	Low	All Outcomes: This 2-year study only included two treatment groups and a control. Although the authors justified the doses used, NTP guidelines specify using 3 treatment groups plus a control. Effects were observed at both doses and a NOAEL could not be determined.
	Metric 12:	Exposure Route and Method	High	All Outcomes: Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	Medium	All Outcomes: The study used male and female F344/N rats. The test animal source (Harlan industries) and age at the start of the study (8-10 weeks old) were reported. Although initial animal body weights for the 16-day and 16-week studies were reported, the initial body weights for the 2-year study are not reported. Body weight data begin after 1 week of dosing.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Low	All Outcomes: The number of animals per cage (5/cage) was reported. According to NTP guidelines for chronic/carcinogenicity studies, male rats should only be housed up to 3 per cage. Food and water were provided ad libiutm. Animal room environments (temperature, humidity, lighting were reported. The humidity ranged considerably from 15% to 84%. This deviates from NTP guidelines which state humidity should not be below 35% or above 65%. Similarly, the temperature range was reported to be between 60 and 86 degrees F. NTP guidelines state that the temperatures shall not be below 69 or above 75 degrees F, with minimal fluctuations. It is unclear whether these deviations had a significant impact on the study results.
	Metric 15:	Number of Animals per Group	Medium	All Outcomes: The study methods specify 50/sex/group which is consistent with NTP guidelines for a chronic/carcinogenicity study. An extra 10/sex/group were added for an interim sacrifice at 66 weeks.
Domain 5: Outcome Assessment				

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Reported Health Effect(s):	Immune/Hematological: Hematology (hematocrit, hemoglobin, erythrocytes, leukocytes with differential, MCV, MCH, MCHC, and reticulocyte count), thymus weights, gross pathology, histopathology (spleen, thymus, lymph nodes (mandibular and mesenteric), bone marrow); Reproductive/Developmental: Gross necropsy and histopathology (clitoral gland, epididymis, mammary glands, ovary, preputial gland, prostate, seminal vesicle, testis, uterus); Cardiovascular: Heart organ weights, gross necropsy, histopathology (heart); Gastrointestinal: Gross necropsy and histopathology (esophagus, gall bladder (mice only), large intestines (cecum, colon, rectum), salivary gland, small intestines (duodenum, ileum, jejunum), stomach, mesentery, tooth); Thyroid: Gross necropsy and histopathology (thyroid); Skin/Connective Tissue: Gross necropsy, histopathology (skin); Musculoskeletal: Gross necropsy, histopathology (skeletal muscle, bone); Ocular/Sensory: Gross necropsy, histopathology (harderian gland); Lung/Respiratory: Gross necropsy, histopathology (lung, nose, trachea); Endocrine (Endocrine): Gross necropsy and histopathology (pancreas, adrenal glands, pituitary glands, parathyroid);
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Domain	Metric		Rating	Comments
	Metric 16:	Outcome Assessment Methodology	High	Immune/Hematological: Hematological analysis was done on animals from the 66-week interim sacrifice, and these animals were subjected to gross necropsy and detailed histopathology. Only histopathology was conducted at the 2-yr terminal sacrifice. The methods for these endpoints were described and were sensitive to the outcomes of interest.; Reproductive/Developmental: Animals from the 66-week interim sacrifice were subjected to gross necropsy and detailed histopathology. Only histopathology was conducted at the 2-yr terminal sacrifice. The methods for these endpoints were described and were sensitive to the outcomes of interest.; Cardiovascular: Animals from the 66-week interim sacrifice were subjected to gross necropsy and detailed histopathology. Only histopathology was conducted at the 2-yr terminal sacrifice. The methods for these endpoints were described and were sensitive to the outcomes of interest.; Gastrointestinal: Animals from the 66-week interim sacrifice were subjected to gross necropsy and detailed histopathology. Only histopathology was conducted at the 2-yr terminal sacrifice. The methods for these endpoints were described and were sensitive to the outcomes of interest.; Thyroid: Animals from the 66-week interim sacrifice were subjected to gross necropsy and detailed histopathology. Only histopathology was conducted at the 2-yr terminal sacrifice. The methods for these endpoints were described and were sensitive to the outcomes of interest.; Skin/Connective Tissue: Animals from the 66-week interim sacrifice were subjected to gross necropsy and detailed histopathology. Only histopathology was conducted at the 2-yr terminal sacrifice. The methods for these endpoints were described and were sensitive to the outcomes of interest.; Musculoskeletal: Animals from the 66-week interim sacrifice were subjected to gross necropsy and detailed histopathology. Only histopathology was conducted at the 2-yr terminal sacrifice. The methods for these endpoints were described and were sensitive to the outcomes of interest.; Ocular/Sensory: Animals from the 66-week interim sacrifice were subjected to gross necropsy and detailed histopathology. Only histopathology was conducted at the 2-yr terminal sacrifice. The methods for these endpoints were described and were sensitive to the outcomes of interest.; Lung/Respiratory: Animals from the 66-week interim sacrifice were subjected to gross necropsy and detailed histopathology. Only histopathology was conducted at the 2-yr terminal sacrifice. The methods for these endpoints were described and were sensitive to the outcomes of interest.; Endocrine (Endocrine): Animals from the 66-week interim sacrifice were subjected to gross necropsy and detailed histopathology. Only histopathology was conducted at the 2-yr terminal sacrifice. The methods for these endpoints were described and were sensitive to the outcomes of interest.

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Domain	Metric		Rating	Comments
	Metric 17:	Consistency of Outcome Assessment	High	All Outcomes: The same protocol was applied to animals from all groups, and animals were consistently assessed for the outcomes of interest.

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Domain	Metric	Rating	Comments
	Metric 18: Sampling Adequacy	Medium	Immune/Hematological: Histopathology was purportedly conducted on all animals from all groups both at the interim and terminal sacrifices, but interim histopathology data were not reported, so sampling cannot be verified. Similarly, sampling cannot be verified for hematology results which were qualitatively reported as being negative in the text.; Reproductive/Developmental: Histopathology was purportedly conducted on all animals from all groups both at the interim and terminal sacrifices, but interim histopathology data were not reported, so sampling cannot be verified. Sampling was adequate for the terminal histopathology.; Cardiovascular: Histopathology was purportedly conducted on all animals from all groups both at the interim and terminal sacrifices, but interim histopathology data were not reported, so sampling cannot be verified. Sampling was adequate for the terminal histopathology.; Gastrointestinal: Histopathology was purportedly conducted on all animals from all groups both at the interim and terminal sacrifices, but interim histopathology data were not reported, so sampling cannot be verified. Sampling was adequate for the terminal histopathology.; Thyroid: Histopathology was purportedly conducted on all animals from all groups both at the interim and terminal sacrifices, but interim histopathology data were not reported, so sampling cannot be verified. Sampling was adequate for the terminal histopathology.; Skin/Connective Tissue: Histopathology was purportedly conducted on all animals from all groups both at the interim and terminal sacrifices, but interim histopathology data were not reported, so sampling cannot be verified. Sampling was adequate for the terminal histopathology.; Musculoskeletal: Histopathology was purportedly conducted on all animals from all groups both at the interim and terminal sacrifices, but interim histopathology data were not reported, so sampling cannot be verified. Sampling was adequate for the terminal histopathology.; Ocular/Sensory: Histopathology was purportedly conducted on all animals from all groups both at the interim and terminal sacrifices, but interim histopathology data were not reported, so sampling cannot be verified. Sampling was adequate for the terminal histopathology.; Lung/Respiratory: Histopathology was purportedly conducted on all animals from all groups both at the interim and terminal sacrifices, but interim histopathology data were not reported, so sampling cannot be verified. Sampling was adequate for the terminal histopathology.; Endocrine (Endocrine): Histopathology was purportedly conducted on all animals from all groups both at the interim and terminal sacrifices, but interim histopathology data were not reported, so sampling cannot be verified. Sampling was adequate for the terminal histopathology.

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Domain	Metric	Rating	Comments
	Metric 19: Blinding of Assessors	N/A	Immune/Hematological: Blinding is not necessary because this outcome of interest is either not subjective in nature, or blinding is not required (e.g., initial histopathology).; Reproductive/Developmental: Blinding is not necessary because blinding is not required for initial histopathology examinations.; Cardiovascular: Blinding is not necessary because blinding is not required for initial histopathology examinations.; Gastrointestinal: Blinding is not necessary because blinding is not required for initial histopathology examinations.; Thyroid: Blinding is not necessary because blinding is not required for initial histopathology examinations.; Skin/Connective Tissue: Blinding is not necessary because blinding is not required for initial histopathology examinations.; Musculoskeletal: Blinding is not necessary because blinding is not required for initial histopathology examinations.; Ocular/Sensory: Blinding is not necessary because blinding is not required for initial histopathology examinations.; Lung/Respiratory: Blinding is not necessary because blinding is not required for initial histopathology examinations.; Endocrine (Endocrine): Blinding is not necessary because blinding is not required for initial histopathology examinations.

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Domain	Metric		Rating	Comments
	Metric 20:	Negative Control Response	Medium	Immune/Hematological: The biological responses of the negative control animals from the interim sacrifice (hematology and histopathology) were not reported. Non-neoplastic lesions incidences of negative controls (main group animals) were reported and were adequate.; Reproductive/Developmental: The biological responses of the negative control animals from the interim sacrifice (histopathology) were not reported. Non-neoplastic lesions incidences of negative controls from the main group animals were reported and were adequate.; Cardiovascular: The biological responses of the negative control animals from the interim sacrifice (histopathology) were not reported. Non-neoplastic lesions incidences of negative controls from the main group animals were reported and were adequate.; Gastrointestinal: The biological responses of the negative control animals from the interim sacrifice (histopathology) were not reported. Non-neoplastic lesions incidences of negative controls from the main group animals were reported and were adequate.; Thyroid: The biological responses of the negative control animals from the interim sacrifice (histopathology) were not reported. Non-neoplastic lesions incidences of negative controls from the main group animals were reported and were adequate.; Skin/Connective Tissue: The biological responses of the negative control animals from the interim sacrifice (histopathology) were not reported. Non-neoplastic lesions incidences of negative controls from the main group animals were reported and were adequate.; Musculoskeletal: The biological responses of the negative control animals from the interim sacrifice (histopathology) were not reported. Non-neoplastic lesions incidences of negative controls from the main group animals were reported and were adequate.; Ocular/Sensory: The biological responses of the negative control animals from the interim sacrifice (histopathology) were not reported. Non-neoplastic lesions incidences of negative controls from the main group animals were reported and were adequate.; Lung/Respiratory: The biological responses of the negative control animals from the interim sacrifice (histopathology) were not reported. Non-neoplastic lesions incidences of negative controls from the main group animals were reported and were adequate.; Endocrine (Endocrine): The biological responses of the negative control animals from the interim sacrifice (histopathology) were not reported. Non-neoplastic lesions incidences of negative controls from the main group animals were reported and were adequate.

Domain 6: Confounding / Variable Control

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Domain	Metric		Rating	Comments
	Metric 21:	Confounding Variables in Test Design and Procedures	High	All Outcomes: No confounding variables in the test design and procedures were identified. The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP. There were no significant body weight changes that were suggestive of palatability issues.
	Metric 22:	Health Outcomes Unrelated to Exposure	Medium	All Outcomes: Gavage-related deaths were noted in 4 controls (all males), 4 animals at 44 mg/kg-day (1 male, 3 females), and 4 at 88 mg/kg-day (all females). There were also 3 accidental deaths; details were only provided for one high-dose male that was inadvertently killed at the 66-week interim sacrifice. The small number of deaths not related to exposure is not expected to have a significant impact on the study results.

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Domain	Metric		Rating	Comments
	Metric 23:	Data Presentation and Analysis	Low	Immune/Hematological: Statistical methods were adequately described and were appropriate for the datasets. Statistical significance was shown and quantitative data/incidences were provided for the main group animals allowing for independent statistical analysis. However, histopathology and hematology data from the interim sacrifices were not provided. Negative findings were generally described, but the lack of statistical significance wasn't specified and these data cannot be independently analyzed.; Reproductive/Developmental: Statistical methods for determining incidences and tests for pairwise comparisons and trends were reported and were appropriate for the datasets. The text reports that lesions identified during the 66-week interim sacrifice were considered to be incidental. It is unclear if these data were statistically analyzed, and the data were not provided for an independent analysis. Quantitative histopathology data from the terminal sacrifice was reported.; Cardiovascular: Statistical methods for determining incidences and tests for pairwise comparisons and trends were reported and were appropriate for the datasets. The text reports that lesions identified during the 66-week interim sacrifice were considered to be incidental. It is unclear if these data were statistically analyzed, and the data were not provided for an independent analysis. Quantitative histopathology data from the terminal sacrifice was reported.; Gastrointestinal: Statistical methods for determining incidences and tests for pairwise comparisons and trends were reported and were appropriate for the datasets. The text reports that lesions identified during the 66-week interim sacrifice were considered to be incidental. It is unclear if these data were statistically analyzed, and the data were not provided for an independent analysis. Quantitative histopathology data from the terminal sacrifice was reported.; Thyroid: Statistical methods for determining incidences and tests for pairwise comparisons and trends were reported and were appropriate for the datasets. The text reports that lesions identified during the 66-week interim sacrifice were considered to be incidental. It is unclear if these data were statistically analyzed, and the data were not provided for an independent analysis. Quantitative histopathology data from the terminal sacrifice was reported.; Skin/Connective Tissue: Statistical methods for determining incidences and tests for pairwise comparisons and trends were reported and were appropriate for the datasets. The text reports that lesions identified during the 66-week interim sacrifice were considered to be incidental. It is unclear if these data were statistically analyzed, and the data were not provided for an independent analysis. Quantitative histopathology data from the terminal sacrifice was reported.; Musculoskeletal: Statistical methods for determining incidences and tests for pairwise comparisons and trends were reported and were appropriate for the datasets. The text reports that lesions identified during the 66-week interim sacrifice were considered to be incidental. It is unclear if these data were statistically analyzed, and the data were not provided for an independent analysis. Quantitative histopathology data from the terminal sacrifice was

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Immune/Hematological; Reproductive/Developmental; Cardiovascular; Gastrointestinal; Thyroid; Skin/Connective Tissue; Musculoskeletal; Ocular/Sensory; Lung/Respiratory; Endocrine (Endocrine);
Reported Health Effect(s):	Immune/Hematological: Hematology (hematocrit, hemoglobin, erythrocytes, leukocytes with differential, MCV, MCH, MCHC, and reticulocyte count), thymus weights, gross pathology, histopathology (spleen, thymus, lymph nodes (mandibular and mesenteric), bone marrow); Reproductive/Developmental: Gross necropsy and histopathology (clitoral gland, epididymis, mammary glands, ovary, preputial gland, prostate, seminal vesicle, testis, uterus); Cardiovascular: Heart organ weights, gross necropsy, histopathology (heart); Gastrointestinal: Gross necropsy and histopathology (esophagus, gall bladder (mice only), large intestines (cecum, colon, rectum), salivary gland, small intestines (duodenum, ileum, jejunum), stomach, mesentery, tooth); Thyroid: Gross necropsy and histopathology (thyroid); Skin/Connective Tissue: Gross necropsy, histopathology (skin); Musculoskeletal: Gross necropsy, histopathology (skeletal muscle, bone); Ocular/Sensory: Gross necropsy, histopathology (harderian gland); Lung/Respiratory: Gross necropsy, histopathology (lung, nose, trachea); Endocrine (Endocrine): Gross necropsy and histopathology (pancreas, adrenal glands, pituitary glands, parathyroid);
Duration:	Chronic (>91 days) 2-yrs (104-weeks rats)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric	Rating	Comments
	Metric 24: Reporting of Data	Low	Immune/Hematological: Incidence data of non-neoplastic lesions from the main group animals at terminal sacrifice were adequately reported, although measures of severity were not included. The methods suggest that histopathology was also conducted on animals sacrificed at 66 weeks, but no quantitative data were reported. Only a brief statement indicating that observed lesions were considered incidental and not related to treatment. Negative hematology findings were reported qualitatively in the text.; Reproductive/Developmental: Incidence data of non-neoplastic lesions from the main group animals at terminal sacrifice were adequately reported, although measures of severity were not included. The methods suggest that histopathology was also conducted on animals sacrificed at 66 weeks, but no quantitative data were reported. Only a brief statement indicating that observed lesions were considered incidental and not related to treatment was provided. Gross findings at either sacrifice time were also not reported.; Cardiovascular: Incidence data of non-neoplastic lesions from the main group animals at terminal sacrifice were adequately reported, although measures of severity were not included. The methods suggest that histopathology was also conducted on animals sacrificed at 66 weeks, but no quantitative data were reported. Only a brief statement indicating that observed lesions were considered incidental and not related to treatment was provided. Gross findings at either sacrifice time were also not reported.; Gastrointestinal: Incidence data of non-neoplastic lesions from the main group animals at terminal sacrifice were adequately reported, although measures of severity were not included. The methods suggest that histopathology was also conducted on animals sacrificed at 66 weeks, but no quantitative data were reported. Only a brief statement indicating that observed lesions were considered incidental and not related to treatment was provided. Gross findings at either sacrifice time were also not reported.; Thyroid: Incidence data of non-neoplastic lesions from the main group animals at terminal sacrifice were adequately reported, although measures of severity were not included. The methods suggest that histopathology was also conducted on animals sacrificed at 66 weeks, but no quantitative data were reported. Only a brief statement indicating that observed lesions were considered incidental and not related to treatment was provided. Gross findings at either sacrifice time were also not reported.; Skin/Connective Tissue: Incidence data of non-neoplastic lesions from the main group animals at terminal sacrifice were adequately reported, although measures of severity were not included. The methods suggest that histopathology was also conducted on animals sacrificed at 66 weeks, but no quantitative data were reported. Only a brief statement indicating that observed lesions were considered incidental and not related to treatment was provided. Gross findings at either sacrifice time were also not reported.; Musculoskeletal: Incidence data of non-neoplastic lesions from the main group animals at terminal sacrifice were adequately reported, although measures of severity were not included. The methods suggest that histopathol-

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Immune/Hematological; Reproductive/Developmental; Cardiovascular; Gastrointestinal; Thyroid; Skin/Connective Tissue; Musculoskeletal; Ocular/Sensory; Lung/Respiratory; Endocrine (Endocrine);
Reported Health Effect(s):	Immune/Hematological: Hematology (hematocrit, hemoglobin, erythrocytes, leukocytes with differential, MCV, MCH, MCHC, and reticulocyte count), thymus weights, gross pathology, histopathology (spleen, thymus, lymph nodes (mandibular and mesenteric), bone marrow); Reproductive/Developmental: Gross necropsy and histopathology (clitoral gland, epididymis, mammary glands, ovary, preputial gland, prostate, seminal vesicle, testis, uterus); Cardiovascular: Heart organ weights, gross necropsy, histopathology (heart); Gastrointestinal: Gross necropsy and histopathology (esophagus, gall bladder (mice only), large intestines (cecum, colon, rectum), salivary gland, small intestines (duodenum, ileum, jejunum), stomach, mesentery, tooth); Thyroid: Gross necropsy and histopathology (thyroid); Skin/Connective Tissue: Gross necropsy, histopathology (skin); Musculoskeletal: Gross necropsy, histopathology (skeletal muscle, bone); Ocular/Sensory: Gross necropsy, histopathology (harderian gland); Lung/Respiratory: Gross necropsy, histopathology (lung, nose, trachea); Endocrine (Endocrine): Gross necropsy and histopathology (pancreas, adrenal glands, pituitary glands, parathyroid);
Duration:	Chronic (>91 days) 2-yrs (104-weeks rats)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric	Rating	Comments
Overall Quality Determination		**High**	

Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Hepatic/Liver; Renal/Kidney; Immune/Hematological;
Reported Health Effect(s):	Hepatic/Liver: Liver weights, gross necropsy, histopathology, clinical chemistry (serum glucose, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, sorbitol dehydrogenase, cholesterol); Renal/Kidney: Serum chemistry (BUN, creatinine), organ weights, gross necropsy, histopathology (kidney, bladder); Immune/Hematological: Hematology (hematocrit, hemoglobin, erythrocytes, leukocytes with differential, MCV, MCH, MCHC, and reticulocyte count), thymus weights, gross pathology, histopathology (spleen, thymus, lymph nodes (mandibular and mesenteric), bone marrow);
Duration:	Chronic (>91 days) 2-yrs (104 weeks- mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	All Outcomes: The test substance was identified definitively as tris(2-chloroethyl phosphate) CASRN 115-96-8. A structure was also provided.
	Metric 2:	Test Substance Source	High	All Outcomes: The test substance was manufactured by Stauffer Chemical Company and obtained from the analytical chemistry laboratory, Midwest Research Institute. The lot number was provided.
	Metric 3:	Test Substance Purity	High	All Outcomes: The test chemical purity was ~98%, and was both provided by the supplier and confirmed via analysis (NMR and elemental analysis) by the study laboratory.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	All Outcomes: The study included concurrent negative vehicle (corn oil) controls and conditions were consistent with the animals that were treated.
	Metric 5:	Positive Controls	N/A	All Outcomes: Positive controls are not required for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	All Outcomes: Animals were distributed into weight classes, and assigned to cages using a random number table. Cages were then assigned to treatment and control groups using another random number table.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	All Outcomes: Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) were also stable for 21 days in the dark at room temperature or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks
	Metric 8:	Consistency of Exposure Administration	High	All Outcomes: All animals were gavaged on the same schedule. Gavage volumes were reported and were consistent across groups.
	Metric 9:	Reporting of Doses/Concentrations	High	All Outcomes: The doses were clearly reported. Animals were exposed to 0, 175, or 350 mg/kg, 5 days per week. Adjusted or time-weighted average doses in mg/kg-day were not provided, but can be determined using the data provided. Dose formulations were analyzed at approximately 8-week intervals by gas chromatography, and remained within 10% of the target concentrations throughout the course of the study. The target and measured concentrations in the solutions (mg/mL) were reported.
	Metric 10:	Exposure Frequency and Duration	High	All Outcomes: Animals were dosed 5 days per week for two years. The exposure frequency and duration are consistent with NTP guidelines.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Hepatic/Liver; Renal/Kidney; Immune/Hematological;
Reported Health Effect(s):	Hepatic/Liver: Liver weights, gross necropsy, histopathology, clinical chemistry (serum glucose, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, sorbitol dehydrogenase, cholesterol); Renal/Kidney: Serum chemistry (BUN, creatinine), organ weights, gross necropsy, histopathology (kidney, bladder); Immune/Hematological: Hematology (hematocrit, hemoglobin, erythrocytes, leukocytes with differential, MCV, MCH, MCHC, and reticulocyte count), thymus weights, gross pathology, histopathology (spleen, thymus, lymph nodes (mandibular and mesenteric), bone marrow);
Duration:	Chronic (>91 days) 2-yrs (104 weeks- mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	Low	All Outcomes: This 2-year study only included two treatment groups and a control. Although the authors justified the doses used, NTP guidelines specify using 3 treatment groups plus a control. Effects were observed at both doses and a NOAEL could not be determined.
	Metric 12:	Exposure Route and Method	High	All Outcomes: Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	Medium	All Outcomes: The study used male and female B6C3F1 mice. The test animal source (Harlan industries), age at the start of the study (8-9 weeks old) were reported. Although initial animal body weights for the 16-day and 16-week studies were reported, the initial body weights for the 2-year study are not reported. Body weight data begin after 1 week of dosing.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Low	All Outcomes: The number of animals per cage (5/cage) was reported. According to NTP guidelines for chronic/carcinogenicity studies, male mice should be housed individually. Food and water were provided ad libiutm. Animal room environments (temperature, humidity, lighting were reported. The humidity ranged considerably from 15% to 84%. This deviates from NTP guidelines which state humidity should not be below 35% or above 65%.Similarly, the temperature range was reported to be between 60 and 86 degrees F. NTP guidelines state that the temperatures shall not be below 69 or above 75 degrees F, with minimal fluctuations. It is unclear whether these deviations had an impact on the study results.
	Metric 15:	Number of Animals per Group	Medium	All Outcomes: The study methods specify 50/sex/group which is consistent with NTP guidelines for a chronic/carcinogenicity study. An extra 10/sex/group were added for an interim sacrifice at 66 weeks.
Domain 5: Outcome Assessment				

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Health Outcome(s):	Hepatic/Liver; Renal/Kidney; Immune/Hematological;
Reported Health Effect(s):	Hepatic/Liver: Liver weights, gross necropsy, histopathology, clinical chemistry (serum glucose, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, sorbitol dehydrogenase, cholesterol); Renal/Kidney: Serum chemistry (BUN, creatinine), organ weights, gross necropsy, histopathology (kidney, bladder); Immune/Hematological: Hematology (hematocrit, hemoglobin, erythrocytes, leukocytes with differential, MCV, MCH, MCHC, and reticulocyte count), thymus weights, gross pathology, histopathology (spleen, thymus, lymph nodes (mandibular and mesenteric), bone marrow);
Duration:	Chronic (>91 days) 2-yrs (104 weeks- mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 16:	Outcome Assessment Methodology	High	Hepatic/Liver: The study included interim sacrifices (10/sex/group) at 66-weeks. Select clinical chemistry and organ weights were recorded and these animals were subjected to gross necropsy and histopathology. Histopathological examination of non-neoplastic lesions was also conducted in the main group of animals at the terminal sacrifice. The outcome assessment methodology was clearly reported and sensitive to the outcomes of interest.; Renal/Kidney: The study included interim sacrifices (10/sex/group) at 66-weeks. Select clinical chemistry and organ weights were recorded and these animals were subjected to gross necropsy and histopathology. Histopathological examination of non-neoplastic lesions was also conducted in the main group of animals at the terminal sacrifice. The outcome assessment methodology was clearly reported and sensitive to the outcomes of interest.; Immune/Hematological: The study included interim sacrifices (10/sex/group) at 66 weeks. Blood was collected for hematological analysis and these animals were subjected to gross necropsy and histopathology. Histopathological examination of non-neoplastic lesions was also conducted in the main group of animals at the terminal sacrifice. A detailed description of histopathological procedures was provided and the methods were sensitive to the outcomes of interest.
	Metric 17:	Consistency of Outcome Assessment	High	All Outcomes: Details of the outcome assessment protocol were reported and the outcomes were consistently assessed for the groups that were examined.
	Metric 18:	Sampling Adequacy	Medium	Hepatic/Liver: Organ weight, serum chemistry, and histopathology data were purportedly collected from all surviving animals at the interim sacrifice; however, no quantitative results confirming sample sizes were provided. At both the 66-week and 104-week terminal sacrifices, histopathological analysis was conducted on tissues from the control and high-dose animals, except for tissues from the harderian gland, kidney, liver, lung, and stomach, which were also examined from low-dose animals.; Renal/Kidney: Organ weight, serum chemistry, and histopathology data were purportedly collected from all surviving animals at the interim sacrifice; however, no quantitative results confirming sample sizes were provided. At both the 66-week and 104-week terminal sacrifices, histopathological analysis was conducted on tissues from the control and high-dose animals, except for tissues from the harderian gland, kidney, liver, lung, and stomach, which were also examined from low-dose animals.; Immune/Hematological: It is assumed that blood was collected from all surviving animals at the interim sacrifice, but since negative hematological results were qualitatively reported in the results, the ”n” or sample size cannot be confirmed. At both the 66-week and 104-week terminal sacrifices, histopathological analysis was conducted on tissues from the control and high-dose animals, except for tissues from the harderian gland, kidney, liver, lung, and stomach, which were also examined from low-dose animals. This is not expected to have a significant impact on the study results because no significant histopathological changes were noted for this outcome at the high dose.

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Health Outcome(s):	Hepatic/Liver; Renal/Kidney; Immune/Hematological;
Reported Health Effect(s):	Hepatic/Liver: Liver weights, gross necropsy, histopathology, clinical chemistry (serum glucose, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, sorbitol dehydrogenase, cholesterol); Renal/Kidney: Serum chemistry (BUN, creatinine), organ weights, gross necropsy, histopathology (kidney, bladder); Immune/Hematological: Hematology (hematocrit, hemoglobin, erythrocytes, leukocytes with differential, MCV, MCH, MCHC, and reticulocyte count), thymus weights, gross pathology, histopathology (spleen, thymus, lymph nodes (mandibular and mesenteric), bone marrow);
Duration:	Chronic (>91 days) 2-yrs (104 weeks- mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 19:	Blinding of Assessors	High	Hepatic/Liver: The study indicated that all histopathology data were sent to an independent quality assessment laboratory and slides, tissue counts, and histotechnique were evaluated. Additionally, all tumor diagnoses, all tissue sections of the brain, kidney, liver, spleen, and thyroid, and tissues randomly selected from 10% of the animals were re-examined by a pathologist. It was not specified whether these examinations were done blinded; however, in any instances where there was a disagreement in diagnosis, a Pathology Working Group chairperson, reviewed the slides without prior knowledge of the dose group, or the previous diagnoses.Other outcomes (organ weights, clinical chemistry) were not subjective in nature.; Renal/Kidney: The study indicated that all histopathology data were sent to an independent quality assessment laboratory and slides, tissue counts, and histotechnique were evaluated. Additionally, all tumor diagnoses, all tissue sections of the brain, kidney, liver, spleen, and thyroid, and tissues randomly selected from 10% of the animals were re-examined by a pathologist. It was not specified whether these examinations were done blinded; however, in any instances where there was a disagreement in diagnosis, a Pathology Working Group chairperson, reviewed the slides without prior knowledge of the dose group, or the previous diagnoses. Other outcomes (organ weights, clinical chemistry) were not subjective in nature.; Immune/Hematological: The study indicated that all histopathology data were sent to an independent quality assessment laboratory and slides, tissue counts, and histotechnique were evaluated. Additionally, all tumor diagnoses, all tissue sections of the brain, kidney, liver, spleen, and thyroid, and tissues randomly selected from 10% of the animals were re-examined by a pathologist. It was not specified whether these examinations were done blinded; however, in any instances where there was a disagreement in diagnosis, a Pathology Working Group chairperson, reviewed the slides without prior knowledge of the dose group or the previous diagnoses.
	Metric 20:	Negative Control Response	Low	Hepatic/Liver: Non-neoplastic control data from the main group animals were reported and the incidences were appropriate. All results from the interim sacrifice were inadequately reported, and the appropriateness of the negative control responses cannot be confirmed.; Renal/Kidney: Non-neoplastic control data from the main group animals were reported and the incidences were appropriate. All results from the interim sacrifice were inadequately reported, and the appropriateness of the negative control responses cannot be confirmed.; Immune/Hematological: Non-neoplastic control data from the main group animals were reported and the incidences were appropriate. Histopathology results from the 66-interim sacrifice were not reported and hematology results were only qualitatively described. No gross pathological control responses were reported. The adequacy of the control responses for these endpoints cannot be determined.

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Health Outcome(s):	Hepatic/Liver; Renal/Kidney; Immune/Hematological;
Reported Health Effect(s):	Hepatic/Liver: Liver weights, gross necropsy, histopathology, clinical chemistry (serum glucose, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, sorbitol dehydrogenase, cholesterol); Renal/Kidney: Serum chemistry (BUN, creatinine), organ weights, gross necropsy, histopathology (kidney, bladder); Immune/Hematological: Hematology (hematocrit, hemoglobin, erythrocytes, leukocytes with differential, MCV, MCH, MCHC, and reticulocyte count), thymus weights, gross pathology, histopathology (spleen, thymus, lymph nodes (mandibular and mesenteric), bone marrow);
Duration:	Chronic (>91 days) 2-yrs (104 weeks- mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	High	All Outcomes: No confounding variables in the test design and procedures were identified. The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP. There were no significant body weight changes that were suggestive of palatability issues.
	Metric 22:	Health Outcomes Unrelated to Exposure	Medium	All Outcomes: Two control and two high-dose male mice, and one control female mouse, all predesignated for the interim sacrifice died before week 66. The causes of death were not specified. Overall, several gavage deaths of both sexes were also noted across groups. These deaths are not expected to have a significant impact on the study results.
	Metric 23:	Data Presentation and Analysis	Low	Hepatic/Liver: Statistical methods were adequately described for different data types and were appropriate for the datasets. For some endpoints (organ weights, gross pathology, interim histopathology), it is assumed these data were statistically analyzed, but the data were not reported, or available for an independent review.; Renal/Kidney: Statistical methods were adequately described for different data types and were appropriate for the datasets. For some endpoints (organ weights, gross pathology, interim histopathology), it is assumed these data were statistically analyzed, but the data were not reported or available for an independent review.; Immune/Hematological: Statistical methods were adequately described for various data types and were appropriate for the datasets. The study did not provide data enabling an independent statistical analysis for several endpoints (e.g., hematology, interim histopathology),
	Metric 24:	Reporting of Data	Low	Hepatic/Liver: Incidence data of non-neoplastic lesions from the main group animals were adequately reported, although measures of severity were not included. Histopathology and organ weight results from the 66-week interim sacrifice were not reported, and no results for gross examinations were reported. A qualitative statement reported that there were "no alterations in clinical chemistry deemed to be related to treatment".; Renal/Kidney: Incidence data of non-neoplastic lesions from the main group animals were adequately reported, although measures of severity were not included. Organ weight results from the 66-week interim sacrifice were not reported, and no results for gross examinations were reported. A qualitative statement reported that there were "no alterations in clinical chemistry deemed to be related to treatment". Interim histopathology results for this outcome were qualitatively reported in the text.; Immune/Hematological: Incidence data of non-neoplastic lesions from the main group animals were adequately reported, although measures of severity were not included. Histopathology results from the 66-week interim sacrifice were not reported, and no results for gross examinations were reported. Negative hematology findings were qualitatively reported in the text.

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Health Outcome(s):	Hepatic/Liver; Renal/Kidney; Immune/Hematological;
Reported Health Effect(s):	Hepatic/Liver: Liver weights, gross necropsy, histopathology, clinical chemistry (serum glucose, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, sorbitol dehydrogenase, cholesterol); Renal/Kidney: Serum chemistry (BUN, creatinine), organ weights, gross necropsy, histopathology (kidney, bladder); Immune/Hematological: Hematology (hematocrit, hemoglobin, erythrocytes, leukocytes with differential, MCV, MCH, MCHC, and reticulocyte count), thymus weights, gross pathology, histopathology (spleen, thymus, lymph nodes (mandibular and mesenteric), bone marrow);
Duration:	Chronic (>91 days) 2-yrs (104 weeks- mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric	Rating	Comments
Overall Quality Determination		**High**	

Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Nutritional/Metabolic
Reported Health Effect(s):	Body weights
Duration:	Chronic (>91 days) 2-yrs (104 weeks- mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was identified definitively as tris(2-chloroethyl phosphate) CASRN 115-96-8. A structure was also provided.
	Metric 2:	Test Substance Source	High	The test substance was manufactured by Stauffer Chemical Company and obtained from the analytical chemistry laboratory, Midwest Research Institute. The lot number was provided.
	Metric 3:	Test Substance Purity	High	The test chemical purity was ~98%, and was both provided by the supplier and confirmed via analysis (NMR and elemental analysis) by the study laboratory.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	The study included concurrent negative vehicle (corn oil) controls and conditions were consistent with the animals that were treated.
	Metric 5:	Positive Controls	N/A	Positive controls are not required for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	Animals were distributed into weight classes, and assigned to cages using a random number table. Cages were then assigned to treatment and control groups using another random number table.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) were also stable for 21 days in the dark at room temperature or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks.
	Metric 8:	Consistency of Exposure Administration	High	All animals were gavaged on the same schedule. Gavage volumes were reported and were consistent across groups.
	Metric 9:	Reporting of Doses/Concentrations	High	The doses were clearly reported. Animals were exposed to 0, 175, or 350 mg/kg, 5 days per week. Adjusted or time-weighted average doses in mg/kg-day were not provided, but can be determined using the data provided. Dose formulations were analyzed at approximately 8-week intervals by gas chromatography, and remained within 10% of the target concentrations throughout the course of the study. The target and measured concentrations in the solutions (mg/mL) were reported.
	Metric 10:	Exposure Frequency and Duration	High	Animals were dosed 5 days per week for two years. The exposure frequency and duration are consistent with NTP guidelines.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	Low	This 2-year study only included two treatment groups and a control. Although the authors justified the doses used, NTP guidelines specify using 3 treatment groups plus a control. Effects were observed at both doses and a NOAEL could not be determined.

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Health Outcome(s):	Nutritional/Metabolic
Reported Health Effect(s):	Body weights
Duration:	Chronic (>91 days) 2-yrs (104 weeks- mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 12:	Exposure Route and Method	High	Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	Medium	The study used male and female B6C3F1 mice. The test animal source (Harlan industries), age at the start of the study (8-9 weeks old) were reported. Although initial animal body weights for the 16-day and 16-week studies were reported, the initial body weights for the 2-year study are not reported. Body weight data begin after 1 week of dosing.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Low	The number of animals per cage (5/cage) was reported. According to NTP guidelines for chronic/carcinogenicity studies, male mice should be housed individually. Food and water were provided ad libitum. Animal room environments (temperature, humidity, lighting) were reported. The humidity ranged considerably from 15% to 84%. This deviates from NTP guidelines which state humidity should not be below 35% or above 65%.Similarly, the temperature range was reported to be between 60 and 86 degrees F. NTP guidelines state that the temperatures shall not be below 69 or above 75 degrees F, with minimal fluctuations. It is unclear whether these deviations had an impact on the study results.
	Metric 15:	Number of Animals per Group	Medium	The study methods specify 50/sex/group which is consistent with NTP guidelines for a chronic/carcinogenicity study. An extra 10/sex/group were added for an interim sacrifice at 66 weeks.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	The outcome assessment methodology was described and sensitive for the outcome of interest. Body weights were measured initially, then weekly through week 13, and monthly after week 13. Weights were recorded at 3-4 week intervals for the last 3 months.
	Metric 17:	Consistency of Outcome Assessment	High	The same protocol was applied to animals from all groups, and animals were consistently assessed for the outcomes of interest.
	Metric 18:	Sampling Adequacy	Medium	There were a few instances noted where the number of animals weighed was less than the number of animals surviving, and one week (study week 5) where body weights of male mice were not recorded (an explanation was not provided). The missing information is not expected to have a significant impact on the study results.
	Metric 19:	Blinding of Assessors	Medium	Blinding was not reported, but blinding is not necessary because this outcome of interest is either not subjective in nature, or blinding is not required for this endpoint (e.g., initial histopathology).
	Metric 20:	Negative Control Response	High	Negative control body weight and growth data were reported and were adequate.
Domain 6: Confounding / Variable Control				

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Nutritional/Metabolic
Reported Health Effect(s):	Body weights
Duration:	Chronic (>91 days) 2-yrs (104 weeks- mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 21:	Confounding Variables in Test Design and Procedures	High	No confounding variables in the test design and procedures were identified. The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP. There were no significant body weight changes that were suggestive of palatability issues.
	Metric 22:	Health Outcomes Unrelated to Exposure	Medium	Two control and two high-dose male mice, and one control female mouse, all predesignated for the interim sacrifice died before week 66. The causes of death were not specified. Overall, several gavage deaths of both sexes were also noted across groups. These deaths are not expected to have a significant impact on the study results.
	Metric 23:	Data Presentation and Analysis	High	Statistical methods were adequately described and were appropriate for the datasets. Statistical significance was shown where appropriate.
	Metric 24:	Reporting of Data	Low	Growth curves and body weight tables were provided. The data were presented as means in the absence of measures of variance. The study indicates that initial body weights were measured, but the body weight data tables start after 1 week of exposure.

Overall Quality Determination High

Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Neurological/Behavioral
Reported Health Effect(s):	Serum cholinesterase activity (special study 16-day and 16-week studies, and as part of serum chemistry in 2-yr study), brain weights, gross necropsy, histopathology (brain)
Duration:	Chronic (>91 days) 2-yrs (104 weeks- mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was identified definitively as tris(2-chloroethyl phosphate) CASRN 115-96-8. A structure was also provided.
	Metric 2:	Test Substance Source	High	The test substance was manufactured by Stauffer Chemical Company and obtained from the analytical chemistry laboratory, Midwest Research Institute. The lot number was provided.
	Metric 3:	Test Substance Purity	High	The test chemical purity was ~98%, and was both provided by the supplier and confirmed via analysis (NMR and elemental analysis) by the study laboratory.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	The study included concurrent negative vehicle (corn oil) controls and conditions were consistent with the animals that were treated.
	Metric 5:	Positive Controls	N/A	Positive controls are not required for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	Animals were distributed into weight classes, and assigned to cages using a random number table. Cages were then assigned to treatment and control groups using another random number table.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) were also stable for 21 days in the dark at room temperature or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks
	Metric 8:	Consistency of Exposure Administration	High	All animals were gavaged on the same schedule. Gavage volumes were reported and were consistent across groups.
	Metric 9:	Reporting of Doses/Concentrations	High	The doses were clearly reported. Animals were exposed to 0, 175, or 350 mg/kg, 5 days per week. Adjusted or time-weighted average doses in mg/kg-day were not provided, but can be determined using the data provided. Dose formulations were analyzed at approximately 8-week intervals by gas chromatography, and remained within 10% of the target concentrations throughout the course of the study. The target and measured concentrations in the solutions (mg/mL) were reported.
	Metric 10:	Exposure Frequency and Duration	High	Animals were dosed 5 days per week for two years. The exposure frequency and duration are consistent with NTP guidelines.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	Low	This 2-year study only included two treatment groups and a control. Although the authors justified the doses used, NTP guidelines specify using 3 treatment groups plus a control. Effects were observed at both doses and a NOAEL could not be determined.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Neurological/Behavioral
Reported Health Effect(s):	Serum cholinesterase activity (special study 16-day and 16-week studies, and as part of serum chemistry in 2-yr study), brain weights, gross necropsy, histopathology (brain)
Duration:	Chronic (>91 days) 2-yrs (104 weeks- mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 12:	Exposure Route and Method	High	Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	Medium	The study used male and female B6C3F1 mice. The test animal source (Harlan industries), age at the start of the study (8-9 weeks old) were reported. Although initial animal body weights for the 16-day and 16-week studies were reported, the initial body weights for the 2-year study are not reported. Body weight data begin after 1 week of dosing.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Low	The number of animals per cage (5/cage) was reported. According to NTP guidelines for chronic/carcinogenicity studies, male mice should be housed individually. Food and water were provided ad libiutm. Animal room environments (temperature, humidity, lighting were reported. The humidity ranged considerably from 15% to 84%. This deviates from NTP guidelines which state humidity should not be below 35% or above 65%.Similarly, the temperature range was reported to be between 60 and 86 degrees F. NTP guidelines state that the temperatures shall not be below 69 or above 75 degrees F, with minimal fluctuations. It is unclear whether these deviations had an impact on the study results.
	Metric 15:	Number of Animals per Group	Medium	The study methods specify 50/sex/group which is consistent with NTP guidelines for a chronic/carcinogenicity study. An extra 10/sex/group were added for an interim sacrifice at 66 weeks.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	The study included interim sacrifices (10/sex/group) at 66-weeks. Select organ weights were recorded and these animals were subjected to gross necropsy and histopathology. Histopathological examination of non-neoplastic lesions was also conducted in the main group of animals at the terminal sacrifice. The outcome assessment methodology was clearly reported and sensitive to the outcomes of interest.
	Metric 17:	Consistency of Outcome Assessment	High	Details of the outcome assessment protocol were reported and the outcomes were consistently assessed for the groups that were examined.
	Metric 18:	Sampling Adequacy	Medium	Organs were purportedly weighed from all surviving animals at the interim sacrifice; however, no quantitative organ weight results were reported and sampling adequacy cannot be confirmed. At both the 66-week and 104-week terminal sacrifices, histopathological analysis was conducted on tissues from the control and high-dose animals, except for tissues from the harderian gland, kidney, liver, lung, and stomach, which were also examined from low-dose animals.
	Metric 19:	Blinding of Assessors	Medium	The study indicated that all histopathology data were sent to an independent quality assessment laboratory and slides, tissue counts, and histotechnique were evaluated. Blinding was not reported but is not required for initial histopathology.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Neurological/Behavioral
Reported Health Effect(s):	Serum cholinesterase activity (special study 16-day and 16-week studies, and as part of serum chemistry in 2-yr study), brain weights, gross necropsy, histopathology (brain)
Duration:	Chronic (>91 days) 2-yrs (104 weeks- mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 20:	Negative Control Response	Low	Non-neoplastic control data from the main group animals were reported and the incidences were appropriate. Gross pathological control responses were not reported. All results from the interim sacrifice were inadequately reported, and the appropriateness of the negative control responses cannot be confirmed.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	High	No confounding variables in the test design and procedures were identified. The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP. There were no significant body weight changes that were suggestive of palatability issues.
	Metric 22:	Health Outcomes Unrelated to Exposure	Medium	Two control and two high-dose male mice, and one control female mouse, all predesignated for the interim sacrifice died before week 66. The causes of death were not specified. Overall, several gavage deaths of both sexes were also noted across groups. These deaths are not expected to have a significant impact on the study results.
	Metric 23:	Data Presentation and Analysis	Low	Statistical methods were adequately described for different data types and were appropriate for the datasets. For some endpoints (organ weights, gross pathology, interim histopathology), it is assumed these data were statistically analyzed, but the data were not reported, or available for an independent review.
	Metric 24:	Reporting of Data	Low	Incidence data of non-neoplastic lesions from the main group animals were adequately reported, although measures of severity were not included. Histopathology results from the 66-week interim sacrifice were not reported, and no results for gross examinations were reported. Organ weight data also were not reported.

Overall Quality Determination High

Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Reproductive/Developmental; Musculoskeletal; Cardiovascular; Skin/Connective Tissue; Endocrine (Endocrine); Thyroid;
Reported Health Effect(s):	Reproductive/Developmental: Gross necropsy and histopathology (clitoral gland, epididymis, mammary glands, ovary, preputial gland, prostate, seminal vesicle, testis, uterus); Musculoskeletal: Gross necropsy, histopathology (skeletal muscle, bone); Cardiovascular: Heart organ weights, gross necropsy, histopathology (heart); Skin/Connective Tissue: Gross necropsy, histopathology (skin); Endocrine (Endocrine): Gross necropsy and histopathology (pancreas, adrenal glands, pituitary glands, parathyroid); Thyroid: Gross necropsy and histopathology (thyroid);
Duration:	Chronic (>91 days) 2-yrs (104 weeks- mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	All Outcomes: The test substance was identified definitively as tris(2-chloroethyl phosphate) CASRN 115-96-8. A structure was also provided.
	Metric 2:	Test Substance Source	High	All Outcomes: The test substance was manufactured by Stauffer Chemical Company and obtained from the analytical chemistry laboratory, Midwest Research Institute. The lot number was provided.
	Metric 3:	Test Substance Purity	High	All Outcomes: The test chemical purity was ~98%, and was both provided by the supplier and confirmed via analysis (NMR and elemental analysis) by the study laboratory.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	All Outcomes: The study included concurrent negative vehicle (corn oil) controls and conditions were consistent with the animals that were treated.
	Metric 5:	Positive Controls	N/A	All Outcomes: Positive controls are not required for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	All Outcomes: Animals were distributed into weight classes, and assigned to cages using a random number table. Cages were then assigned to treatment and control groups using another random number table.
Domain 3: Exposure Characterization				

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Health Outcome(s):	Reproductive/Developmental; Musculoskeletal; Cardiovascular; Skin/Connective Tissue; Endocrine (Endocrine); Thyroid;
Reported Health Effect(s):	Reproductive/Developmental: Gross necropsy and histopathology (clitoral gland, epididymis, mammary glands, ovary, preputial gland, prostate, seminal vesicle, testis, uterus); Musculoskeletal: Gross necropsy, histopathology (skeletal muscle, bone); Cardiovascular: Heart organ weights, gross necropsy, histopathology (heart); Skin/Connective Tissue: Gross necropsy, histopathology (skin); Endocrine (Endocrine): Gross necropsy and histopathology (pancreas, adrenal glands, pituitary glands, parathyroid); Thyroid: Gross necropsy and histopathology (thyroid);
Duration:	Chronic (>91 days) 2-yrs (104 weeks- mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 7:	Preparation and Storage of Test Substance	High	Reproductive/Developmental: Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) were also stable for 21 days in the dark at room temperature or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks.; Musculoskeletal: Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) were also stable for 21 days in the dark at room temperature or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks.; Cardiovascular: Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) were also stable for 21 days in the dark at room temperature or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks; Skin/Connective Tissue: Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) were also stable for 21 days in the dark at room temperature or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks.; Endocrine (Endocrine): Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) were also stable for 21 days in the dark at room temperature or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks.; Thyroid: Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) were also stable for 21 days in the dark at room temperature or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks
	Metric 8:	Consistency of Exposure Administration	High	All Outcomes: All animals were gavaged on the same schedule. Gavage volumes were reported and were consistent across groups.

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Health Outcome(s):	Reproductive/Developmental; Musculoskeletal; Cardiovascular; Skin/Connective Tissue; Endocrine (Endocrine); Thyroid;
Reported Health Effect(s):	Reproductive/Developmental: Gross necropsy and histopathology (clitoral gland, epididymis, mammary glands, ovary, preputial gland, prostate, seminal vesicle, testis, uterus); Musculoskeletal: Gross necropsy, histopathology (skeletal muscle, bone); Cardiovascular: Heart organ weights, gross necropsy, histopathology (heart); Skin/Connective Tissue: Gross necropsy, histopathology (skin); Endocrine (Endocrine): Gross necropsy and histopathology (pancreas, adrenal glands, pituitary glands, parathyroid); Thyroid: Gross necropsy and histopathology (thyroid);
Duration:	Chronic (>91 days) 2-yrs (104 weeks- mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 9:	Reporting of Doses/Concentrations	High	All Outcomes: The doses were clearly reported. Animals were exposed to 0, 175, or 350 mg/kg, 5 days per week. Adjusted or time-weighted average doses in mg/kg-day were not provided, but can be determined using the data provided. Dose formulations were analyzed at approximately 8-week intervals by gas chromatography, and remained within 10% of the target concentrations throughout the course of the study. The target and measured concentrations in the solutions (mg/mL) were reported.
	Metric 10:	Exposure Frequency and Duration	High	All Outcomes: Animals were dosed 5 days per week for two years. The exposure frequency and duration are consistent with NTP guidelines.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	Low	All Outcomes: This 2-year study only included two treatment groups and a control. Although the authors justified the doses used, NTP guidelines specify using 3 treatment groups plus a control. Effects were observed at both doses and a NOAEL could not be determined.
	Metric 12:	Exposure Route and Method	High	All Outcomes: Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	Medium	All Outcomes: The study used male and female B6C3F1 mice. The test animal source (Harlan industries), age at the start of the study (8-9 weeks old) were reported. Although initial animal body weights for the 16-day and 16-week studies were reported, the initial body weights for the 2-year study are not reported. Body weight data begin after 1 week of dosing.

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Health Outcome(s):	Reproductive/Developmental; Musculoskeletal; Cardiovascular; Skin/Connective Tissue; Endocrine (Endocrine); Thyroid;
Reported Health Effect(s):	Reproductive/Developmental: Gross necropsy and histopathology (clitoral gland, epididymis, mammary glands, ovary, preputial gland, prostate, seminal vesicle, testis, uterus); Musculoskeletal: Gross necropsy, histopathology (skeletal muscle, bone); Cardiovascular: Heart organ weights, gross necropsy, histopathology (heart); Skin/Connective Tissue: Gross necropsy, histopathology (skin); Endocrine (Endocrine): Gross necropsy and histopathology (pancreas, adrenal glands, pituitary glands, parathyroid); Thyroid: Gross necropsy and histopathology (thyroid);
Duration:	Chronic (>91 days) 2-yrs (104 weeks- mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Low	Reproductive/Developmental: The number of animals per cage (5/cage) was reported. According to NTP guidelines for chronic/carcinogenicity studies, male mice should be housed individually. Food and water were provided ad libitum. Animal room environments (temperature, humidity, lighting) were reported. The humidity ranged considerably from 15% to 84%. This deviates from NTP guidelines which state humidity should not be below 35% or above 65%.Similarly, the temperature range was reported to be between 60 and 86 degrees F. NTP guidelines state that the temperatures shall not be below 69 or above 75 degrees F, with minimal fluctuations. It is unclear whether these deviations had an impact on the study results.; Musculoskeletal: The number of animals per cage (5/cage) was reported. According to NTP guidelines for chronic/carcinogenicity studies, male mice should be housed individually. Food and water were provided ad libiutm. Animal room environments (temperature, humidity, lighting were reported. The humidity ranged considerably from 15% to 84%. This deviates from NTP guidelines which state humidity should not be below 35% or above 65%.Similarly, the temperature range was reported to be between 60 and 86 degrees F. NTP guidelines state that the temperatures shall not be below 69 or above 75 degrees F, with minimal fluctuations. It is unclear whether these deviations had an impact on the study results.; Cardiovascular: The number of animals per cage (5/cage) was reported. According to NTP guidelines for chronic/carcinogenicity studies, male mice should be housed individually. Food and water were provided ad libiutm. Animal room environments (temperature, humidity, lighting were reported. The humidity ranged considerably from 15% to 84%. This deviates from NTP guidelines which state humidity should not be below 35% or above 65%.Similarly, the temperature range was reported to be between 60 and 86 degrees F. NTP guidelines state that the temperatures shall not be below 69 or above 75 degrees F, with minimal fluctuations. It is unclear whether these deviations had an impact on the study results.; Skin/Connective Tissue: The number of animals per cage (5/cage) was reported. According to NTP guidelines for chronic/carcinogenicity studies, male mice should be housed individually. Food and water were provided ad libiutm. Animal room environments (temperature, humidity, lighting were reported. The humidity ranged considerably from 15% to 84%. This deviates from NTP guidelines which state humidity should not be below 35% or above 65%.Similarly, the temperature range was reported to be between 60 and 86 degrees F. NTP guidelines state that the temperatures shall not be below 69 or above 75 degrees F, with minimal fluctuations. It is unclear whether these deviations had an impact on the study results.; Endocrine (Endocrine): The number of animals per cage (5/cage) was reported. According to NTP guidelines for chronic/carcinogenicity studies, male mice should be housed individually. Food and water were provided ad libiutm. Animal room environments (temperature, humidity, lighting were reported. The humidity ranged considerably from 15% to 84%. This deviates from NTP guidelines which state humidity should not be below 35% or above 65%.Similarly, the temperature range was reported to be between 60 and 86 degrees F. NTP guidelines state that the temperatures shall not be below 69 or above 75 degrees F, with minimal fluctuations. It is unclear whether these deviations had an impact on the study results.; Thyroid: The number of animals per cage

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Health Outcome(s):	Reproductive/Developmental; Musculoskeletal; Cardiovascular; Skin/Connective Tissue; Endocrine (Endocrine); Thyroid;
Reported Health Effect(s):	Reproductive/Developmental: Gross necropsy and histopathology (clitoral gland, epididymis, mammary glands, ovary, preputial gland, prostate, seminal vesicle, testis, uterus); Musculoskeletal: Gross necropsy, histopathology (skeletal muscle, bone); Cardiovascular: Heart organ weights, gross necropsy, histopathology (heart); Skin/Connective Tissue: Gross necropsy, histopathology (skin); Endocrine (Endocrine): Gross necropsy and histopathology (pancreas, adrenal glands, pituitary glands, parathyroid); Thyroid: Gross necropsy and histopathology (thyroid);
Duration:	Chronic (>91 days) 2-yrs (104 weeks- mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 15:	Number of Animals per Group	Medium	All Outcomes: The study methods specify 50/sex/group which is consistent with NTP guidelines for a chronic/carcinogenicity study. An extra 10/sex/group were added for an interim sacrifice at 66 weeks.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	All Outcomes: The study included interim sacrifices (10/sex/group) at 66-weeks. These animals were subjected to gross necropsy and histopathology. Histopathological examination of non-neoplastic lesions was also conducted in the main group of animals at the terminal sacrifice. A detailed description of histopathological procedures was provided and the methods were sensitive to the outcomes of interest.
	Metric 17:	Consistency of Outcome Assessment	High	All Outcomes: Details of the outcome assessment protocol were reported and the outcomes were consistently assessed for the groups that were examined.
	Metric 18:	Sampling Adequacy	Medium	All Outcomes: At both the 66-week and 104-week terminal sacrifices, histopathological analysis was conducted on tissues from the control and high-dose animals, except for tissues from the harderian gland, kidney, liver, lung, and stomach, which were also examined from low-dose animals. This is not expected to have a significant impact on the study results because no histopathological changes were noted for this outcome at the high dose.
	Metric 19:	Blinding of Assessors	Medium	All Outcomes: The study indicated that all histopathology data were sent to an independent quality assessment laboratory and slides, tissue counts, and histotechnique were evaluated. Blinding was not reported but is not required for initial histopathology.

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Health Outcome(s):	Reproductive/Developmental; Musculoskeletal; Cardiovascular; Skin/Connective Tissue; Endocrine (Endocrine); Thyroid;
Reported Health Effect(s):	Reproductive/Developmental: Gross necropsy and histopathology (clitoral gland, epididymis, mammary glands, ovary, preputial gland, prostate, seminal vesicle, testis, uterus); Musculoskeletal: Gross necropsy, histopathology (skeletal muscle, bone); Cardiovascular: Heart organ weights, gross necropsy, histopathology (heart); Skin/Connective Tissue: Gross necropsy, histopathology (skin); Endocrine (Endocrine): Gross necropsy and histopathology (pancreas, adrenal glands, pituitary glands, parathyroid); Thyroid: Gross necropsy and histopathology (thyroid);
Duration:	Chronic (>91 days) 2-yrs (104 weeks- mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 20:	Negative Control Response	Medium	Reproductive/Developmental: 98% of control females had hyperplasia in the endometrium and 38% had ovarian cysts. It is assumed that these frequently occur in these animals. Similar incidences also occurred in the treatment groups.; Musculoskeletal: Non-neoplastic control data from the main group animals were reported and the incidences were appropriate. Histopathology results from the 66-interim sacrifice were not reported. Gross pathological control responses were not reported.; Cardiovascular: Non-neoplastic control data from the main group animals were reported and the incidences were appropriate. Histopathology results from the 66-interim sacrifice were not reported. Gross pathological control responses were not reported.; Skin/Connective Tissue: Non-neoplastic control data from the main group animals were reported and the incidences were appropriate. Histopathology results from the 66-interim sacrifice were not reported. Gross pathological control responses were not reported.; Endocrine (Endocrine): Non-neoplastic control data from the main group animals were reported and the incidences were appropriate. Histopathology results from the 66-interim sacrifice were not reported. Gross pathological control responses were not reported.; Thyroid: Non-neoplastic control data from the main group animals were reported and the incidences were appropriate. Histopathology results from the 66-interim sacrifice were not reported. Gross pathological control responses were not reported.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	High	All Outcomes: No confounding variables in the test design and procedures were identified. The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP. There were no significant body weight changes that were suggestive of palatability issues.
	Metric 22:	Health Outcomes Unrelated to Exposure	Medium	All Outcomes: Two control and two high-dose male mice, and one control female mouse, all predesignated for the interim sacrifice died before week 66. The causes of death were not specified. Overall, several gavage deaths of both sexes were also noted across groups. These deaths are not expected to have a significant impact on the study results.
	Metric 23:	Data Presentation and Analysis	High	All Outcomes: Statistical methods were adequately described and were appropriate for the datasets. Statistical significance was shown where appropriate.
	Metric 24:	Reporting of Data	Low	All Outcomes: Incidence data of non-neoplastic lesions from the main group animals were adequately reported, although measures of severity were not included. Histopathology results from the 66-week interim sacrifice were not reported, and no results for gross examinations were reported.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Reproductive/Developmental; Musculoskeletal; Cardiovascular; Skin/Connective Tissue; Endocrine (Endocrine); Thyroid;
Reported Health Effect(s):	Reproductive/Developmental: Gross necropsy and histopathology (clitoral gland, epididymis, mammary glands, ovary, preputial gland, prostate, seminal vesicle, testis, uterus); Musculoskeletal: Gross necropsy, histopathology (skeletal muscle, bone); Cardiovascular: Heart organ weights, gross necropsy, histopathology (heart); Skin/Connective Tissue: Gross necropsy, histopathology (skin); Endocrine (Endocrine): Gross necropsy and histopathology (pancreas, adrenal glands, pituitary glands, parathyroid); Thyroid: Gross necropsy and histopathology (thyroid);
Duration:	Chronic (>91 days) 2-yrs (104 weeks- mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric	Rating	Comments
Overall Quality Determination		**High**	

Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Unspecified clinical observations (Clinical signs); Unspecified clinical observations (Clinical signs);
Reported Health Effect(s):	Unspecified clinical observations (Clinical signs): Clinical signs (clinical observations); Unspecified clinical observations (Clinical signs): Clinical signs (clinical observations);
Duration:	Chronic (>91 days) 2-yrs (104-weeks rats)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	Unspecified clinical observations (Clinical signs): The test substance was identified definitively as tris(2-chloroethyl phosphate) CASRN 115-96-8. A structure was also provided.; Unspecified clinical observations (Clinical signs): The test substance was identified definitively as tris(2-chloroethyl phosphate) CASRN 115-96-8. A structure was also provided.
	Metric 2:	Test Substance Source	High	All Outcomes: The test substance was manufactured by Stauffer Chemical Company and obtained from the analytical chemistry laboratory, Midwest Research Institute. The lot number was provided.
	Metric 3:	Test Substance Purity	High	All Outcomes: The test chemical purity was ~98%, and was both provided by the supplier and confirmed via analysis (NMR and elemental analysis) by the study laboratory.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	All Outcomes: The study included concurrent negative vehicle (corn oil) controls and conditions were consistent with the animals that were treated.
	Metric 5:	Positive Controls	N/A	All Outcomes: Positive controls are not required for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	All Outcomes: Animals were distributed into weight classes, and assigned to cages using a random number table. Cages were then assigned to treatment and control groups using another random number table.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	All Outcomes: Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) were also stable for 21 days in the dark at room temperature or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks
	Metric 8:	Consistency of Exposure Administration	High	All Outcomes: All animals were gavaged on the same schedule. Gavage volumes were reported and were consistent across groups.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Unspecified clinical observations (Clinical signs); Unspecified clinical observations (Clinical signs);
Reported Health Effect(s):	Unspecified clinical observations (Clinical signs): Clinical signs (clinical observations); Unspecified clinical observations (Clinical signs): Clinical signs (clinical observations);
Duration:	Chronic (>91 days) 2-yrs (104-weeks rats)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 9:	Reporting of Doses/Concentrations	High	Unspecified clinical observations (Clinical signs): Animals were dosed with 0, 44, or 88 mg/kg/day, 5 days per week. Doses were selected based on a subchronic study. Dose formulations were analyzed at approximately 8-week intervals by gas chromatography, and remained within 10% of the target concentrations throughout the course of the study. The target and measured concentrations in the solutions (mg/mL) were reported.; Unspecified clinical observations (Clinical signs): The doses were clearly reported. Animals were exposed to 0, 175, or 350 mg/kg, 5 days per week. Adjusted or time-weighted average doses in mg/kg-day were not provided, but can be determined using the data provided. Dose formulations were analyzed at approximately 8-week intervals by gas chromatography, and remained within 10% of the target concentrations throughout the course of the study. The target and measured concentrations in the solutions (mg/mL) were reported.
	Metric 10:	Exposure Frequency and Duration	High	All Outcomes: Animals were dosed 5 days per week for two years. The exposure frequency and duration are consistent with NTP guidelines.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	Low	All Outcomes: This 2-year study only included two treatment groups and a control. Although the authors justified the doses used, NTP guidelines specify using 3 treatment groups plus a control. Effects were observed at both doses and a NOAEL could not be determined.
	Metric 12:	Exposure Route and Method	High	All Outcomes: Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	Medium	Unspecified clinical observations (Clinical signs): The study used male and female F344/N rats. The test animal source (Harlan industries) and age at the start of the study (8-10 weeks old) were reported. Although initial animal body weights for the 16-day and 16-week studies were reported, the initial body weights for the 2-year study are not reported. Body weight data begin after 1 week of dosing.; Unspecified clinical observations (Clinical signs): The study used male and female B6C3F1 mice. The test animal source (Harlan industries), age at the start of the study (8-9 weeks old) were reported. Although initial animal body weights for the 16-day and 16-week studies were reported, the initial body weights for the 2-year study are not reported. Body weight data begin after 1 week of dosing.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Unspecified clinical observations (Clinical signs); Unspecified clinical observations (Clinical signs);
Reported Health Effect(s):	Unspecified clinical observations (Clinical signs): Clinical signs (clinical observations); Unspecified clinical observations (Clinical signs): Clinical signs (clinical observations);
Duration:	Chronic (>91 days) 2-yrs (104-weeks rats)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Low	Unspecified clinical observations (Clinical signs): The number of animals per cage (5/cage) was reported. According to NTP guidelines for chronic/carcinogenicity studies, male rats should only be housed up to 3 per cage. Food and water were provided ad li-biutm. Animal room environments (temperature, humidity, lighting were reported. The humidity ranged considerably from 15% to 84%. This deviates from NTP guidelines which state humidity should not be below 35% or above 65%. Similarly, the temperature range was reported to be between 60 and 86 degrees F. NTP guidelines state that the temperatures shall not be below 69 or above 75 degrees F, with minimal fluctuations. It is unclear whether these deviations had a significant impact on the study results.; Unspecified clinical observations (Clinical signs): The number of animals per cage (5/cage) was reported. According to NTP guidelines for chronic/carcinogenicity studies, male mice should be housed individually. Food and water were provided ad libiutm. Animal room environments (temperature, humidity, lighting were reported. The humidity ranged considerably from 15% to 84%. This deviates from NTP guidelines which state humidity should not be below 35% or above 65%.Similarly, the temperature range was reported to be between 60 and 86 degrees F. NTP guidelines state that the temperatures shall not be below 69 or above 75 degrees F, with minimal fluctuations. It is unclear whether these deviations had an impact on the study results.
	Metric 15:	Number of Animals per Group	Medium	All Outcomes: The study methods specify 50/sex/group which is consistent with NTP guidelines for a chronic/carcinogenicity study. An extra 10/sex/group were added for an interim sacrifice at 66 weeks.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	Medium	Unspecified clinical observations (Clinical signs): The study indicated that clinical observations were performed monthly. No additional details were provided, but this frequency is consistent with NTP guidelines that specify formal examinations should be conducted every four weeks.; Unspecified clinical observations (Clinical signs): The study indicated that clinical observations were performed monthly. No additional details were provided. This frequency is consistent with NTP guidelines that specify formal examinations every four weeks.
	Metric 17:	Consistency of Outcome Assessment	Low	Unspecified clinical observations (Clinical signs): Details regarding the execution of the study protocol for outcome assessment were limited and not sufficient for determining the consistency of the assessment across groups.; Unspecified clinical observations (Clinical signs): Because limited details on the protocol for clinical observations were provided, consistency of assessment across groups cannot be confirmed.

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Health Outcome(s):	Unspecified clinical observations (Clinical signs); Unspecified clinical observations (Clinical signs);
Reported Health Effect(s):	Unspecified clinical observations (Clinical signs): Clinical signs (clinical observations); Unspecified clinical observations (Clinical signs): Clinical signs (clinical observations);
Duration:	Chronic (>91 days) 2-yrs (104-weeks rats)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 18:	Sampling Adequacy	Low	Unspecified clinical observations (Clinical signs): No quantitative data were provided. The adequacy of the sampling for this outcome cannot be determined.; Unspecified clinical observations (Clinical signs): Results for this endpoint were qualitatively reported as negative in the text. Although the methods suggest that all animals were observed, data are not available to confirm the sample size.
	Metric 19:	Blinding of Assessors	Medium	Unspecified clinical observations (Clinical signs): Blinding was not reported and clinical observations can be somewhat subjective in nature.; Unspecified clinical observations (Clinical signs): The study did not specify whether assessors were blinded for clinical observations which may be somewhat subjective in nature.
	Metric 20:	Negative Control Response	Low	Unspecified clinical observations (Clinical signs): The biological responses of the negative control animals cannot be determined because the data were not reported.; Unspecified clinical observations (Clinical signs): No quantitative clinical signs data were reported so the adequacy of the control response cannot be determined.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	High	All Outcomes: No confounding variables in the test design and procedures were identified. The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP. There were no significant body weight changes that were suggestive of palatability issues.
	Metric 22:	Health Outcomes Unrelated to Exposure	Medium	Unspecified clinical observations (Clinical signs): Gavage-related deaths were noted in 4 controls (all males), 4 animals at 44 mg/kg-day (1 male, 3 females), and 4 at 88 mg/kg-day (all females). There were also 3 accidental deaths; details were only provided for one high-dose male that was inadvertently killed at the 66-week interim sacrifice. The small number of deaths not related to exposure is not expected to have a significant impact on the study results.; Unspecified clinical observations (Clinical signs): Two control and two high-dose male mice, and one control female mouse, all predesignated for the interim sacrifice died before week 66. The causes of death were not specified. Overall, several gavage deaths of both sexes were also noted across groups. These deaths are not expected to have a significant impact on the study results.
	Metric 23:	Data Presentation and Analysis	Low	Unspecified clinical observations (Clinical signs): Statistical methods for determining incidences and tests for pairwise comparisons and trends were reported and were appropriate for those types of datasets, but it is unclear if clinical signs data were statistically analyzed or not, and data were not provided for an independent analysis. The study indicated that there were no clinical signs that were attributed to treatment.; Unspecified clinical observations (Clinical signs): Statistical methods were adequately described in general and were appropriate for the datasets. Statistical significance was shown where appropriate. However, it is not entirely clear whether clinical signs data were statistically analyzed, and data were not provided for independent review.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Unspecified clinical observations (Clinical signs); Unspecified clinical observations (Clinical signs);
Reported Health Effect(s):	Unspecified clinical observations (Clinical signs): Clinical signs (clinical observations); Unspecified clinical observations (Clinical signs): Clinical signs (clinical observations);
Duration:	Chronic (>91 days) 2-yrs (104-weeks rats)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric	Rating	Comments
	Metric 24: Reporting of Data	High	Unspecified clinical observations (Clinical signs): Negative findings were reported qualitatively in the text. No clinical signs were attributed to treatment.; Unspecified clinical observations (Clinical signs): Negative findings were reported qualitatively in the text.

Overall Quality Determination High

Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Mortality
Reported Health Effect(s):	Survival
Duration:	Chronic (>91 days) 16-weeks (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was identified definitively as tris(2-chloroethyl phosphate) CASRN 115-96-8. A structure was also provided.
	Metric 2:	Test Substance Source	High	The test substance was manufactured by Stauffer Chemical Company and obtained from the analytical chemistry laboratory, Midwest Research Institute. The lot number was provided.
	Metric 3:	Test Substance Purity	High	The test chemical purity was ~98%, and was both provided by the supplier and confirmed via analysis (NMR and elemental analysis) by the study laboratory.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	The study included concurrent negative vehicle (corn oil) controls and conditions were consistent with the animals that were treated.
	Metric 5:	Positive Controls	N/A	Positive controls are not required for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	Animals were distributed into weight classes, and assigned to cages using a random number table. Cages were then assigned to treatment and control groups using another random number table.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) were also stable for 21 days in the dark at room temperature or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks.
	Metric 8:	Consistency of Exposure Administration	High	All animals were gavaged on the same schedule. Gavage volumes were reported and were consistent across groups.
	Metric 9:	Reporting of Doses/Concentrations	Medium	Animals were dosed with 0, 44, 88, 175, 350, or 700 mg/kg-day, 5 days per week. Time-adjusted doses in mg/kg-day were not reported, but can be determined using the information provided. Dose formulations were analyzed twice during the study by gas chromatography and the target and measured concentrations in the solutions (mg/mL) were reported. The concentrations generally remained with 10% of the target concentration throughout the course of the study; however, during the second reading, the concentration used for the second-highest dose group was only 75% of the target.
	Metric 10:	Exposure Frequency and Duration	Medium	All mice were dosed 5 days per week for 16 weeks. Generally, the NTP guideline indicates that the subchronic studies should not be more than 97 days. The longer duration was not justified by the study authors. Dosing 5 days per week for a gavage study is consistent with NTP guidelines.

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Health Outcome(s):	Mortality
Reported Health Effect(s):	Survival
Duration:	Chronic (>91 days) 16-weeks (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	The study tested 5 dose groups plus a control. This is consistent with NTP guidelines. The spacing was sufficient to identify NOAEL and LOAEL values.
	Metric 12:	Exposure Route and Method	High	Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	High	The study used male and female B6C3F1 mice. The test animal source (Harlan industries), age at the start of the study (9-10 weeks old), and initial body weights were reported and appropriate.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Low	The number of animals per cage (5/cage) was reported; however, the NTP guideline specifies that male mice should always be housed individually. Food and water were provided ad libiutm. Animal room environments (temperature, humidity, lighting) were reported. The humidity ranged considerably from 10% to 78%. This deviates from NTP guidelines which state humidity should not be below 35% or above 65%. It is not clear what impact these deviations may have had on the study results.
	Metric 15:	Number of Animals per Group	Medium	The number of animals per group (10/sex) was reported and consistent with NTP guidelines.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	Animals were observed twice daily for morbidity and mortality. The outcome assessment was sensitive and appropriate for the outcome of interest.
	Metric 17:	Consistency of Outcome Assessment	High	Sufficient details of the outcome assessment protocols were provided, and outcome assessment was carried out consistently across groups.
	Metric 18:	Sampling Adequacy	High	All animals were sampled for this outcome of interest.
	Metric 19:	Blinding of Assessors	N/A	Blinding is not necessary because this outcome of interest is either not subjective in nature, or blinding is not required (e.g., initial histopathology).
	Metric 20:	Negative Control Response	High	No control animals died.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	High	The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP. There were no significant body weight changes that were suggestive of any palatability issues (only increased body weights were observed).

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Health Outcome(s):	Mortality
Reported Health Effect(s):	Survival
Duration:	Chronic (>91 days) 16-weeks (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 22:	Health Outcomes Unrelated to Exposure	Low	The study text noted that during week 4, the two highest dose groups were prepared incorrectly, and for the first three days of that week, the animals were administered double the target levels. Animals in the 350 mg/kg group, were instead dosed with 700 mg/kg, and animals in the 700 mg/kg group were dosed with 1,400 mg/kg. No deaths occurred as a result of the dosing error, but two male mice had convulsions and labored breathing on the third day of overdosing. These animals were not dosed on the 4th day of the week to allow them to recover. Dosing resumed on the 5th day. Three males and two females died during the study due to gavage trauma. The males were from the 175, 350, and 700 mg/kg groups, and the females were from the 175 and 350 mg/kg groups, respectively.
	Metric 23:	Data Presentation and Analysis	High	General statistical methods for evaluating continuous data and incidence data were adequately reported and were appropriate for those data types.
	Metric 24:	Reporting of Data	High	Survival data were quantitatively reported and described in the text. The causes (gavage trauma) and times of death were reported.

Overall Quality Determination High

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Health Outcome(s):	Nutritional/Metabolic
Reported Health Effect(s):	Body weights
Duration:	Chronic (>91 days) 16-weeks (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was identified definitively as tris(2-chloroethyl phosphate) CASRN 115-96-8. A structure was also provided.
	Metric 2:	Test Substance Source	High	The test substance was manufactured by Stauffer Chemical Company and obtained from the analytical chemistry laboratory, Midwest Research Institute. The lot number was provided.
	Metric 3:	Test Substance Purity	High	The test chemical purity was ~98%, and was both provided by the supplier and confirmed via analysis (NMR and elemental analysis) by the study laboratory.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	The study included concurrent negative vehicle (corn oil) controls and conditions were consistent with the animals that were treated.
	Metric 5:	Positive Controls	N/A	Positive controls are not required for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	Animals were distributed into weight classes, and assigned to cages using a random number table. Cages were then assigned to treatment and control groups using another random number table.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) were also stable for 21 days in the dark at room temperature or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks
	Metric 8:	Consistency of Exposure Administration	High	All animals were gavaged on the same schedule. Gavage volumes were reported and were consistent across groups.
	Metric 9:	Reporting of Doses/Concentrations	Medium	Animals were dosed with 0, 44, 88, 175, 350, or 700 mg/kg-day, 5 days per week. Time-adjusted doses in mg/kg-day were not reported, but can be determined using the information provided. Dose formulations were analyzed twice during the study by gas chromatography and the target and measured concentrations in the solutions (mg/mL) were reported. The concentrations generally remained with 10% of the target concentration throughout the course of the study; however, during the second reading, the concentration used for the second-highest dose group was only 75% of the target.
	Metric 10:	Exposure Frequency and Duration	Medium	All mice were dosed 5 days per week for 16 weeks. Generally, the NTP guideline indicates that the subchronic studies should not be more than 97 days. The longer duration was not justified by the study authors. Dosing 5 days per week for a gavage study is consistent with NTP guidelines.

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Health Outcome(s):	Nutritional/Metabolic
Reported Health Effect(s):	Body weights
Duration:	Chronic (>91 days) 16-weeks (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	The study tested 5 dose groups plus a control. This is consistent with NTP guidelines. The spacing was sufficient to identify NOAEL and LOAEL values.
	Metric 12:	Exposure Route and Method	High	Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	High	The study used male and female B6C3F1 mice. The test animal source (Harlan industries), age at the start of the study (9-10 weeks old), and initial body weights were reported and appropriate.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Low	The number of animals per cage (5/cage) was reported; however, the NTP guideline specifies that male mice should always be housed individually. Food and water were provided ad libiutm. Animal room environments (temperature, humidity, lighting) were reported. The humidity ranged considerably from 10% to 78%. This deviates from NTP guidelines which state humidity should not be below 35% or above 65%. It is not clear what impact these deviations may have had on the study results.
	Metric 15:	Number of Animals per Group	Medium	The number of animals per group (10/sex) was reported and consistent with NTP guidelines.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	The outcome assessment methods were sensitive and appropriate for the outcome of interest. Body weights were recorded at study initiation, then weekly thereafter, and again at termination as per NTP guidelines.
	Metric 17:	Consistency of Outcome Assessment	High	Sufficient details of the outcome assessment protocols were provided, and outcome assessment was carried out consistently across groups.
	Metric 18:	Sampling Adequacy	High	All animals were sampled for this outcome of interest.
	Metric 19:	Blinding of Assessors	N/A	Blinding is not necessary because this outcome of interest is either not subjective in nature, or blinding is not required (e.g., initial histopathology).
	Metric 20:	Negative Control Response	High	The control responses were reported and were appropriate.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	High	The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP. There were no significant body weight changes that were suggestive of any palatability issues (only increased body weights were observed).

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Health Outcome(s):	Nutritional/Metabolic
Reported Health Effect(s):	Body weights
Duration:	Chronic (>91 days) 16-weeks (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 22:	Health Outcomes Unrelated to Exposure	Low	The study text noted that during week 4, the two highest dose groups were prepared incorrectly, and for the first three days of that week, the animals were administered double the target levels. Animals in the 350 mg/kg group, were instead dosed with 700 mg/kg, and animals in the 700 mg/kg group were dosed with 1,400 mg/kg. No deaths occurred as a result of the dosing error, but two male mice had convulsions and labored breathing on the third day of overdosing. These animals were not dosed on the 4th day of the week to allow them to recover. Dosing resumed on the 5th day. Three males and two females died during the study due to gavage trauma. The males were from the 175, 350, and 700 mg/kg groups, and the females were from the 175 and 350 mg/kg groups, respectively.
	Metric 23:	Data Presentation and Analysis	High	General statistical methods for evaluating continuous data and incidence data were adequately reported and were appropriate for those data types.
	Metric 24:	Reporting of Data	Medium	Only initial and final animal body weights were reported (as means ± SE). Weekly body weights were measured but not reported, and individual animal data were not provided. The missing information is not expected to significantly impact the ability to interpret the study results.

Overall Quality Determination High

Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Renal/Kidney
Reported Health Effect(s):	Serum chemistry (BUN, creatinine), organ weights, gross necropsy, histopathology (kidney, bladder)
Duration:	Chronic (>91 days) 16-weeks (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was identified definitively as tris(2-chloroethyl phosphate) CASRN 115-96-8. A structure was also provided.
	Metric 2:	Test Substance Source	High	The test substance was manufactured by Stauffer Chemical Company and obtained from the analytical chemistry laboratory, Midwest Research Institute. The lot number was provided.
	Metric 3:	Test Substance Purity	High	The test chemical purity was ~98%, and was both provided by the supplier and confirmed via analysis (NMR and elemental analysis) by the study laboratory.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	The study included concurrent negative vehicle (corn oil) controls and conditions were consistent with the animals that were treated.
	Metric 5:	Positive Controls	N/A	Positive controls are not required for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	Animals were distributed into weight classes, and assigned to cages using a random number table. Cages were then assigned to treatment and control groups using another random number table.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) were also stable for 21 days in the dark at room temperature or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks
	Metric 8:	Consistency of Exposure Administration	High	All animals were gavaged on the same schedule. Gavage volumes were reported and were consistent across groups.
	Metric 9:	Reporting of Doses/Concentrations	Medium	Animals were dosed with 0, 44, 88, 175, 350, or 700 mg/kg-day, 5 days per week. Time-adjusted doses in mg/kg-day were not reported, but can be determined using the information provided. Dose formulations were analyzed twice during the study by gas chromatography and the target and measured concentrations in the solutions (mg/mL) were reported. The concentrations generally remained with 10% of the target concentration throughout the course of the study; however, during the second reading, the concentration used for the second-highest dose group was only 75% of the target.
	Metric 10:	Exposure Frequency and Duration	Medium	All mice were dosed 5 days per week for 16 weeks. Generally, the NTP guideline indicates that the subchronic studies should not be more than 97 days. The longer duration was not justified by the study authors. Dosing 5 days per week for a gavage study is consistent with NTP guidelines.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Renal/Kidney
Reported Health Effect(s):	Serum chemistry (BUN, creatinine), organ weights, gross necropsy, histopathology (kidney, bladder)
Duration:	Chronic (>91 days) 16-weeks (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	The study tested 5 dose groups plus a control. This is consistent with NTP guidelines. The spacing was sufficient to identify NOAEL and LOAEL values.
	Metric 12:	Exposure Route and Method	High	Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	High	The study used male and female B6C3F1 mice. The test animal source (Harlan industries), age at the start of the study (9-10 weeks old), and initial body weights were reported and appropriate.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Low	The number of animals per cage (5/cage) was reported; however, the NTP guideline specifies that male mice should always be housed individually. Food and water were provided ad libiutm. Animal room environments (temperature, humidity, lighting) were reported. The humidity ranged considerably from 10% to 78%. This deviates from NTP guidelines which state humidity should not be below 35% or above 65%. It is not clear what impact these deviations may have had on the study results.
	Metric 15:	Number of Animals per Group	Medium	The number of animals per group (10/sex) was reported and consistent with NTP guidelines.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	Organ weights and histopathological analysis were conducted on tissue(s) from this organ/system and the outcome assessment methods are considered to be sensitive and appropriate for this outcome of interest.
	Metric 17:	Consistency of Outcome Assessment	High	Sufficient details of the outcome assessment protocols were provided, and outcome assessment was carried out consistently across groups.
	Metric 18:	Sampling Adequacy	High	Histopathology was conducted on control animals and animals from the 44, 88, 175, 350, and 700 mg/kg-day groups. The sampling size for organ weight data was reported and was adequate.
	Metric 19:	Blinding of Assessors	N/A	Blinding is not necessary because this outcome of interest is either not subjective in nature, or blinding is not required (e.g., initial histopathology)
	Metric 20:	Negative Control Response	Medium	The appropriateness of the negative control response for histopathology cannot be determined because incidence data were not provided. The study authors did not describe any concerns about high background levels in controls. Organ weight data for controls appeared to be appropriate.
Domain 6: Confounding / Variable Control				

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Renal/Kidney
Reported Health Effect(s):	Serum chemistry (BUN, creatinine), organ weights, gross necropsy, histopathology (kidney, bladder)
Duration:	Chronic (>91 days) 16-weeks (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 21:	Confounding Variables in Test Design and Procedures	High	The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP. There were no significant body weight changes that were suggestive of any palatability issues (only increased body weights were observed).
	Metric 22:	Health Outcomes Unrelated to Exposure	Low	The study text noted that during week 4, the two highest dose groups were prepared incorrectly, and for the first three days of that week, the animals were administered double the target levels. Animals in the 350 mg/kg group, were instead dosed with 700 mg/kg, and animals in the 700 mg/kg group were dosed with 1,400 mg/kg. No deaths occurred as a result of the dosing error, but two male mice had convulsions and labored breathing on the third day of overdosing. These animals were not dosed on the 4th day of the week to allow them to recover. Dosing resumed on the 5th day. Three males and two females died during the study due to gavage trauma. The males were from the 175, 350, and 700 mg/kg groups, and the females were from the 175 and 350 mg/kg groups, respectively.
	Metric 23:	Data Presentation and Analysis	High	General statistical methods for evaluating continuous data and incidence data were adequately reported and were appropriate for those data types.
	Metric 24:	Reporting of Data	Low	Organ weight data were reported quantitatively. Data were presented as means ± SE. The text qualitatively stated that there were no gross lesions attributable to the test chemical. Treatment-related histopathology results in the kidney were described qualitatively in the text. Dose groups in which lesions were observed were noted; incidences were not specified but the text stated that lesions were observed in "all male and female mice" at the high dose. Statistical significance was not reported.

Overall Quality Determination High

Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Cardiovascular; Immune/Hematological; Hepatic/Liver; Lung/Respiratory;
Reported Health Effect(s):	Cardiovascular: Heart organ weights, gross necropsy, histopathology (heart); Immune/Hematological: Hematology (hematocrit, hemoglobin, erythrocytes, leukocytes with differential, MCV, MCH, MCHC, and reticulocyte count), thymus weights, gross pathology, histopathology (spleen, thymus, lymph nodes (mandibular and mesenteric), bone marrow); Hepatic/Liver: Liver weights, gross necropsy, histopathology, clinical chemistry (serum glucose, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, sorbitol dehydrogenase, cholesterol); Lung/Respiratory: Gross necropsy, histopathology (lung, nose, trachea);
Duration:	Chronic (>91 days) 16-weeks (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	All Outcomes: The test substance was identified definitively as tris(2-chloroethyl phosphate) CASRN 115-96-8. A structure was also provided.
	Metric 2:	Test Substance Source	High	All Outcomes: The test substance was manufactured by Stauffer Chemical Company and obtained from the analytical chemistry laboratory, Midwest Research Institute. The lot number was provided.
	Metric 3:	Test Substance Purity	High	All Outcomes: The test chemical purity was ~98%, and was both provided by the supplier and confirmed via analysis (NMR and elemental analysis) by the study laboratory.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	All Outcomes: The study included concurrent negative vehicle (corn oil) controls and conditions were consistent with the animals that were treated.
	Metric 5:	Positive Controls	N/A	All Outcomes: Positive controls are not required for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	All Outcomes: Animals were distributed into weight classes, and assigned to cages using a random number table. Cages were then assigned to treatment and control groups using another random number table.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	All Outcomes: Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) were also stable for 21 days in the dark at room temperature or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks
	Metric 8:	Consistency of Exposure Administration	High	All Outcomes: All animals were gavaged on the same schedule. Gavage volumes were reported and were consistent across groups.
	Metric 9:	Reporting of Doses/Concentrations	Medium	All Outcomes: Animals were dosed with 0, 44, 88, 175, 350, or 700 mg/kg-day, 5 days per week. Time-adjusted doses in mg/kg-day were not reported, but can be determined using the information provided. Dose formulations were analyzed twice during the study by gas chromatography and the target and measured concentrations in the solutions (mg/mL) were reported. The concentrations generally remained with 10% of the target concentration throughout the course of the study; however, during the second reading, the concentration used for the second-highest dose group was only 75% of the target.

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Health Outcome(s):	Cardiovascular; Immune/Hematological; Hepatic/Liver; Lung/Respiratory;
Reported Health Effect(s):	Cardiovascular: Heart organ weights, gross necropsy, histopathology (heart); Immune/Hematological: Hematology (hematocrit, hemoglobin, erythrocytes, leukocytes with differential, MCV, MCH, MCHC, and reticulocyte count), thymus weights, gross pathology, histopathology (spleen, thymus, lymph nodes (mandibular and mesenteric), bone marrow); Hepatic/Liver: Liver weights, gross necropsy, histopathology, clinical chemistry (serum glucose, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, sorbitol dehydrogenase, cholesterol); Lung/Respiratory: Gross necropsy, histopathology (lung, nose, trachea);
Duration:	Chronic (>91 days) 16-weeks (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 10:	Exposure Frequency and Duration	Medium	All Outcomes: All mice were dosed 5 days per week for 16 weeks. Generally, the NTP guideline indicates that the subchronic studies should not be more than 97 days. The longer duration was not justified by the study authors. Dosing 5 days per week for a gavage study is consistent with NTP guidelines.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	All Outcomes: The study tested 5 dose groups plus a control. This is consistent with NTP guidelines. The spacing was sufficient to identify NOAEL and LOAEL values.
	Metric 12:	Exposure Route and Method	High	All Outcomes: Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	High	All Outcomes: The study used male and female B6C3F1 mice. The test animal source (Harlan industries), age at the start of the study (9-10 weeks old), and initial body weights were reported and appropriate.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Low	All Outcomes: The number of animals per cage (5/cage) was reported; however, the NTP guideline specifies that male mice should always be housed individually. Food and water were provided ad libiutm. Animal room environments (temperature, humidity, lighting) were reported. The humidity ranged considerably from 10% to 78%. This deviates from NTP guidelines which state humidity should not be below 35% or above 65%. It is not clear what impact these deviations may have had on the study results.
	Metric 15:	Number of Animals per Group	Medium	All Outcomes: The number of animals per group (10/sex) was reported and consistent with NTP guidelines.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	All Outcomes: Organ weights and histopathological analysis were conducted on tissue(s) from this organ/system and the outcome assessment methods are considered to be sensitive and appropriate for this outcome of interest.
	Metric 17:	Consistency of Outcome Assessment	High	All Outcomes: Sufficient details of the outcome assessment protocols were provided, and outcome assessment was carried out consistently across groups.
	Metric 18:	Sampling Adequacy	High	All Outcomes: Histopathology was conducted on all control animals and animals from the highest dose group. This is not expected to have a significant impact on the study results because no lesions were purportedly observed for this outcome. The sampling size for organ weight data was reported and was adequate.
	Metric 19:	Blinding of Assessors	N/A	All Outcomes: Blinding is not necessary because this outcome of interest is either not subjective in nature, or blinding is not required (e.g., initial histopathology)

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Cardiovascular; Immune/Hematological; Hepatic/Liver; Lung/Respiratory;
Reported Health Effect(s):	Cardiovascular: Heart organ weights, gross necropsy, histopathology (heart); Immune/Hematological: Hematology (hematocrit, hemoglobin, erythrocytes, leukocytes with differential, MCV, MCH, MCHC, and reticulocyte count), thymus weights, gross pathology, histopathology (spleen, thymus, lymph nodes (mandibular and mesenteric), bone marrow); Hepatic/Liver: Liver weights, gross necropsy, histopathology, clinical chemistry (serum glucose, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, sorbitol dehydrogenase, cholesterol); Lung/Respiratory: Gross necropsy, histopathology (lung, nose, trachea);
Duration:	Chronic (>91 days) 16-weeks (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 20:	Negative Control Response	Medium	All Outcomes: The appropriateness of the negative control response for histopathology cannot be determined because incidence data were not provided. The study authors did not describe any concerns about high background levels in controls. Organ weight data for controls appeared to be appropriate.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	High	All Outcomes: The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP. There were no significant body weight changes that were suggestive of any palatability issues (only increased body weights were observed).
	Metric 22:	Health Outcomes Unrelated to Exposure	Low	All Outcomes: The study text noted that during week 4, the two highest dose groups were prepared incorrectly, and for the first three days of that week, the animals were administered double the target levels. Animals in the 350 mg/kg group, were instead dosed with 700 mg/kg, and animals in the 700 mg/kg group were dosed with 1,400 mg/kg. No deaths occurred as a result of the dosing error, but two male mice had convulsions and labored breathing on the third day of overdosing. These animals were not dosed on the 4th day of the week to allow them to recover. Dosing resumed on the 5th day. Three males and two females died during the study due to gavage trauma. The males were from the 175, 350, and 700 mg/kg groups, and the females were from the 175 and 350 mg/kg groups, respectively.
	Metric 23:	Data Presentation and Analysis	High	All Outcomes: General statistical methods for evaluating continuous data and incidence data were adequately reported and were appropriate for those data types.
	Metric 24:	Reporting of Data	Medium	All Outcomes: Organ weight data were reported quantitatively. Data were presented as means ± SE. The text qualitatively stated that there were no gross lesions attributable to the test chemical. Although histopathology results were observed for one organ/system (kidney), no statements noting the absence of effects were made for other tissues.

Overall Quality Determination High

Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Reproductive/Developmental
Reported Health Effect(s):	Gross necropsy and histopathology (clitoral gland, epididymis, mammary glands, ovary, preputial gland, prostate, seminal vesicle, testis, uterus)
Duration:	Chronic (>91 days) 16-weeks (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was identified definitively as tris(2-chloroethyl phosphate) CASRN 115-96-8. A structure was also provided.
	Metric 2:	Test Substance Source	High	The test substance was manufactured by Stauffer Chemical Company and obtained from the analytical chemistry laboratory, Midwest Research Institute. The lot number was provided.
	Metric 3:	Test Substance Purity	High	The test chemical purity was ~98%, and was both provided by the supplier and confirmed via analysis (NMR and elemental analysis) by the study laboratory.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	The study included concurrent negative vehicle (corn oil) controls and conditions were consistent with the animals that were treated.
	Metric 5:	Positive Controls	N/A	Positive controls are not required for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	Animals were distributed into weight classes, and assigned to cages using a random number table. Cages were then assigned to treatment and control groups using another random number table.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) were also stable for 21 days in the dark at room temperature or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks
	Metric 8:	Consistency of Exposure Administration	High	All animals were gavaged on the same schedule. Gavage volumes were reported and were consistent across groups.
	Metric 9:	Reporting of Doses/Concentrations	Medium	Animals were dosed with 0, 44, 88, 175, 350, or 700 mg/kg-day, 5 days per week. Time-adjusted doses in mg/kg-day were not reported, but can be determined using the information provided. Dose formulations were analyzed twice during the study by gas chromatography and the target and measured concentrations in the solutions (mg/mL) were reported. The concentrations generally remained with 10% of the target concentration throughout the course of the study; however, during the second reading, the concentration used for the second-highest dose group was only 75% of the target.
	Metric 10:	Exposure Frequency and Duration	Medium	All mice were dosed 5 days per week for 16 weeks. Generally, the NTP guideline indicates that the subchronic studies should not be more than 97 days. The longer duration was not justified by the study authors. Dosing 5 days per week for a gavage study is consistent with NTP guidelines.

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Health Outcome(s):	Reproductive/Developmental
Reported Health Effect(s):	Gross necropsy and histopathology (clitoral gland, epididymis, mammary glands, ovary, preputial gland, prostate, seminal vesicle, testis, uterus)
Duration:	Chronic (>91 days) 16-weeks (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	The study tested 5 dose groups plus a control. This is consistent with NTP guidelines. The spacing was sufficient to identify NOAEL and LOAEL values.
	Metric 12:	Exposure Route and Method	High	Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	High	The study used male and female B6C3F1 mice. The test animal source (Harlan industries), age at the start of the study (9-10 weeks old), and initial body weights were reported and appropriate.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Low	The number of animals per cage (5/cage) was reported; however, the NTP guideline specifies that male mice should always be housed individually. Food and water were provided ad libiutm. Animal room environments (temperature, humidity, lighting) were reported. The humidity ranged considerably from 10% to 78%. This deviates from NTP guidelines which state humidity should not be below 35% or above 65%. It is not clear what impact these deviations may have had on the study results.
	Metric 15:	Number of Animals per Group	Medium	The number of animals per group (10/sex) was reported and consistent with NTP guidelines.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	Organ weights and histopathological analysis were conducted on tissue(s) from this organ/system and the outcome assessment methods are considered to be sensitive and appropriate for this outcome of interest. Testis was not listed in the methods as an organ that was being weighed, but the results reported organ weight results.
	Metric 17:	Consistency of Outcome Assessment	High	Sufficient details of the outcome assessment protocols were provided, and outcome assessment was carried out consistently across groups.
	Metric 18:	Sampling Adequacy	Low	Histopathology was conducted on all control animals and animals from the highest dose group. This is not expected to have a significant impact on the study results because no lesions were purportedly observed for this outcome. Less than two measurements of testis weights were available for the 88 mg/kg group. No testes weights were reported for the 350 mg/kg group but significant changes were observed at the high dose. It is unclear why there were deficiencies in sampling.
	Metric 19:	Blinding of Assessors	N/A	Blinding is not necessary because this outcome of interest is either not subjective in nature, or blinding is not required (e.g., initial histopathology)
	Metric 20:	Negative Control Response	Medium	The appropriateness of the negative control response for histopathology cannot be determined because incidence data were not provided. The study authors did not describe any concerns about high background levels in controls. Organ weight data for controls appeared to be appropriate.

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Health Outcome(s):	Reproductive/Developmental
Reported Health Effect(s):	Gross necropsy and histopathology (clitoral gland, epididymis, mammary glands, ovary, preputial gland, prostate, seminal vesicle, testis, uterus)
Duration:	Chronic (>91 days) 16-weeks (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric	Rating	Comments
Domain 6: Confounding / Variable Control			
	Metric 21: Confounding Variables in Test Design and Procedures	High	The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP. There were no significant body weight changes that were suggestive of any palatability issues (only increased body weights were observed).
	Metric 22: Health Outcomes Unrelated to Exposure	Low	The study text noted that during week 4, the two highest dose groups were prepared incorrectly, and for the first three days of that week, the animals were administered double the target levels. Animals in the 350 mg/kg group, were instead dosed with 700 mg/kg, and animals in the 700 mg/kg group were dosed with 1,400 mg/kg. No deaths occurred as a result of the dosing error, but two male mice had convulsions and labored breathing on the third day of overdosing. These animals were not dosed on the 4th day of the week to allow them to recover. Dosing resumed on the 5th day. Three males and two females died during the study due to gavage trauma. The males were from the 175, 350, and 700 mg/kg groups, and the females were from the 175 and 350 mg/kg groups, respectively.
	Metric 23: Data Presentation and Analysis	High	General statistical methods for evaluating continuous data and incidence data were adequately reported and were appropriate for those data types.
	Metric 24: Reporting of Data	Medium	Organ weight data were reported quantitatively. Data were presented as means ± SE. The text qualitatively stated that there were no gross lesions attributable to the test chemical. Although histopathology results were observed for one organ/system (kidney), no statements noting the absence of effects were made for other tissues.

Overall Quality Determination High

Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Gastrointestinal; Thyroid; Skin/Connective Tissue; Musculoskeletal; Ocular/Sensory; Endocrine (Endocrine);
Reported Health Effect(s):	Gastrointestinal: Gross necropsy and histopathology (esophagus, gall bladder (mice only), large intestines (cecum, colon, rectum), salivary gland, small intestines (duodenum, ileum, jejunum), stomach, mesentery, tooth); Thyroid: Gross necropsy and histopathology (thyroid); Skin/Connective Tissue: Gross necropsy, histopathology (skin); Musculoskeletal: Gross necropsy, histopathology (skeletal muscle, bone); Ocular/Sensory: Gross necropsy, histopathology (harderian gland); Endocrine (Endocrine): Gross necropsy and histopathology (pancreas, adrenal glands, pituitary glands, parathyroid);
Duration:	Chronic (>91 days) 16-weeks (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	All Outcomes: The test substance was identified definitively as tris(2-chloroethyl phosphate) CASRN 115-96-8. A structure was also provided.
	Metric 2:	Test Substance Source	High	All Outcomes: The test substance was manufactured by Stauffer Chemical Company and obtained from the analytical chemistry laboratory, Midwest Research Institute. The lot number was provided.
	Metric 3:	Test Substance Purity	High	All Outcomes: The test chemical purity was ~98%, and was both provided by the supplier and confirmed via analysis (NMR and elemental analysis) by the study laboratory.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	All Outcomes: The study included concurrent negative vehicle (corn oil) controls and conditions were consistent with the animals that were treated.
	Metric 5:	Positive Controls	N/A	All Outcomes: Positive controls are not required for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	All Outcomes: Animals were distributed into weight classes, and assigned to cages using a random number table. Cages were then assigned to treatment and control groups using another random number table.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	All Outcomes: Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) were also stable for 21 days in the dark at room temperature or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks
	Metric 8:	Consistency of Exposure Administration	High	All Outcomes: All animals were gavaged on the same schedule. Gavage volumes were reported and were consistent across groups.
	Metric 9:	Reporting of Doses/Concentrations	Medium	All Outcomes: Animals were dosed with 0, 44, 88, 175, 350, or 700 mg/kg-day, 5 days per week. Time-adjusted doses in mg/kg-day were not reported, but can be determined using the information provided. Dose formulations were analyzed twice during the study by gas chromatography and the target and measured concentrations in the solutions (mg/mL) were reported. The concentrations generally remained with 10% of the target concentration throughout the course of the study; however, during the second reading, the concentration used for the second-highest dose group was only 75% of the target.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Gastrointestinal; Thyroid; Skin/Connective Tissue; Musculoskeletal; Ocular/Sensory; Endocrine (Endocrine);
Reported Health Effect(s):	Gastrointestinal: Gross necropsy and histopathology (esophagus, gall bladder (mice only), large intestines (cecum, colon, rectum), salivary gland, small intestines (duodenum, ileum, jejunum), stomach, mesentery, tooth); Thyroid: Gross necropsy and histopathology (thyroid); Skin/Connective Tissue: Gross necropsy, histopathology (skin); Musculoskeletal: Gross necropsy, histopathology (skeletal muscle, bone); Ocular/Sensory: Gross necropsy, histopathology (harderian gland); Endocrine (Endocrine): Gross necropsy and histopathology (pancreas, adrenal glands, pituitary glands, parathyroid);
Duration:	Chronic (>91 days) 16-weeks (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 10:	Exposure Frequency and Duration	Medium	All Outcomes: All mice were dosed 5 days per week for 16 weeks. Generally, the NTP guideline indicates that the subchronic studies should not be more than 97 days. The longer duration was not justified by the study authors. Dosing 5 days per week for a gavage study is consistent with NTP guidelines.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	All Outcomes: The study tested 5 dose groups plus a control. This is consistent with NTP guidelines. The spacing was sufficient to identify NOAEL and LOAEL values.
	Metric 12:	Exposure Route and Method	High	All Outcomes: Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	High	All Outcomes: The study used male and female B6C3F1 mice. The test animal source (Harlan industries), age at the start of the study (9-10 weeks old), and initial body weights were reported and appropriate.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Low	All Outcomes: The number of animals per cage (5/cage) was reported; however, the NTP guideline specifies that male mice should always be housed individually. Food and water were provided ad libiutm. Animal room environments (temperature, humidity, lighting) were reported. The humidity ranged considerably from 10% to 78%. This deviates from NTP guidelines which state humidity should not be below 35% or above 65%. It is not clear what impact these deviations may have had on the study results.
	Metric 15:	Number of Animals per Group	Medium	All Outcomes: The number of animals per group (10/sex) was reported and consistent with NTP guidelines.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	All Outcomes: Histopathological analysis was conducted on tissue(s) from this organ/system and histopathology is considered to be a sensitive and appropriate method for this outcome of interest.
	Metric 17:	Consistency of Outcome Assessment	High	All Outcomes: Sufficient details of the outcome assessment protocols were provided, and outcome assessment was carried out consistently across groups.
	Metric 18:	Sampling Adequacy	Medium	All Outcomes: Histopathology was conducted on all control animals and animals from the highest dose group. This is not expected to have a significant impact on the study results because no lesions were purportedly observed for this outcome.
	Metric 19:	Blinding of Assessors	N/A	All Outcomes: Blinding is not necessary because this outcome of interest is either not subjective in nature, or blinding is not required (e.g., initial histopathology)

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Gastrointestinal; Thyroid; Skin/Connective Tissue; Musculoskeletal; Ocular/Sensory; Endocrine (Endocrine);
Reported Health Effect(s):	Gastrointestinal: Gross necropsy and histopathology (esophagus, gall bladder (mice only), large intestines (cecum, colon, rectum), salivary gland, small intestines (duodenum, ileum, jejunum), stomach, mesentery, tooth); Thyroid: Gross necropsy and histopathology (thyroid); Skin/Connective Tissue: Gross necropsy, histopathology (skin); Musculoskeletal: Gross necropsy, histopathology (skeletal muscle, bone); Ocular/Sensory: Gross necropsy, histopathology (harderian gland); Endocrine (Endocrine): Gross necropsy and histopathology (pancreas, adrenal glands, pituitary glands, parathyroid);
Duration:	Chronic (>91 days) 16-weeks (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 20:	Negative Control Response	Low	All Outcomes: The appropriateness of the negative control response for histopathology cannot be determined because incidence data were not provided. The study authors did not describe any concerns of high background in controls.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	High	All Outcomes: The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP. There were no significant body weight changes that were suggestive of any palatability issues (only increased body weights were observed).
	Metric 22:	Health Outcomes Unrelated to Exposure	Low	All Outcomes: The study text noted that during week 4, the two highest dose groups were prepared incorrectly, and for the first three days of that week, the animals were administered double the target levels. Animals in the 350 mg/kg group, were instead dosed with 700 mg/kg, and animals in the 700 mg/kg group were dosed with 1,400 mg/kg. No deaths occurred as a result of the dosing error, but two male mice had convulsions and labored breathing on the third day of overdosing. These animals were not dosed on the 4th day of the week to allow them to recover. Dosing resumed on the 5th day. Three males and two females died during the study due to gavage trauma. The males were from the 175, 350, and 700 mg/kg groups, and the females were from the 175 and 350 mg/kg groups, respectively.
	Metric 23:	Data Presentation and Analysis	High	All Outcomes: General statistical methods for evaluating continuous data and incidence data were adequately reported and were appropriate for those data types.
	Metric 24:	Reporting of Data	Medium	All Outcomes: The text qualitatively stated that there were no gross lesions attributable to the test chemical. Although histopathology results were observed for one organ/system (kidney), no statements noting the absence of effects were made for other tissues.

Overall Quality Determination High

Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Neurological/Behavioral
Reported Health Effect(s):	Serum cholinesterase activity (special study 16-day and 16-week studies, and as part of serum chemistry in 2-yr study), brain weights, gross necropsy, histopathology (brain)
Duration:	Chronic (>91 days) 16-weeks (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was identified definitively as tris(2-chloroethyl phosphate) CASRN 115-96-8. A structure was also provided.
	Metric 2:	Test Substance Source	High	The test substance was manufactured by Stauffer Chemical Company and obtained from the analytical chemistry laboratory, Midwest Research Institute. The lot number was provided.
	Metric 3:	Test Substance Purity	High	The test chemical purity was ~98%, and was both provided by the supplier and confirmed via analysis (NMR and elemental analysis) by the study laboratory.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	The study included concurrent negative vehicle (corn oil) controls and conditions were consistent with the animals that were treated.
	Metric 5:	Positive Controls	N/A	Positive controls are not required for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	Animals were distributed into weight classes, and assigned to cages using a random number table. Cages were then assigned to treatment and control groups using another random number table.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) were also stable for 21 days in the dark at room temperature or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks
	Metric 8:	Consistency of Exposure Administration	High	All animals were gavaged on the same schedule. Gavage volumes were reported and were consistent across groups.
	Metric 9:	Reporting of Doses/Concentrations	Medium	Animals were dosed with 0, 44, 88, 175, 350, or 700 mg/kg-day, 5 days per week. Time-adjusted doses in mg/kg-day were not reported, but can be determined using the information provided. Dose formulations were analyzed twice during the study by gas chromatography and the target and measured concentrations in the solutions (mg/mL) were reported. The concentrations generally remained with 10% of the target concentration throughout the course of the study; however, during the second reading, the concentration used for the second-highest dose group was only 75% of the target.
	Metric 10:	Exposure Frequency and Duration	Medium	All mice were dosed 5 days per week for 16 weeks. Generally, the NTP guideline indicates that the subchronic studies should not be more than 97 days. The longer duration was not justified by the study authors. Dosing 5 days per week for a gavage study is consistent with NTP guidelines.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Neurological/Behavioral
Reported Health Effect(s):	Serum cholinesterase activity (special study 16-day and 16-week studies, and as part of serum chemistry in 2-yr study), brain weights, gross necropsy, histopathology (brain)
Duration:	Chronic (>91 days) 16-weeks (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	The study tested 5 dose groups plus a control. This is consistent with NTP guidelines. The spacing was sufficient to identify NOAEL and LOAEL values.
	Metric 12:	Exposure Route and Method	High	Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	High	The study used male and female B6C3F1 mice. The test animal source (Harlan industries), age at the start of the study (9-10 weeks old), and initial body weights were reported and appropriate.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Low	The number of animals per cage (5/cage) was reported; however, the NTP guideline specifies that male mice should always be housed individually. Food and water were provided ad libiutm. Animal room environments (temperature, humidity, lighting) were reported. The humidity ranged considerably from 10% to 78%. This deviates from NTP guidelines which state humidity should not be below 35% or above 65%. It is not clear what impact these deviations may have had on the study results.
	Metric 15:	Number of Animals per Group	Medium	The number of animals per group (10/sex) was reported and consistent with NTP guidelines.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	Serum cholinesterase activity was determined at study termination. Absolute and relative organ weights were recorded and histopathological analysis was conducted on tissue(s) from this organ/system. The outcome assessment methods were sensitive and appropriate for this outcome of interest.
	Metric 17:	Consistency of Outcome Assessment	Medium	Sufficient details of the outcome assessment protocols (organ weights and histopathology) were provided, and outcome assessment was carried out consistently across groups. Blood for measurement of cholinesterase activity was collected from all animals at terminal sacrifice.
	Metric 18:	Sampling Adequacy	High	Histopathology was conducted on all control animals and animals from the highest dose group. This is not expected to have a significant impact on the study results because no lesions were purportedly observed for this outcome. The sampling size for organ weights and cholinesterase measurements was reported and were adequate.
	Metric 19:	Blinding of Assessors	N/A	Blinding is not necessary because this outcome of interest is either not subjective in nature, or blinding is not required (e.g., initial histopathology)
	Metric 20:	Negative Control Response	Medium	The appropriateness of the negative control response for histopathology cannot be determined because incidence data were not provided. The study authors did not describe any concerns about high background levels in controls. Organ weight and serum cholinesterase data for controls appeared to be appropriate.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Neurological/Behavioral
Reported Health Effect(s):	Serum cholinesterase activity (special study 16-day and 16-week studies, and as part of serum chemistry in 2-yr study), brain weights, gross necropsy, histopathology (brain)
Duration:	Chronic (>91 days) 16-weeks (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric	Rating	Comments
Domain 6: Confounding / Variable Control			
	Metric 21: Confounding Variables in Test Design and Procedures	High	The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP. There were no significant body weight changes that were suggestive of any palatability issues (only increased body weights were observed).
	Metric 22: Health Outcomes Unrelated to Exposure	Low	The study text noted that during week 4, the two highest dose groups were prepared incorrectly, and for the first three days of that week, the animals were administered double the target levels. Animals in the 350 mg/kg group, were instead dosed with 700 mg/kg, and animals in the 700 mg/kg group were dosed with 1,400 mg/kg. No deaths occurred as a result of the dosing error, but two male mice had convulsions and labored breathing on the third day of overdosing. These animals were not dosed on the 4th day of the week to allow them to recover. Dosing resumed on the 5th day. Three males and two females died during the study due to gavage trauma. The males were from the 175, 350, and 700 mg/kg groups, and the females were from the 175 and 350 mg/kg groups, respectively.
	Metric 23: Data Presentation and Analysis	High	General statistical methods for evaluating continuous data and incidence data were adequately reported and were appropriate for those data types.
	Metric 24: Reporting of Data	Medium	Cholinesterase activity and organ weight data were quantitatively reported as means $\pm$ SE. The text qualitatively stated that there were no gross lesions attributable to the test chemical. Although histopathology results were observed for one organ/system (kidney), no statements noting the absence of effects were made for other tissues.

Overall Quality Determination High

Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Unspecified clinical observations (Clinical signs)
Reported Health Effect(s):	Clinical signs (clinical observations)
Duration:	Chronic (>91 days) 16-weeks (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was identified definitively as tris(2-chloroethyl phosphate) CASRN 115-96-8. A structure was also provided.
	Metric 2:	Test Substance Source	High	The test substance was manufactured by Stauffer Chemical Company and obtained from the analytical chemistry laboratory, Midwest Research Institute. The lot number was provided.
	Metric 3:	Test Substance Purity	High	The test chemical purity was ~98%, and was both provided by the supplier and confirmed via analysis (NMR and elemental analysis) by the study laboratory.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	The study included concurrent negative vehicle (corn oil) controls and conditions were consistent with the animals that were treated.
	Metric 5:	Positive Controls	N/A	Positive controls are not required for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	Animals were distributed into weight classes, and assigned to cages using a random number table. Cages were then assigned to treatment and control groups using another random number table.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) were also stable for 21 days in the dark at room temperature or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks
	Metric 8:	Consistency of Exposure Administration	High	All animals were gavaged on the same schedule. Gavage volumes were reported and were consistent across groups.
	Metric 9:	Reporting of Doses/Concentrations	Medium	Animals were dosed with 0, 44, 88, 175, 350, or 700 mg/kg-day, 5 days per week. Time-adjusted doses in mg/kg-day were not reported, but can be determined using the information provided. Dose formulations were analyzed twice during the study by gas chromatography and the target and measured concentrations in the solutions (mg/mL) were reported. The concentrations generally remained with 10% of the target concentration throughout the course of the study; however, during the second reading, the concentration used for the second-highest dose group was only 75% of the target.
	Metric 10:	Exposure Frequency and Duration	Medium	All mice were dosed 5 days per week for 16 weeks. Generally, the NTP guideline indicates that the subchronic studies should not be more than 97 days. The longer duration was not justified by the study authors. Dosing 5 days per week for a gavage study is consistent with NTP guidelines.

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Health Outcome(s):	Unspecified clinical observations (Clinical signs)
Reported Health Effect(s):	Clinical signs (clinical observations)
Duration:	Chronic (>91 days) 16-weeks (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	The study tested 5 dose groups plus a control. This is consistent with NTP guidelines. The spacing was sufficient to identify NOAEL and LOAEL values.
	Metric 12:	Exposure Route and Method	High	Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	High	The study used male and female B6C3F1 mice. The test animal source (Harlan industries), age at the start of the study (9-10 weeks old), and initial body weights were reported and appropriate.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Low	The number of animals per cage (5/cage) was reported; however, the NTP guideline specifies that male mice should always be housed individually. Food and water were provided ad libiutm. Animal room environments (temperature, humidity, lighting) were reported. The humidity ranged considerably from 10% to 78%. This deviates from NTP guidelines which state humidity should not be below 35% or above 65%. It is not clear what impact these deviations may have had on the study results.
	Metric 15:	Number of Animals per Group	Medium	The number of animals per group (10/sex) was reported and consistent with NTP guidelines.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	Medium	Animals were subjected to clinical examinations weekly in accordance with NTP guidelines. No methodological details were provided. The guideline also specifies that expanded clinical observations should be done by a pathologist at a minimum of at least once every other week. It is unclear if this was done.
	Metric 17:	Consistency of Outcome Assessment	Medium	Based on the information provided, all animals were observed daily. Additional outcome assessment methods (e.g., the time of observations (time of day)) were not provided, but based on the available information, there is no indication that there were differences across groups.
	Metric 18:	Sampling Adequacy	Low	All animals were observed for clinical signs, but since findings were qualitatively reported, the sample size cannot be verified.
	Metric 19:	Blinding of Assessors	Medium	Blinding was not reported and clinical signs can be somewhat subjective in nature.
	Metric 20:	Negative Control Response	Low	The appropriateness of the negative control response cannot be definitively determined because incidence data were not reported, the text mentioned some clinical signs in treated animals but did not explicitly report that there were no clinical signs in controls.
Domain 6: Confounding / Variable Control				

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Health Outcome(s):	Unspecified clinical observations (Clinical signs)
Reported Health Effect(s):	Clinical signs (clinical observations)
Duration:	Chronic (>91 days) 16-weeks (mice)
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 21:	Confounding Variables in Test Design and Procedures	High	The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP. There were no significant body weight changes that were suggestive of any palatability issues (only increased body weights were observed).
	Metric 22:	Health Outcomes Unrelated to Exposure	Low	The study text noted that during week 4, the two highest dose groups were prepared incorrectly, and for the first three days of that week, the animals were administered double the target levels. Animals in the 350 mg/kg group, were instead dosed with 700 mg/kg, and animals in the 700 mg/kg group were dosed with 1,400 mg/kg. No deaths occurred as a result of the dosing error, but two male mice had convulsions and labored breathing on the third day of overdosing. These animals were not dosed on the 4th day of the week to allow them to recover. Dosing resumed on the 5th day. Three males and two females died during the study due to gavage trauma. The males were from the 175, 350, and 700 mg/kg groups, and the females were from the 175 and 350 mg/kg groups, respectively.
	Metric 23:	Data Presentation and Analysis	Uninformative	Statistical methods were adequately described in general for different types of data sets; however, methods for statistical analysis specifically for clinical observations were not described, and the text does not report whether incidences of the observed effects were significantly increased compared to controls. It is unclear whether the data were statistically analyzed and quantitative data were not provided to do an independent analysis.
	Metric 24:	Reporting of Data	Low	Transient clinical signs were qualitatively reported in the text and statistical significance was not specified.

Overall Quality Determination — Uninformative

Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Nutritional/Metabolic
Reported Health Effect(s):	Body weights
Duration:	Chronic (>91 days) 16-weeks (females) 18-weeks (males) - rat
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was identified definitively as tris(2-chloroethyl phosphate) CASRN 115-96-8. A structure was also provided.
	Metric 2:	Test Substance Source	High	The test substance was manufactured by Stauffer Chemical Company and obtained from the analytical chemistry laboratory, Midwest Research Institute. The lot number was provided.
	Metric 3:	Test Substance Purity	High	The test chemical purity was ~98%, and was both provided by the supplier and confirmed via analysis (NMR and elemental analysis) by the study laboratory.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	The study included concurrent negative vehicle (corn oil) controls and conditions were consistent with the animals that were treated.
	Metric 5:	Positive Controls	N/A	Positive controls are not required for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	Animals were distributed into weight classes, and assigned to cages using a random number table. Cages were then assigned to treatment and control groups using another random number table.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) were also stable for 21 days in the dark at room temperature or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks
	Metric 8:	Consistency of Exposure Administration	High	All animals were gavaged on the same schedule. Gavage volumes were reported and were consistent across groups.
	Metric 9:	Reporting of Doses/Concentrations	Medium	Animals were dosed with 0, 22, 44, 88, 175, or 350 mg/kg-day, 5 days per week. Adjusted daily doses were not reported, but can be determined using the information provided. Dose formulations were analyzed twice during the study by gas chromatography and the target and measured concentrations in the solutions (mg/mL) were reported. The concentrations generally remained with 10% of the target concentrations throughout the course of the study; however, during the second reading, the concentration used for the second highest dose group was only 75% of the target.

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Health Outcome(s):	Nutritional/Metabolic
Reported Health Effect(s):	Body weights
Duration:	Chronic (>91 days) 16-weeks (females) 18-weeks (males) - rat
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 10:	Exposure Frequency and Duration	Medium	Females were dosed 5 days per week for 16 weeks, and males were dosed 5 days per week for 18 weeks. It is unclear why the duration of exposure was different for males and females. Generally, the NTP guideline indicates that the subchronic studies should not be more than 97 days. The 16-18-week durations were not justified by the study authors. Dosing 5 days per week for a gavage study is consistent with NTP guidelines.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	Medium	The study tested 5 dose groups plus a control. This is consistent with NTP guidelines. The spacing was sufficient to identify NOAEL and LOAEL values.
	Metric 12:	Exposure Route and Method	High	Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	High	The study used male and female F344/N rats. The test animal source (Harlan industries), age at the start of the study (8-9-weeks old), and initial body weights were reported and appropriate.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	The number of animals per cage (5/cage) was reported. Food and water were provided ad libitum. Animal room environments (temperature, humidity, lighting) were reported. The humidity ranged considerably from 10% to 78%. This deviates from NTP guidelines which state humidity should not be below 35% or above 65%. It is unclear whether these deviations had an impact on the study results
	Metric 15:	Number of Animals per Group	Medium	The number of animals per group (10/sex) was reported and consistent with NTP guidelines.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	The outcome assessment methods were sensitive and appropriate for the outcome of interest. Body weights were recorded at study initiation, then weekly thereafter, and again at termination as per NTP guidelines.
	Metric 17:	Consistency of Outcome Assessment	High	Body weights were consistently assessed across groups using the same protocol.
	Metric 18:	Sampling Adequacy	High	All animals were sampled for this outcome of interest.
	Metric 19:	Blinding of Assessors	N/A	Blinding is not necessary because this outcome of interest is not subjective in nature, or blinding is not required for this outcome of interest.
	Metric 20:	Negative Control Response	High	The control responses were reported and were appropriate.
Domain 6: Confounding / Variable Control				

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Health Outcome(s):	Nutritional/Metabolic
Reported Health Effect(s):	Body weights
Duration:	Chronic (>91 days) 16-weeks (females) 18-weeks (males) - rat
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	The initial body weights of the females in the 175 mg/kg group were statistically significantly lower than controls by 5%. The study authors had claimed animals were normalized by weight, so this is surprising. The difference didn't seem to have an impact on later body weight measurements. The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP. There were no significant body weight changes that were suggestive of any palatability issues (only increased body weights were observed).
	Metric 22:	Health Outcomes Unrelated to Exposure	Low	The study text noted that during week 4, the two highest dose groups were prepared incorrectly, and for the first three days of that week, the animals were administered double the target levels. Animals in the 175 mg/kg group, were instead dosed with 350 mg/kg, and animals in the 350 mg/kg group were dosed with 700 mg/kg. As a result, 2 females in each group died, and others showed excessive signs of acute toxicity (e.g., ataxia, excessive salivation, gasping, and convulsions). The overdose caused no deaths in males, and males showed no signs of toxicity. The surviving animals were not dosed on the 4th day of the week to allow them to recover. Dosing resumed on the 5th day. The study authors did not believe this error had a significant impact on the outcomes assessed at the end of the study. In addition to the deaths due to overdose, three animals died due to gavage error including 1 male and 1 female at 22 mg/kg and 1 female at 175 mg/kg.
	Metric 23:	Data Presentation and Analysis	High	Statistical methods were adequately described and were appropriate for the dataset. Statistical significance was shown where appropriate.
	Metric 24:	Reporting of Data	Medium	Only initial and final animal body weights were reported (as means ± SE). Weekly body weights were measured but were not provided, and individual animal data were not provided. The missing information is not expected to significantly impact the ability to interpret the study results.

Overall Quality Determination — High

Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Gastrointestinal; Musculoskeletal; Ocular/Sensory; Thyroid; Skin/Connective Tissue; Endocrine (Endocrine);
Reported Health Effect(s):	Gastrointestinal: Gross necropsy and histopathology (esophagus, gall bladder (mice only), large intestines (cecum, colon, rectum), salivary gland, small intestines (duodenum, ileum, jejunum), stomach, mesentery, tooth); Musculoskeletal: Gross necropsy, histopathology (skeletal muscle, bone); Ocular/Sensory: Gross necropsy, histopathology (harderian gland); Thyroid: Gross necropsy and histopathology (thyroid); Skin/Connective Tissue: Gross necropsy, histopathology (skin); Endocrine (Endocrine): Gross necropsy and histopathology (pancreas, adrenal glands, pituitary glands, parathyroid);
Duration:	Chronic (>91 days) 16-weeks (females) 18-weeks (males) - rat
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	All Outcomes: The test substance was identified definitively as tris(2-chloroethyl phosphate) CASRN 115-96-8. A structure was also provided.
	Metric 2:	Test Substance Source	High	All Outcomes: The test substance was manufactured by Stauffer Chemical Company and obtained from the analytical chemistry laboratory, Midwest Research Institute. The lot number was provided.
	Metric 3:	Test Substance Purity	High	All Outcomes: The test chemical purity was ~98%, and was both provided by the supplier and confirmed via analysis (NMR and elemental analysis) by the study laboratory.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	All Outcomes: The study included concurrent negative vehicle (corn oil) controls and conditions were consistent with the animals that were treated.
	Metric 5:	Positive Controls	N/A	All Outcomes: Positive controls are not required for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	All Outcomes: Animals were distributed into weight classes, and assigned to cages using a random number table. Cages were then assigned to treatment and control groups using another random number table.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	All Outcomes: Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) were also stable for 21 days in the dark at room temperature or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks
	Metric 8:	Consistency of Exposure Administration	High	All Outcomes: All animals were gavaged on the same schedule. Gavage volumes were reported and were consistent across groups.
	Metric 9:	Reporting of Doses/Concentrations	Medium	All Outcomes: Animals were dosed with 0, 22, 44, 88, 175, or 350 mg/kg-day, 5 days per week. Adjusted daily doses were not reported, but can be determined using the information provided. Dose formulations were analyzed twice during the study by gas chromatography and the target and measured concentrations in the solutions (mg/mL) were reported. The concentrations generally remained with 10% of the target concentrations throughout the course of the study; however, during the second reading, the concentration used for the second highest dose group was only 75% of the target.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Gastrointestinal; Musculoskeletal; Ocular/Sensory; Thyroid; Skin/Connective Tissue; Endocrine (Endocrine);
Reported Health Effect(s):	Gastrointestinal: Gross necropsy and histopathology (esophagus, gall bladder (mice only), large intestines (cecum, colon, rectum), salivary gland, small intestines (duodenum, ileum, jejunum), stomach, mesentery, tooth); Musculoskeletal: Gross necropsy, histopathology (skeletal muscle, bone); Ocular/Sensory: Gross necropsy, histopathology (harderian gland); Thyroid: Gross necropsy and histopathology (thyroid); Skin/Connective Tissue: Gross necropsy, histopathology (skin); Endocrine (Endocrine): Gross necropsy and histopathology (pancreas, adrenal glands, pituitary glands, parathyroid);
Duration:	Chronic (>91 days) 16-weeks (females) 18-weeks (males) - rat
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 10:	Exposure Frequency and Duration	Medium	All Outcomes: Females were dosed 5 days per week for 16 weeks, and males were dosed 5 days per week for 18 weeks. It is unclear why the duration of exposure was different for males and females. Generally, the NTP guideline indicates that the subchronic studies should not be more than 97 days. The 16-18-week durations were not justified by the study authors. Dosing 5 days per week for a gavage study is consistent with NTP guidelines.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	Medium	All Outcomes: The study tested 5 dose groups plus a control. This is consistent with NTP guidelines. The spacing was sufficient to identify NOAEL and LOAEL values.
	Metric 12:	Exposure Route and Method	High	All Outcomes: Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	High	All Outcomes: The study used male and female F344/N rats. The test animal source (Harlan industries), age at the start of the study (8-9-weeks old), and initial body weights were reported and appropriate.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	All Outcomes: The number of animals per cage (5/cage) was reported. Food and water were provided ad libitum. Animal room environments (temperature, humidity, lighting) were reported. The humidity ranged considerably from 10% to 78%. This deviates from NTP guidelines which state humidity should not be below 35% or above 65%. It is unclear whether these deviations had an impact on the study results
	Metric 15:	Number of Animals per Group	Medium	All Outcomes: The number of animals per group (10/sex) was reported and consistent with NTP guidelines.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	All Outcomes: Histopathological analyses were conducted on tissue(s) from this organ/system. This method is sensitive and appropriate for this outcome of interest and is consistent with NTP guidelines.
	Metric 17:	Consistency of Outcome Assessment	High	All Outcomes: Sufficient details of the outcome assessment protocols were provided, and outcome assessment was carried out consistently across groups.
	Metric 18:	Sampling Adequacy	High	All Outcomes: Histopathology was conducted on tissues from controls and the top two dose groups; this was appropriate given the lack of effects observed for this outcome.
	Metric 19:	Blinding of Assessors	N/A	All Outcomes: Blinding is not necessary because this outcome of interest is not subjective in nature, or blinding is not required for this outcome of interest.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Gastrointestinal; Musculoskeletal; Ocular/Sensory; Thyroid; Skin/Connective Tissue; Endocrine (Endocrine);
Reported Health Effect(s):	Gastrointestinal: Gross necropsy and histopathology (esophagus, gall bladder (mice only), large intestines (cecum, colon, rectum), salivary gland, small intestines (duodenum, ileum, jejunum), stomach, mesentery, tooth); Musculoskeletal: Gross necropsy, histopathology (skeletal muscle, bone); Ocular/Sensory: Gross necropsy, histopathology (harderian gland); Thyroid: Gross necropsy and histopathology (thyroid); Skin/Connective Tissue: Gross necropsy, histopathology (skin); Endocrine (Endocrine): Gross necropsy and histopathology (pancreas, adrenal glands, pituitary glands, parathyroid);
Duration:	Chronic (>91 days) 16-weeks (females) 18-weeks (males) - rat
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 20:	Negative Control Response	Low	All Outcomes: The appropriateness of the negative control response for histopathology cannot be determined because incidence data were not provided. The study authors did not describe any concerns about high background in controls.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	All Outcomes: The initial body weights of the females in the 175 mg/kg group were statistically significantly lower than controls by 5%. The study authors had claimed animals were normalized by weight, so this is surprising. The difference didn't seem to have an impact on later body weight measurements. The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP. There were no significant body weight changes that were suggestive of any palatability issues (only increased body weights were observed).
	Metric 22:	Health Outcomes Unrelated to Exposure	Low	All Outcomes: The study text noted that during week 4, the two highest dose groups were prepared incorrectly, and for the first three days of that week, the animals were administered double the target levels. Animals in the 175 mg/kg group, were instead dosed with 350 mg/kg, and animals in the 350 mg/kg group were dosed with 700 mg/kg. As a result, 2 females in each group died, and others showed excessive signs of acute toxicity (e.g., ataxia, excessive salivation, gasping, and convulsions). The overdose caused no deaths in males, and males showed no signs of toxicity. The surviving animals were not dosed on the 4th day of the week to allow them to recover. Dosing resumed on the 5th day. The study authors did not believe this error had a significant impact on the outcomes assessed at the end of the study. In addition to the deaths due to overdose, three animals died due to gavage error including 1 male and 1 female at 22 mg/kg and 1 female at 175 mg/kg.
	Metric 23:	Data Presentation and Analysis	High	All Outcomes: Statistical methods were adequately described and were appropriate for the dataset. Statistical significance was shown where appropriate.
	Metric 24:	Reporting of Data	High	All Outcomes: Negative gross and histopathological findings were qualitatively reported in the text. The text indicated that histopathological examinations resulted in no significantly increased incidences of lesions that could be attributed to treatment (except for in the brain).

Overall Quality Determination High

Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Cardiovascular; Hepatic/Liver; Renal/Kidney; Lung/Respiratory; Immune/Hematological;
Reported Health Effect(s):	Cardiovascular: Heart organ weights, gross necropsy, histopathology (heart); Hepatic/Liver: Liver weights, gross necropsy, histopathology, clinical chemistry (serum glucose, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, sorbitol dehydrogenase, cholesterol); Renal/Kidney: Serum chemistry (BUN, creatinine), organ weights, gross necropsy, histopathology (kidney, bladder); Lung/Respiratory: Gross necropsy, histopathology (lung, nose, trachea); Immune/Hematological: Hematology (hematocrit, hemoglobin, erythrocytes, leukocytes with differential, MCV, MCH, MCHC, and reticulocyte count), thymus weights, gross pathology, histopathology (spleen, thymus, lymph nodes (mandibular and mesenteric), bone marrow);
Duration:	Chronic (>91 days) 16-weeks (females) 18-weeks (males) - rat
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	All Outcomes: The test substance was identified definitively as tris(2-chloroethyl phosphate) CASRN 115-96-8. A structure was also provided.
	Metric 2:	Test Substance Source	High	All Outcomes: The test substance was manufactured by Stauffer Chemical Company and obtained from the analytical chemistry laboratory, Midwest Research Institute. The lot number was provided.
	Metric 3:	Test Substance Purity	High	All Outcomes: The test chemical purity was ~98%, and was both provided by the supplier and confirmed via analysis (NMR and elemental analysis) by the study laboratory.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	All Outcomes: The study included concurrent negative vehicle (corn oil) controls and conditions were consistent with the animals that were treated.
	Metric 5:	Positive Controls	N/A	All Outcomes: Positive controls are not required for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	All Outcomes: Animals were distributed into weight classes, and assigned to cages using a random number table. Cages were then assigned to treatment and control groups using another random number table.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	All Outcomes: Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) were also stable for 21 days in the dark at room temperature or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks
	Metric 8:	Consistency of Exposure Administration	High	All Outcomes: All animals were gavaged on the same schedule. Gavage volumes were reported and were consistent across groups.
	Metric 9:	Reporting of Doses/Concentrations	Medium	All Outcomes: Animals were dosed with 0, 22, 44, 88, 175, or 350 mg/kg-day, 5 days per week. Adjusted daily doses were not reported, but can be determined using the information provided. Dose formulations were analyzed twice during the study by gas chromatography and the target and measured concentrations in the solutions (mg/mL) were reported. The concentrations generally remained with 10% of the target concentrations throughout the course of the study; however, during the second reading, the concentration used for the second highest dose group was only 75% of the target.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Cardiovascular; Hepatic/Liver; Renal/Kidney; Lung/Respiratory; Immune/Hematological;
Reported Health Effect(s):	Cardiovascular: Heart organ weights, gross necropsy, histopathology (heart); Hepatic/Liver: Liver weights, gross necropsy, histopathology, clinical chemistry (serum glucose, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, sorbitol dehydrogenase, cholesterol); Renal/Kidney: Serum chemistry (BUN, creatinine), organ weights, gross necropsy, histopathology (kidney, bladder); Lung/Respiratory: Gross necropsy, histopathology (lung, nose, trachea); Immune/Hematological: Hematology (hematocrit, hemoglobin, erythrocytes, leukocytes with differential, MCV, MCH, MCHC, and reticulocyte count), thymus weights, gross pathology, histopathology (spleen, thymus, lymph nodes (mandibular and mesenteric), bone marrow);
Duration:	Chronic (>91 days) 16-weeks (females) 18-weeks (males) - rat
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 10:	Exposure Frequency and Duration	Medium	All Outcomes: Females were dosed 5 days per week for 16 weeks, and males were dosed 5 days per week for 18 weeks. It is unclear why the duration of exposure was different for males and females. Generally, the NTP guideline indicates that the subchronic studies should not be more than 97 days. The 16-18-week durations were not justified by the study authors. Dosing 5 days per week for a gavage study is consistent with NTP guidelines.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	Medium	All Outcomes: The study tested 5 dose groups plus a control. This is consistent with NTP guidelines. The spacing was sufficient to identify NOAEL and LOAEL values.
	Metric 12:	Exposure Route and Method	High	All Outcomes: Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	High	All Outcomes: The study used male and female F344/N rats. The test animal source (Harlan industries), age at the start of the study (8-9-weeks old), and initial body weights were reported and appropriate.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	All Outcomes: The number of animals per cage (5/cage) was reported. Food and water were provided ad libitum. Animal room environments (temperature, humidity, lighting) were reported. The humidity ranged considerably from 10% to 78%. This deviates from NTP guidelines which state humidity should not be below 35% or above 65%. It is unclear whether these deviations had an impact on the study results.
	Metric 15:	Number of Animals per Group	Medium	All Outcomes: The number of animals per group (10/sex) was reported and consistent with NTP guidelines.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	All Outcomes: Organ weights and histopathological examinations were conducted on tissue(s) from this organ/system. The methods of outcome assessment were sensitive and appropriate for the outcomes of interest.
	Metric 17:	Consistency of Outcome Assessment	High	All Outcomes: Sufficient details of the outcome assessment protocols (organ weights and histopathology) were provided, and outcome assessment was carried out consistently across groups.
	Metric 18:	Sampling Adequacy	High	All Outcomes: Organ weights were measured from all surviving animals. Histopathology was conducted on tissues from controls and the top two dose groups; this was appropriate given the lack of effects observed for this outcome.
	Metric 19:	Blinding of Assessors	N/A	All Outcomes: Blinding is not necessary because this outcome of interest is not subjective in nature, or is not required (initial histopathology).

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Cardiovascular; Hepatic/Liver; Renal/Kidney; Lung/Respiratory; Immune/Hematological;
Reported Health Effect(s):	Cardiovascular: Heart organ weights, gross necropsy, histopathology (heart); Hepatic/Liver: Liver weights, gross necropsy, histopathology, clinical chemistry (serum glucose, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, sorbitol dehydrogenase, cholesterol); Renal/Kidney: Serum chemistry (BUN, creatinine), organ weights, gross necropsy, histopathology (kidney, bladder); Lung/Respiratory: Gross necropsy, histopathology (lung, nose, trachea); Immune/Hematological: Hematology (hematocrit, hemoglobin, erythrocytes, leukocytes with differential, MCV, MCH, MCHC, and reticulocyte count), thymus weights, gross pathology, histopathology (spleen, thymus, lymph nodes (mandibular and mesenteric), bone marrow);
Duration:	Chronic (>91 days) 16-weeks (females) 18-weeks (males) - rat
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 20:	Negative Control Response	Medium	All Outcomes: The appropriateness of the negative control response for histopathology cannot be determined because incidence data were not provided. The study authors did not describe any concerns about high background in controls. Organ weight data for controls appeared to be appropriate.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	All Outcomes: The initial body weights of the females in the 175 mg/kg group were statistically significantly lower than controls by 5%. The study authors had claimed animals were normalized by weight, so this is surprising. The difference didn't seem to have an impact on later body weight measurements. The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP. There were no significant body weight changes that were suggestive of any palatability issues (only increased body weights were observed).
	Metric 22:	Health Outcomes Unrelated to Exposure	Low	All Outcomes: The study text noted that during week 4, the two highest dose groups were prepared incorrectly, and for the first three days of that week, the animals were administered double the target levels. Animals in the 175 mg/kg group, were instead dosed with 350 mg/kg, and animals in the 350 mg/kg group were dosed with 700 mg/kg. As a result, 2 females in each group died, and others showed excessive signs of acute toxicity (e.g., ataxia, excessive salivation, gasping, and convulsions). The overdose caused no deaths in males, and males showed no signs of toxicity. The surviving animals were not dosed on the 4th day of the week to allow them to recover. Dosing resumed on the 5th day. The study authors did not believe this error had a significant impact on the outcomes assessed at the end of the study. In addition to the deaths due to overdose, three animals died due to gavage error including 1 male and 1 female at 22 mg/kg and 1 female at 175 mg/kg.
	Metric 23:	Data Presentation and Analysis	High	All Outcomes: Statistical methods were adequately described and were appropriate for the dataset. Statistical significance was shown where appropriate.
	Metric 24:	Reporting of Data	High	All Outcomes: Organ weight data were reported quantitatively. Data were presented as means ± SE. Negative gross and histopathological findings were qualitatively reported in the text. The text indicated that histopathological examinations resulted in no significantly increased incidences of lesions that could be attributed to treatment (except for in the brain).

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Cardiovascular; Hepatic/Liver; Renal/Kidney; Lung/Respiratory; Immune/Hematological;
Reported Health Effect(s):	Cardiovascular: Heart organ weights, gross necropsy, histopathology (heart); Hepatic/Liver: Liver weights, gross necropsy, histopathology, clinical chemistry (serum glucose, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, sorbitol dehydrogenase, cholesterol); Renal/Kidney: Serum chemistry (BUN, creatinine), organ weights, gross necropsy, histopathology (kidney, bladder); Lung/Respiratory: Gross necropsy, histopathology (lung, nose, trachea); Immune/Hematological: Hematology (hematocrit, hemoglobin, erythrocytes, leukocytes with differential, MCV, MCH, MCHC, and reticulocyte count), thymus weights, gross pathology, histopathology (spleen, thymus, lymph nodes (mandibular and mesenteric), bone marrow);
Duration:	Chronic (>91 days) 16-weeks (females) 18-weeks (males) - rat
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric	Rating	Comments
Overall Quality Determination		**High**	

Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Neurological/Behavioral
Reported Health Effect(s):	Serum cholinesterase activity (special study 16-day and 16-week studies, and as part of serum chemistry in 2-yr study), brain weights, gross necropsy, histopathology (brain)
Duration:	Chronic (>91 days) 16-weeks (females) 18-weeks (males) - rat
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was identified definitively as tris(2-chloroethyl phosphate) CASRN 115-96-8. A structure was also provided.
	Metric 2:	Test Substance Source	High	The test substance was manufactured by Stauffer Chemical Company and obtained from the analytical chemistry laboratory, Midwest Research Institute. The lot number was provided.
	Metric 3:	Test Substance Purity	High	The test chemical purity was ~98%, and was both provided by the supplier and confirmed via analysis (NMR and elemental analysis) by the study laboratory.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	The study included concurrent negative vehicle (corn oil) controls and conditions were consistent with the animals that were treated.
	Metric 5:	Positive Controls	N/A	Positive controls are not required for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	Animals were distributed into weight classes, and assigned to cages using a random number table. Cages were then assigned to treatment and control groups using another random number table.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) were also stable for 21 days in the dark at room temperature or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks
	Metric 8:	Consistency of Exposure Administration	High	All animals were gavaged on the same schedule. Gavage volumes were reported and were consistent across groups.
	Metric 9:	Reporting of Doses/Concentrations	Medium	Animals were dosed with 0, 22, 44, 88, 175, or 350 mg/kg-day, 5 days per week. Adjusted daily doses were not reported, but can be determined using the information provided. Dose formulations were analyzed twice during the study by gas chromatography and the target and measured concentrations in the solutions (mg/mL) were reported. The concentrations generally remained with 10% of the target concentrations throughout the course of the study; however, during the second reading, the concentration used for the second highest dose group was only 75% of the target.

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Health Outcome(s):	Neurological/Behavioral
Reported Health Effect(s):	Serum cholinesterase activity (special study 16-day and 16-week studies, and as part of serum chemistry in 2-yr study), brain weights, gross necropsy, histopathology (brain)
Duration:	Chronic (>91 days) 16-weeks (females) 18-weeks (males) - rat
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 10:	Exposure Frequency and Duration	Medium	Females were dosed 5 days per week for 16 weeks, and males were dosed 5 days per week for 18 weeks. It is unclear why the duration of exposure was different for males and females. Generally, the NTP guideline indicates that the subchronic studies should not be more than 97 days. The 16-18-week durations were not justified by the study authors. Dosing 5 days per week for a gavage study is consistent with NTP guidelines.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	Medium	The study tested 5 dose groups plus a control. This is consistent with NTP guidelines. The spacing was sufficient to identify NOAEL and LOAEL values.
	Metric 12:	Exposure Route and Method	High	Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	High	The study used male and female F344/N rats. The test animal source (Harlan industries), age at the start of the study (8-9-weeks old), and initial body weights were reported and appropriate.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	The number of animals per cage (5/cage) was reported. Food and water were provided ad libitum. Animal room environments (temperature, humidity, lighting) were reported. The humidity ranged considerably from 10% to 78%. This deviates from NTP guidelines which state humidity should not be below 35% or above 65%. It is unclear whether these deviations had an impact on the study results
	Metric 15:	Number of Animals per Group	Medium	The number of animals per group (10/sex) was reported and consistent with NTP guidelines.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	Serum Cholinesterase activity was determined at study termination. Absolute and relative organ weights were measured, and all animals were subjected to gross necropsy. Brain tissue was examined histologically and included a second more detailed pathological review. The outcome assessment methodologies were sensitive to the outcome of interest.
	Metric 17:	Consistency of Outcome Assessment	High	Sufficient details of the outcome assessment protocols (organ weights and histopathology) were provided, and outcome assessment was carried out consistently across groups. Blood for measurement of cholinesterase activity was collected from all surviving animals at terminal sacrifice.
	Metric 18:	Sampling Adequacy	High	The sampling size for organ weight data was reported and was adequate. Histopathology was conducted on all control animals and animals from the two highest dose groups; brain tissues were also examined from the 88 mg/kg group.
	Metric 19:	Blinding of Assessors	High	Initial histopathology was not blinded, a second re-examination of the hippocampus was evaluated in a blinded manner by a pathologist.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Neurological/Behavioral
Reported Health Effect(s):	Serum cholinesterase activity (special study 16-day and 16-week studies, and as part of serum chemistry in 2-yr study), brain weights, gross necropsy, histopathology (brain)
Duration:	Chronic (>91 days) 16-weeks (females) 18-weeks (males) - rat
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 20:	Negative Control Response	High	Control responses (including the absence of brain lesions) were reported and appropriate.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	The initial body weights of the females in the 175 mg/kg group were statistically significantly lower than controls by 5%. The study authors had claimed animals were normalized by weight, so this is surprising. The difference didn't seem to have an impact on later body weight measurements. The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP. There were no significant body weight changes that were suggestive of any palatability issues (only increased body weights were observed).
	Metric 22:	Health Outcomes Unrelated to Exposure	Low	The study text noted that during week 4, the two highest dose groups were prepared incorrectly, and for the first three days of that week, the animals were administered double the target levels. Animals in the 175 mg/kg group, were instead dosed with 350 mg/kg, and animals in the 350 mg/kg group were dosed with 700 mg/kg. As a result, 2 females in each group died, and others showed excessive signs of acute toxicity (e.g., ataxia, excessive salivation, gasping, and convulsions). The overdose caused no deaths in males, and males showed no signs of toxicity. The surviving animals were not dosed on the 4th day of the week to allow them to recover. Dosing resumed on the 5th day. The study authors did not believe this error had a significant impact on the outcomes assessed at the end of the study. In addition to the deaths due to overdose, three animals died due to gavage error including 1 male and 1 female at 22 mg/kg and 1 female at 175 mg/kg.
	Metric 23:	Data Presentation and Analysis	High	Statistical methods were adequately described and were appropriate for the dataset. Statistical significance was shown where appropriate.
	Metric 24:	Reporting of Data	Medium	Cholinesterase activity and organ weights were quantitatively reported as means ± SE, and the number of animals sampled was reported. Histopathology results were described in the text. Incidences were reported for some, but not all dose groups and statistical significance was noted.

Overall Quality Determination — High

Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Reproductive/Developmental
Reported Health Effect(s):	Gross necropsy and histopathology (clitoral gland, epididymis, mammary glands, ovary, preputial gland, prostate, seminal vesicle, testis, uterus)
Duration:	Chronic (>91 days) 16-weeks (females) 18-weeks (males) - rat
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was identified definitively as tris(2-chloroethyl phosphate) CASRN 115-96-8. A structure was also provided.
	Metric 2:	Test Substance Source	High	The test substance was manufactured by Stauffer Chemical Company and obtained from the analytical chemistry laboratory, Midwest Research Institute. The lot number was provided.
	Metric 3:	Test Substance Purity	High	The test chemical purity was ~98%, and was both provided by the supplier and confirmed via analysis (NMR and elemental analysis) by the study laboratory.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	The study included concurrent negative vehicle (corn oil) controls and conditions were consistent with the animals that were treated.
	Metric 5:	Positive Controls	N/A	Positive controls are not required for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	Animals were distributed into weight classes, and assigned to cages using a random number table. Cages were then assigned to treatment and control groups using another random number table.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) were also stable for 21 days in the dark at room temperature or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks
	Metric 8:	Consistency of Exposure Administration	High	All animals were gavaged on the same schedule. Gavage volumes were reported and were consistent across groups.
	Metric 9:	Reporting of Doses/Concentrations	Medium	Animals were dosed with 0, 22, 44, 88, 175, or 350 mg/kg-day, 5 days per week. Adjusted daily doses were not reported, but can be determined using the information provided. Dose formulations were analyzed twice during the study by gas chromatography and the target and measured concentrations in the solutions (mg/mL) were reported. The concentrations generally remained with 10% of the target concentrations throughout the course of the study; however, during the second reading, the concentration used for the second highest dose group was only 75% of the target.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Reproductive/Developmental
Reported Health Effect(s):	Gross necropsy and histopathology (clitoral gland, epididymis, mammary glands, ovary, preputial gland, prostate, seminal vesicle, testis, uterus)
Duration:	Chronic (>91 days) 16-weeks (females) 18-weeks (males) - rat
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 10:	Exposure Frequency and Duration	Medium	Females were dosed 5 days per week for 16 weeks, and males were dosed 5 days per week for 18 weeks. It is unclear why the duration of exposure was different for males and females. Generally, the NTP guideline indicates that the subchronic studies should not be more than 97 days. The 16-18-week durations were not justified by the study authors. Dosing 5 days per week for a gavage study is consistent with NTP guidelines.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	Medium	The study tested 5 dose groups plus a control. This is consistent with NTP guidelines. The spacing was sufficient to identify NOAEL and LOAEL values.
	Metric 12:	Exposure Route and Method	High	Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	High	The study used male and female F344/N rats. The test animal source (Harlan industries), age at the start of the study (8-9-weeks old), and initial body weights were reported and appropriate.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	The number of animals per cage (5/cage) was reported. Food and water were provided ad libitum. Animal room environments (temperature, humidity, lighting) were reported. The humidity ranged considerably from 10% to 78%. This deviates from NTP guidelines which state humidity should not be below 35% or above 65%. It is unclear whether these deviations had an impact on the study results
	Metric 15:	Number of Animals per Group	Medium	The number of animals per group (10/sex) was reported and consistent with NTP guidelines.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	Organ weights and Histopathological analysis were conducted on tissue(s) from this organ/system. These methods are sensitive and appropriate for this outcome of interest and are consistent with NTP guidelines.
	Metric 17:	Consistency of Outcome Assessment	High	Sufficient details of the outcome assessment protocols were provided, and outcome assessment was carried out consistently across groups.
	Metric 18:	Sampling Adequacy	Low	Only two samples for testis weights in males from the 44 mg/kg group were collected, and a mean was not determined. It is unclear why only two samples were collected. No testis weights were reported at the high dose. Histopathology was conducted on tissues from controls and the top two dose-groups; this was appropriate given the lack of effects observed for this outcome.
	Metric 19:	Blinding of Assessors	N/A	Blinding is not necessary because this outcome of interest is not subjective in nature, or blinding is not required for this outcome of interest.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Reproductive/Developmental
Reported Health Effect(s):	Gross necropsy and histopathology (clitoral gland, epididymis, mammary glands, ovary, preputial gland, prostate, seminal vesicle, testis, uterus)
Duration:	Chronic (>91 days) 16-weeks (females) 18-weeks (males) - rat
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 20:	Negative Control Response	Medium	The appropriateness of the negative control response for histopathology cannot be determined because incidence data were not provided. The study authors did not describe any concerns of high background in controls. Organ weight data for controls appeared to be appropriate.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	The initial body weights of the females in the 175 mg/kg group were statistically significantly lower than controls by 5%. The study authors had claimed animals were normalized by weight, so this is surprising. The difference didn't seem to have an impact on later body weight measurements. The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP. There were no significant body weight changes that were suggestive of any palatability issues (only increased body weights were observed).
	Metric 22:	Health Outcomes Unrelated to Exposure	Low	The study text noted that during week 4, the two highest dose groups were prepared incorrectly, and for the first three days of that week, the animals were administered double the target levels. Animals in the 175 mg/kg group, were instead dosed with 350 mg/kg, and animals in the 350 mg/kg group were dosed with 700 mg/kg. As a result, 2 females in each group died, and others showed excessive signs of acute toxicity (e.g., ataxia, excessive salivation, gasping, and convulsions). The overdose caused no deaths in males, and males showed no signs of toxicity. The surviving animals were not dosed on the 4th day of the week to allow them to recover. Dosing resumed on the 5th day. The study authors did not believe this error had a significant impact on the outcomes assessed at the end of the study. In addition to the deaths due to overdose, three animals died due to gavage error including 1 male and 1 female at 22 mg/kg and 1 female at 175 mg/kg.
	Metric 23:	Data Presentation and Analysis	High	Statistical methods were adequately described and were appropriate for the dataset. Statistical significance was shown where appropriate.
	Metric 24:	Reporting of Data	Medium	Negative gross and histopathological findings were qualitatively reported in the text. The text indicated that histopathological examinations resulted in no significantly increased incidences of lesions that could be attributed to treatment (except for in the brain). Testis weights were reported as means ± SE, but weights for some groups were not reported and this was not explained by the study authors.

Overall Quality Determination High

Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Mortality
Reported Health Effect(s):	Survival
Duration:	Chronic (>91 days) 16-weeks (females) 18-weeks (males) - rat
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was identified definitively as tris(2-chloroethyl phosphate) CASRN 115-96-8. A structure was also provided.
	Metric 2:	Test Substance Source	High	The test substance was manufactured by Stauffer Chemical Company and obtained from the analytical chemistry laboratory, Midwest Research Institute. The lot number was provided.
	Metric 3:	Test Substance Purity	High	The test chemical purity was ~98%, and was both provided by the supplier and confirmed via analysis (NMR and elemental analysis) by the study laboratory.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	The study included concurrent negative vehicle (corn oil) controls and conditions were consistent with the animals that were treated.
	Metric 5:	Positive Controls	N/A	Positive controls are not required for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	Animals were distributed into weight classes, and assigned to cages using a random number table. Cages were then assigned to treatment and control groups using another random number table.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) were also stable for 21 days in the dark at room temperature or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks
	Metric 8:	Consistency of Exposure Administration	High	All animals were gavaged on the same schedule. Gavage volumes were reported and were consistent across groups.
	Metric 9:	Reporting of Doses/Concentrations	Medium	Animals were dosed with 0, 22, 44, 88, 175, or 350 mg/kg-day, 5 days per week. Adjusted daily doses were not reported, but can be determined using the information provided. Dose formulations were analyzed twice during the study by gas chromatography and the target and measured concentrations in the solutions (mg/mL) were reported. The concentrations generally remained with 10% of the target concentrations throughout the course of the study; however, during the second reading, the concentration used for the second highest dose group was only 75% of the target.

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Health Outcome(s):	Mortality
Reported Health Effect(s):	Survival
Duration:	Chronic (>91 days) 16-weeks (females) 18-weeks (males) - rat
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 10:	Exposure Frequency and Duration	Medium	Females were dosed 5 days per week for 16 weeks, and males were dosed 5 days per week for 18 weeks. It is unclear why the duration of exposure was different for males and females. Generally, the NTP guideline indicates that the subchronic studies should not be more than 97 days. The 16-18-week durations were not justified by the study authors. Dosing 5 days per week for a gavage study is consistent with NTP guidelines.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	Medium	The study tested 5 dose groups plus a control. This is consistent with NTP guidelines. The spacing was sufficient to identify NOAEL and LOAEL values.
	Metric 12:	Exposure Route and Method	High	Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	High	The study used male and female F344/N rats. The test animal source (Harlan industries), age at the start of the study (8-9-weeks old), and initial body weights were reported and appropriate.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	The number of animals per cage (5/cage) was reported. Food and water were provided ad libitum. Animal room environments (temperature, humidity, lighting) were reported. The humidity ranged considerably from 10% to 78%. This deviates from NTP guidelines which state humidity should not be below 35% or above 65%. It is unclear whether these deviations had an impact on the study results
	Metric 15:	Number of Animals per Group	Medium	The number of animals per group (10/sex) was reported and consistent with NTP guidelines.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	Animals were observed twice daily for morbidity and mortality. The outcome assessment was sensitive and appropriate for the outcome of interest.
	Metric 17:	Consistency of Outcome Assessment	Medium	There was consistency in the timing and methods of outcome assessment within each sex; however, since males and females were exposed for different durations, the timing of the outcome assessments is different between sexes, making it difficult to make comparisons across sex.
	Metric 18:	Sampling Adequacy	High	All animals were sampled for this outcome of interest.
	Metric 19:	Blinding of Assessors	N/A	Blinding is not necessary because this outcome of interest is not subjective in nature, or blinding is not required for this outcome of interest.
	Metric 20:	Negative Control Response	High	No control animals died.
Domain 6: Confounding / Variable Control				

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Mortality
Reported Health Effect(s):	Survival
Duration:	Chronic (>91 days) 16-weeks (females) 18-weeks (males) - rat
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	The initial body weights of the females in the 175 mg/kg group were statistically significantly lower than controls by 5%. The study authors had claimed animals were normalized by weight, so this is surprising. The difference didn't seem to have an impact on later body weight measurements. The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP. There were no significant body weight changes that were suggestive of any palatability issues (only increased body weights were observed).
	Metric 22:	Health Outcomes Unrelated to Exposure	Low	The study text noted that during week 4, the two highest dose groups were prepared incorrectly, and for the first three days of that week, the animals were administered double the target levels. Animals in the 175 mg/kg group, were instead dosed with 350 mg/kg, and animals in the 350 mg/kg group were dosed with 700 mg/kg. As a result, 2 females in each group died, and others showed excessive signs of acute toxicity (e.g., ataxia, excessive salivation, gasping, and convulsions). The overdose caused no deaths in males, and males showed no signs of toxicity. The surviving animals were not dosed on the 4th day of the week to allow them to recover. Dosing resumed on the 5th day. The study authors did not believe this error had a significant impact on the outcomes assessed at the end of the study. In addition to the deaths due to overdose, three animals died due to gavage error including 1 male and 1 female at 22 mg/kg and 1 female at 175 mg/kg.
	Metric 23:	Data Presentation and Analysis	High	Statistical methods were adequately described and were appropriate for the dataset. Statistical significance was shown where appropriate.
	Metric 24:	Reporting of Data	Medium	Survival data were quantitatively reported and described in the text Some animals died as a result of an accidental overdose during the 4th week, and other animals died due to gavage trauma. The causes of death for some animals weren't specified other than being "treatment-related." The times of death are specified.

Overall Quality Determination High

Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Unspecified clinical observations (Clinical observations)
Reported Health Effect(s):	Clinical signs (clinical observations)
Duration:	Chronic (>91 days) 16-weeks (females) 18-weeks (males) - rat
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was identified definitively as tris(2-chloroethyl phosphate) CASRN 115-96-8. A structure was also provided.
	Metric 2:	Test Substance Source	High	The test substance was manufactured by Stauffer Chemical Company and obtained from the analytical chemistry laboratory, Midwest Research Institute. The lot number was provided.
	Metric 3:	Test Substance Purity	High	The test chemical purity was ~98%, and was both provided by the supplier and confirmed via analysis (NMR and elemental analysis) by the study laboratory.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	The study included concurrent negative vehicle (corn oil) controls and conditions were consistent with the animals that were treated.
	Metric 5:	Positive Controls	N/A	Positive controls are not required for this study type.
	Metric 6:	Randomized Allocation of Animals	Medium	Animals were distributed into weight classes, and assigned to cages using a random number table. Cages were then assigned to treatment and control groups using another random number table.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	Stability studies were conducted. The bulk chemical was stable for at least 2 weeks in sealed containers at room temperature. Stability was monitored throughout the study and no degradation was observed. Additionally, the test solutions (TCEP in corn oil) were also stable for 21 days in the dark at room temperature or open to air and light for 3 hours. For the studies, the dose formulations were stored at 0-5 degrees C for 2 weeks. Fresh solutions were made every two weeks
	Metric 8:	Consistency of Exposure Administration	High	All animals were gavaged on the same schedule. Gavage volumes were reported and were consistent across groups.
	Metric 9:	Reporting of Doses/Concentrations	Medium	Animals were dosed with 0, 22, 44, 88, 175, or 350 mg/kg-day, 5 days per week. Adjusted daily doses were not reported, but can be determined using the information provided. Dose formulations were analyzed twice during the study by gas chromatography and the target and measured concentrations in the solutions (mg/mL) were reported. The concentrations generally remained with 10% of the target concentrations throughout the course of the study; however, during the second reading, the concentration used for the second highest dose group was only 75% of the target.

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Health Outcome(s):	Unspecified clinical observations (Clinical observations)
Reported Health Effect(s):	Clinical signs (clinical observations)
Duration:	Chronic (>91 days) 16-weeks (females) 18-weeks (males) - rat
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 10:	Exposure Frequency and Duration	Medium	Females were dosed 5 days per week for 16 weeks, and males were dosed 5 days per week for 18 weeks. It is unclear why the duration of exposure was different for males and females. Generally, the NTP guideline indicates that the subchronic studies should not be more than 97 days. The 16-18-week durations were not justified by the study authors. Dosing 5 days per week for a gavage study is consistent with NTP guidelines.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	Medium	The study tested 5 dose groups plus a control. This is consistent with NTP guidelines. The spacing was sufficient to identify NOAEL and LOAEL values.
	Metric 12:	Exposure Route and Method	High	Animals were exposed via gavage. The study provided detailed methods and the route is appropriate for the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	High	The study used male and female F344/N rats. The test animal source (Harlan industries), age at the start of the study (8-9-weeks old), and initial body weights were reported and appropriate.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Medium	The number of animals per cage (5/cage) was reported. Food and water were provided ad libitum. Animal room environments (temperature, humidity, lighting) were reported. The humidity ranged considerably from 10% to 78%. This deviates from NTP guidelines which state humidity should not be below 35% or above 65%. It is unclear whether these deviations had an impact on the study results.
	Metric 15:	Number of Animals per Group	Medium	The number of animals per group (10/sex) was reported and consistent with NTP guidelines.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	Medium	Animals were subjected to clinical examinations weekly in accordance with NTP guidelines. No additional methodological details were provided. The guideline also specifies that expanded clinical observations should be done by a pathologist at a minimum of at least once every other week. It is unclear if this was done.
	Metric 17:	Consistency of Outcome Assessment	Medium	Based on the information provided, all animals were observed daily. Additional outcome assessment methods (e.g., the time of observations (time of day)) were not provided, but based on the available information, there is no indication that there were differences across groups.
	Metric 18:	Sampling Adequacy	Medium	All animals were observed for clinical signs, but since negative findings were qualitatively reported, the sample size cannot be verified.
	Metric 19:	Blinding of Assessors	Medium	Blinding was not reported and clinical signs can be somewhat subjective in nature; however, lack of blinding is not expected to have a significant impact on results.

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Study Citation:	NTP, (1991). NTP Toxicology and Carcinogenesis Studies of Tris(2-chloroethyl) Phosphate (CAS No. 115-96-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series 391:1-233.
Health Outcome(s):	Unspecified clinical observations (Clinical observations)
Reported Health Effect(s):	Clinical signs (clinical observations)
Duration:	Chronic (>91 days) 16-weeks (females) 18-weeks (males) - rat
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469669

Domain	Metric		Rating	Comments
	Metric 20:	Negative Control Response	Low	The appropriateness of the negative control response cannot be definitively determined because incidence data were not reported, the text mentioned some clinical signs in treated animals but did not explicitly report that there were no clinical signs in controls.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	The initial body weights of the females in the 175 mg/kg group were statistically significantly lower than controls by 5%. The study authors had claimed animals were normalized by weight, so this is surprising. The difference didn't seem to have an impact on later body weight measurements. The study did not measure food or water intake, but this was not a dietary or drinking water study, and these endpoints are not required for this study type according to NTP. There were no significant body weight changes that were suggestive of any palatability issues (only increased body weights were observed).
	Metric 22:	Health Outcomes Unrelated to Exposure	Low	The study text noted that during week 4, the two highest dose groups were prepared incorrectly, and for the first three days of that week, the animals were administered double the target levels. Animals in the 175 mg/kg group, were instead dosed with 350 mg/kg, and animals in the 350 mg/kg group were dosed with 700 mg/kg. As a result, 2 females in each group died, and others showed excessive signs of acute toxicity (e.g., ataxia, excessive salivation, gasping, and convulsions). The overdose caused no deaths in males, and males showed no signs of toxicity. The surviving animals were not dosed on the 4th day of the week to allow them to recover. Dosing resumed on the 5th day. The study authors did not believe this error had a significant impact on the outcomes assessed at the end of the study. In addition to the deaths due to overdose, three animals died due to gavage error including 1 male and 1 female at 22 mg/kg and 1 female at 175 mg/kg.
	Metric 23:	Data Presentation and Analysis	Uninformative	Statistical methods were adequately described in general for different types of data sets; however, methods for statistical analysis specifically for clinical observations were not described, and the text does not report whether incidences of the observed effects were significantly increased compared to controls. It is unclear whether the data were statistically analyzed and quantitative data were not provided to do an independent analysis.
	Metric 24:	Reporting of Data	Low	Data for exposure-related findings were described in the text. Results were only mentioned for some dose groups.

Overall Quality Determination — Uninformative

Study Citation:	Sala, M., Gu, Z. G., Moens, G., Chouroulinkov, I. (1982). In vivo and in vitro biological effects of the flame retardants tris(2,3-dibromopropyl) phosphate and tris(2-chlorethyl)orthophosphate. European Journal of Cancer & Clinical Oncology 18(12):1337-1344.
Health Outcome(s):	Cancer/Carcinogenesis (Lung); Skin/Connective Tissue (Skin tumors);
Reported Health Effect(s):	Cancer/Carcinogenesis (Lung): Due to the lack of concurrent control data and the reporting of the laboratory historical data, it is difficult to interpret the significance of the reported lung cancer effects (i.e., study authors report that TCEP induced lung adenomas when used as a promoter).; Skin/Connective Tissue (Skin tumors): Short term skin test: mouse skin treated with TCEP showed that sebaceous glands were not suppressed and hyperplasia was not induced. Long term skin test: mouse skin treated with TCEP showed negative results for complete carcinogenic or promoting activity on mouse skin.;
Duration:	Chronic (>91 days) Long term skin test
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469568

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	All Outcomes: The substance was characterized by nomenclature and commercial name (i.e., Tris(2-chloroethyl), orthophosphate; Genomoll P). The density (chemical property) was also reported.
	Metric 2:	Test Substance Source	High	All Outcomes: source: Hoechst
	Metric 3:	Test Substance Purity	Low	All Outcomes: Purity and/or grade of test substance were not reported.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	Uninformative	All Outcomes: Concurrent solvent controls were not included.
	Metric 5:	Positive Controls	N/A	All Outcomes: The study type does not require a positive control.
	Metric 6:	Randomized Allocation of Animals	Medium	All Outcomes: Female mice were randomized into groups.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Low	All Outcomes: Information on preparation and storage was not reported and lack of details could substantially impact results (e.g. storage for long-term studies).
	Metric 8:	Consistency of Exposure Administration	High	All Outcomes: Details of exposure administration were reported and exposures were administered consistently across study groups.
	Metric 9:	Reporting of Doses/Concentrations	High	All Outcomes: Administered doses were reported without ambiguity.
	Metric 10:	Exposure Frequency and Duration	High	All Outcomes: The exposure frequency and duration of exposure were reported and appropriate for this study type and/or outcome(s) of interest.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	All Outcomes: Despite no justification the selected range sufficiently covered the full range of responses.
	Metric 12:	Exposure Route and Method	High	All Outcomes: The route and method of exposure were reported and were suited to the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	High	All Outcomes: The test animal species, strain, sex, age, and starting body weight were reported, and the test animal was obtained from a commercial source or laboratory-maintained colony. The test species and strain were an appropriate animal model for the evaluation of the specific outcome(s) of interest (e.g., routinely used for similar study types).

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Study Citation:	Sala, M., Gu, Z. G., Moens, G., Chouroulinkov, I. (1982). In vivo and in vitro biological effects of the flame retardants tris(2,3-dibromopropyl) phosphate and tris(2-chlorethyl)orthophosphate. European Journal of Cancer & Clinical Oncology 18(12):1337-1344.
Health Outcome(s):	Cancer/Carcinogenesis (Lung); Skin/Connective Tissue (Skin tumors);
Reported Health Effect(s):	Cancer/Carcinogenesis (Lung): Due to the lack of concurrent control data and the reporting of the laboratory historical data, it is difficult to interpret the significance of the reported lung cancer effects (i.e., study authors report that TCEP induced lung adenomas when used as a promoter).; Skin/Connective Tissue (Skin tumors): Short term skin test: mouse skin treated with TCEP showed that sebaceous glands were not suppressed and hyperplasia was not induced. Long term skin test: mouse skin treated with TCEP showed negative results for complete carcinogenic or promoting activity on mouse skin.;
Duration:	Chronic (>91 days) Long term skin test
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	5469568

Domain	Metric		Rating	Comments
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	Low	All Outcomes: Husbandry conditions were not sufficiently reported to evaluate if husbandry was adequate and whether differences occurred between control and exposed populations. These deficiencies are likely to have a substantial impact on results.
	Metric 15:	Number of Animals per Group	Low	All Outcomes: The reported number of animals per study group was lower than the typical number used in studies of the same or similar type,, but sufficient for statistical analysis.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	All Outcomes: The outcome assessment methodology addressed the intended outcome(s) of interest and the assessment methodology was sensitive and appropriate for the outcomes(s) of interest.
	Metric 17:	Consistency of Outcome Assessment	High	All Outcomes: Outcomes were assessed consistently across study groups (e.g., at the same time after initial exposure) using the same protocol in all study groups.
	Metric 18:	Sampling Adequacy	High	All Outcomes: Reported information indicates the study used adequate sampling for the outcome(s) of interest.
	Metric 19:	Blinding of Assessors	N/A	Cancer/Carcinogenesis (Lung): Outcomes are not subjective and blinding of assessors is not necessary.; Skin/Connective Tissue (Skin tumors): Study outcomes are not subjective and blinding of assessors is not necessary.
	Metric 20:	Negative Control Response	Uninformative	All Outcomes: There were no concurrent negative controls.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Low	All Outcomes: Body weight changes, food/water intake and differences in use of surgery were not reported
	Metric 22:	Health Outcomes Unrelated to Exposure	High	All Outcomes: Based on reported information, there were no health outcomes unrelated to exposure.
	Metric 23:	Data Presentation and Analysis	Low	All Outcomes: Statistical analysis was performed but not described adequately.
	Metric 24:	Reporting of Data	High	All Outcomes: Data for exposure-related findings were presented for all outcomes by exposure group.

Overall Quality Determination Uninformative

Study Citation:	Hazleton Laboratories, (1983). Screening of priority chemicals for potential reproductive hazard (final report) with attachments and cover sheet.
Health Outcome(s):	Reproductive/Developmental
Reported Health Effect(s):	Live/dead pups, litter size, litter weight, pup weight change, nongravid uteri staining
Duration:	Reproductive/Developmental 8 day Reproductive Study - Reproductive
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	790471

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	Test substances used were identified by established nomenclature.
	Metric 2:	Test Substance Source	High	Test Substance was supplied by NIOSH.
	Metric 3:	Test Substance Purity	High	Each chemical purity was determined by Hazelton laboratory.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	Vehicle control with corn oil were used for the test substance.
	Metric 5:	Positive Controls	N/A	Positive Controls for this study were not necessary.
	Metric 6:	Randomized Allocation of Animals	Low	No mention of allocation of animals in this study.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	Preparation of test substances for experiment was adequate for study.
	Metric 8:	Consistency of Exposure Administration	High	Exposure administration was consistent.
	Metric 9:	Reporting of Doses/Concentrations	High	All doses were reported.
	Metric 10:	Exposure Frequency and Duration	Low	There was no premating dosing and gestational dosing was on GD 7- 14.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	N/A	There is only one exposure dose in the reproductive study.
	Metric 12:	Exposure Route and Method	High	Exposure route and method was suitable for this study.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	High	Test animal characteristics were explained in detail.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	High	Animal husbandry conditions were reported.
	Metric 15:	Number of Animals per Group	Medium	50 pregnant mice were dosed at 940 mg/kg-d.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	The assessment of outcome methodology was suitable for this study.
	Metric 17:	Consistency of Outcome Assessment	High	Consistency of outcome assessment was suitable for this study.
	Metric 18:	Sampling Adequacy	High	Sampling in this study was adequate.
	Metric 19:	Blinding of Assessors	N/A	Assessors did not need to be blind for this study.
	Metric 20:	Negative Control Response	High	Negative control/vehicle response was appropriately compared to the treated animals.

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Study Citation:	Hazleton Laboratories, (1983). Screening of priority chemicals for potential reproductive hazard (final report) with attachments and cover sheet.
Health Outcome(s):	Reproductive/Developmental
Reported Health Effect(s):	Live/dead pups, litter size, litter weight, pup weight change, nongravid uteri staining
Duration:	Reproductive/Developmental 8 day Reproductive Study - Reproductive
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	790471

Domain	Metric		Rating	Comments
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	High	No reported differences in the variables between each animal.
	Metric 22:	Health Outcomes Unrelated to Exposure	High	No outcomes related to health exposure.
	Metric 23:	Data Presentation and Analysis	High	Statistical analysis was suitable for this study.
	Metric 24:	Reporting of Data	High	All data was reported in this study.

Overall Quality Determination High

Study Citation:	Kawashima, K., Tanaka, S., Nakaura, S., Nagao, S., Endo, T., Onoda, K., Takanaka, A., Omori, Y. (1983). [Effect of oral administration of tris(2-chloroethyl) phosphate to pregnant rats on prenatal and postnatal development]. Eisei Shikenjo Hokoku / Bulletin of the National Institute of Hygienic Sciences (101):55-61.
Health Outcome(s):	Reproductive/Developmental
Reported Health Effect(s):	Reproductive: numbers of corpora lutea, implantations (count, #deaths, ratio) , live/dead fetuses, fetal weight, delivery and viability indices.Developmental: External, visceral, and skeletal fetal examinations of fetuses; pup sex, number live/dead born and number at 4 days, 4 weeks, and 10 weeks), general condition, pup neurobehavioral effects (spontaneous behavior, coordinated movement, pain perception, hearing, and learning ability) at 6-7 weeks old, necropsy/pup organ weights (brain, pituitary, thyroid, thymus, heart, lung, spleen, liver, kidney, adrenal, ovary, uterus, testis) at 10 weeks old, lactation and survival indices.
Duration:	Reproductive/Developmental GD 7-15
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	4992702

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was identified definitively by name.
	Metric 2:	Test Substance Source	Low	The source other than the manufacturer (Tokyo Chemical Industry Co., Ltd) was cited and it was not analytically verified.
	Metric 3:	Test Substance Purity	Low	The test substance purity was not provided in the study report. Current TCEP products have a purity of >93% but it is not clear whether the products are the same as a product used when the toxicology study was published.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	Low	The preparation of the test solution was reported. The test substance was suspended in 4% olive oil using an ultrasonic crusher. Storage conditions (whether in a sealed container, room temperature conditions, in the dark) were not reported but are not likely to have a large impact on the stability/volatility of TCEP.
	Metric 5:	Positive Controls	N/A	Positive controls are not necessary for the study type.
	Metric 6:	Randomized Allocation of Animals	Low	The study did not report how dams were allocated into study groups, or whether they were distributed based on body weight. Randomization was specified later in the experiment for the selection of dams and pups for sacrifice and pups used for behavioral tests.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Medium	The preparation of the test solution was reported. The test substance was suspended in 4% olive oil using an ultrasonic crusher. Storage conditions (whether in a sealed container, room temperature conditions, in the dark) were not reported but are not likely to have a large impact on the stability/volatility of TCEP.
	Metric 8:	Consistency of Exposure Administration	Low	Animals from all groups were dosed once daily. The time of day of dosing and the dose volume was not reported. This missing information may have a substantial impact on the study results.
	Metric 9:	Reporting of Doses/Concentrations	Medium	The doses were clearly reported without ambiguity; however, there is no indication that dosing was analytically verified.
	Metric 10:	Exposure Frequency and Duration	Low	The dosing frequency and duration were reported but were inconsistent with current guidelines. The study specified the desire to expose animals during organogenesis and dosing occurred during GD 7-15, rather than GD 5-15 as per OECD guidelines.

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Study Citation:	Kawashima, K., Tanaka, S., Nakaura, S., Nagao, S., Endo, T., Onoda, K., Takanaka, A., Omori, Y. (1983). [Effect of oral administration of tris(2-chloroethyl) phosphate to pregnant rats on prenatal and postnatal development]. Eisei Shikenjo Hokoku / Bulletin of the National Institute of Hygienic Sciences (101):55-61.
Health Outcome(s):	Reproductive/Developmental
Reported Health Effect(s):	Reproductive: numbers of corpora lutea, implantations (count, #deaths, ratio) , live/dead fetuses, fetal weight, delivery and viability indices.Developmental: External, visceral, and skeletal fetal examinations of fetuses; pup sex, number live/dead born and number at 4 days, 4 weeks, and 10 weeks), general condition, pup neurobehavioral effects (spontaneous behavior, coordinated movement, pain perception, hearing, and learning ability) at 6-7 weeks old, necropsy/pup organ weights (brain, pituitary, thyroid, thymus, heart, lung, spleen, liver, kidney, adrenal, ovary, uterus, testis) at 10 weeks old, lactation and survival indices.
Duration:	Reproductive/Developmental GD 7-15
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	4992702

Domain	Metric		Rating	Comments
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	Low	The number and spacing of doses seemed reasonable but the publication lacked a justification for the chosen doses and the percent of dams (23%) dying at the top dose was excessive for a study with three dose groups.
	Metric 12:	Exposure Route and Method	High	Animals were dosed via gavage, which is an acceptable route of exposure for the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	Medium	The test animal species, strain, source, sex, and age were reported and were appropriate. Starting body weights were not specified in the study text, but means could be extracted from a figure provided.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	High	Animal husbandry conditions including the number of animals per cage, temperature, humidity, light/dark cycle, food and water availability, and room ventilation frequencies were reported and were appropriate. Conditions were consistent across groups.
	Metric 15:	Number of Animals per Group	Low	The initial number of dams exposed (23-30/group) was generally consistent with OECD 414 guidelines for a teratology study; however, because this study also included an early development assessment, only 15 dams were included for fetal examination. OECD indicates that groups containing fewer than 16 females with implantation sites may be inappropriate. Similarly, the number of dams allowed to deliver (n=8), and the number of offspring used for neurobehavioral assessments (n =12-16), are less than current guideline recommendations.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	Medium	The methods for the various reproductive/developmental outcomes were sufficiently described and were sensitive to the outcomes of interest. However, no histopathology was not conducted on the 10-week old offspring.
	Metric 17:	Consistency of Outcome Assessment	High	Based on the available figures and text, there is no indication that there were any inconsistencies between groups in the outcome assessments.
	Metric 18:	Sampling Adequacy	High	Sample sizes were reported and were sufficient to allow for statistical analysis.
	Metric 19:	Blinding of Assessors	N/A	Blinding is not required for the outcomes of interest.
	Metric 20:	Negative Control Response	High	The study noted cannibalism in two control litters and multiple skeletal abnormalities that were present in all groups including controls. There was no indication however, that these were considered to be abnormal responses.

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Study Citation:	Kawashima, K., Tanaka, S., Nakaura, S., Nagao, S., Endo, T., Onoda, K., Takanaka, A., Omori, Y. (1983). [Effect of oral administration of tris(2-chloroethyl) phosphate to pregnant rats on prenatal and postnatal development]. Eisei Shikenjo Hokoku / Bulletin of the National Institute of Hygienic Sciences (101):55-61.
Health Outcome(s):	Reproductive/Developmental
Reported Health Effect(s):	Reproductive: numbers of corpora lutea, implantations (count, #deaths, ratio) , live/dead fetuses, fetal weight, delivery and viability indices.Developmental: External, visceral, and skeletal fetal examinations of fetuses; pup sex, number live/dead born and number at 4 days, 4 weeks, and 10 weeks), general condition, pup neurobehavioral effects (spontaneous behavior, coordinated movement, pain perception, hearing, and learning ability) at 6-7 weeks old, necropsy/pup organ weights (brain, pituitary, thyroid, thymus, heart, lung, spleen, liver, kidney, adrenal, ovary, uterus, testis) at 10 weeks old, lactation and survival indices.
Duration:	Reproductive/Developmental GD 7-15
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	4992702

Domain	Metric	Rating	Comments
Domain 6: Confounding / Variable Control			
	Metric 21: Confounding Variables in Test Design and Procedures	High	The study reported all information to determine confounding. Decreases in maternal feed consumption and maternal body weights were recorded in the high-dose group. No differences in body weight were reported and any decreases in feed consumption were not expected to substantially influence the hazard outcomes.
	Metric 22: Health Outcomes Unrelated to Exposure	Medium	The only mortalities observed were at the high dose. The study authors did not detail the causes of death but believed them to be exposure-related.
	Metric 23: Data Presentation and Analysis	Low	Statistical methods did not explicitly report whether the fetus was used as the experimental unit where appropriate.
	Metric 24: Reporting of Data	Medium	Data were reported quantitatively including means ± SD for most outcomes. Some outcomes (offspring body weights) were qualitatively reported in the study text.

Overall Quality Determination Medium

Study Citation:	Kawashima, K., Tanaka, S., Nakaura, S., Nagao, S., Endo, T., Onoda, K., Takanaka, A., Omori, Y. (1983). [Effect of oral administration of tris(2-chloroethyl) phosphate to pregnant rats on prenatal and postnatal development]. Eisei Shikenjo Hokoku / Bulletin of the National Institute of Hygienic Sciences (101):55-61.
Health Outcome(s):	Neurological/Behavioral
Reported Health Effect(s):	Dams were observed for general appearance (e.g., signs of intoxication)
Duration:	Reproductive/Developmental GD 7-15
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	4992702

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was identified definitively by name.
	Metric 2:	Test Substance Source	Low	The source other than the manufacturer (Tokyo Chemical Industry Co., Ltd) was cited and it was not analytically verified.
	Metric 3:	Test Substance Purity	Low	The test substance purity was not provided in the study report. Current TCEP products have a purity of >93% but it is not clear whether the products are the same as a product used when the toxicology study was published.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	Low	A concurrent negative control group was included, but the nature of the controls was not explicitly stated (e.g., untreated or vehicle). A 4% olive oil vehicle was used in the study.
	Metric 5:	Positive Controls	N/A	Positive controls are not necessary for the study type.
	Metric 6:	Randomized Allocation of Animals	Low	The study did not report how dams were allocated into study groups, or whether they were distributed based on body weight. Randomization was specified later in the experiment for the selection of dams and pups for sacrifice and pups used for behavioral tests.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Medium	The preparation of the test solution was reported. The test substance was suspended in 4% olive oil using an ultrasonic crusher. Storage conditions (whether in a sealed container, room temperature conditions, in the dark) were not reported but are not likely to have a large impact on the stability/volatility of TCEP.
	Metric 8:	Consistency of Exposure Administration	Low	Animals from all groups were dosed once daily. The time of day of dosing and the dose volume was not reported. This missing information may have a substantial impact on the study results.
	Metric 9:	Reporting of Doses/Concentrations	Medium	The doses were clearly reported without ambiguity; however, there is no indication that dosing was analytically verified.
	Metric 10:	Exposure Frequency and Duration	Low	The dosing frequency and duration were appropriate for the maternal endpoints evaluated. However, the study specified the desire to expose animals during organogenesis and dosing occurred during GD 7-15, rather than GD 5-15 as per OECD guidelines.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	Medium	The number and spacing of doses seemed reasonable but the publication lacked a justification for the chosen doses and the percent of dams (23%) dying at the top dose was excessive for a study with three dose groups.
	Metric 12:	Exposure Route and Method	High	Animals were dosed via gavage, which is an acceptable route of exposure for the test substance.

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Study Citation:	Kawashima, K., Tanaka, S., Nakaura, S., Nagao, S., Endo, T., Onoda, K., Takanaka, A., Omori, Y. (1983). [Effect of oral administration of tris(2-chloroethyl) phosphate to pregnant rats on prenatal and postnatal development]. Eisei Shikenjo Hokoku / Bulletin of the National Institute of Hygienic Sciences (101):55-61.
Health Outcome(s):	Neurological/Behavioral
Reported Health Effect(s):	Dams were observed for general appearance (e.g., signs of intoxication)
Duration:	Reproductive/Developmental GD 7-15
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	4992702

Domain	Metric		Rating	Comments
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	Medium	The test animal species, strain, source, sex, and age were reported and were appropriate. Starting body weights were not specified in the study text, but means could be extracted from a figure provided.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	High	Animal husbandry conditions including the number of animals per cage, temperature, humidity, light/dark cycle, food and water availability, and room ventilation frequencies were reported and were appropriate. Conditions were consistent across groups.
	Metric 15:	Number of Animals per Group	Medium	The number of animals per group was appropriate for the outcomes of interest.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	Low	Limited to no details of the outcome assessment methodology were provided (e.g., the frequency of observations and whether animals were observed cage-side or if they were subjected to detailed clinical observations). No other neurological/behavioral assessments (e.g., organ weights, histopathology) were conducted, and clinical signs are not a sensitive method for the outcomes of interest; however, in a teratology study, maternal neurological/behavioral effects on the dams is not a primary focus.
	Metric 17:	Consistency of Outcome Assessment	High	Based on the available figures and text, there is no indication that there were any inconsistencies between groups in the outcome assessments.
	Metric 18:	Sampling Adequacy	Low	Sampling was described and no quantitative data were provided reporting (n). All animals were likely observed, but this is not explicitly stated.
	Metric 19:	Blinding of Assessors	Low	Blinding was not reported and the outcome is somewhat subjective in nature.
	Metric 20:	Negative Control Response	Low	The biological response of the negative controls was not reported.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	High	The study reported all information to determine confounding. Decreases in maternal feed consumption and maternal body weights were recorded in the high-dose group. No differences in body weight were reported and any decreases in feed consumption were not expected to substantially influence the hazard outcomes.
	Metric 22:	Health Outcomes Unrelated to Exposure	Medium	The only mortalities observed were at the high dose. The study authors did not detail the causes of death but believed them to be exposure-related.
	Metric 23:	Data Presentation and Analysis	Low	No statistical methods were described for clinical signs and the data were not provided for an independent analysis. Offspring functional and neurobehavioral effects were evaluated using either the t-test or the rank sum test.

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Study Citation:	Kawashima, K., Tanaka, S., Nakaura, S., Nagao, S., Endo, T., Onoda, K., Takanaka, A., Omori, Y. (1983). [Effect of oral administration of tris(2-chloroethyl) phosphate to pregnant rats on prenatal and postnatal development]. Eisei Shikenjo Hokoku / Bulletin of the National Institute of Hygienic Sciences (101):55-61.
Health Outcome(s):	Neurological/Behavioral
Reported Health Effect(s):	Dams were observed for general appearance (e.g., signs of intoxication)
Duration:	Reproductive/Developmental GD 7-15
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	4992702

Domain	Metric	Rating	Comments
	Metric 24: Reporting of Data	Low	A general statement indicating that there were "no particular changes in general condition" was provided for the two lowest dose groups. Effects were described for the high-dose group; however, no incidence data were provided and it was not specified whether the observed incidences were significantly different from the controls.

Overall Quality Determination Medium

Study Citation:	Kawashima, K., Tanaka, S., Nakaura, S., Nagao, S., Endo, T., Onoda, K., Takanaka, A., Omori, Y. (1983). [Effect of oral administration of tris(2-chloroethyl) phosphate to pregnant rats on prenatal and postnatal development]. Eisei Shikenjo Hokoku / Bulletin of the National Institute of Hygienic Sciences (101):55-61.
Health Outcome(s):	Renal/Kidney
Reported Health Effect(s):	Dam absolute and relative kidney weight
Duration:	Reproductive/Developmental GD 7-15
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	4992702

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was identified definitively by name.
	Metric 2:	Test Substance Source	Low	The source other than the manufacturer (Tokyo Chemical Industry Co., Ltd) was cited and it was not analytically verified.
	Metric 3:	Test Substance Purity	Low	The test substance purity was not provided in the study report. Current TCEP products have a purity of >93% but it is not clear whether the products are the same as a product used when the toxicology study was published.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	Low	A concurrent negative control group was included, but the nature of the controls was not explicitly stated (e.g., untreated or vehicle). A 4% olive oil vehicle was used in the study.
	Metric 5:	Positive Controls	N/A	Positive controls are not necessary for the study type.
	Metric 6:	Randomized Allocation of Animals	Low	The study did not report how dams were allocated into study groups, or whether they were distributed based on body weight. Randomization was specified later in the experiment for the selection of dams and pups for sacrifice and pups used for behavioral tests.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Medium	The preparation of the test solution was reported. The test substance was suspended in 4% olive oil using an ultrasonic crusher. Storage conditions (whether in a sealed container, room temperature conditions, in the dark) were not reported but are not likely to have a large impact on the stability/volatility of TCEP.
	Metric 8:	Consistency of Exposure Administration	Low	Animals from all groups were dosed once daily. The time of day of dosing and the dose volume was not reported. This missing information may have a substantial impact on the study results.
	Metric 9:	Reporting of Doses/Concentrations	Medium	The doses were clearly reported without ambiguity; however, there is no indication that dosing was analytically verified.
	Metric 10:	Exposure Frequency and Duration	Low	The dosing frequency and duration were appropriate for the maternal endpoints evaluated. However, the study specified the desire to expose animals during organogenesis and dosing occurred during GD 7-15, rather than GD 5-15 as per OECD guidelines.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	Medium	The number and spacing of doses seemed reasonable but the publication lacked a justification for the chosen doses and the percent of dams (23%) dying at the top dose was excessive for a study with three dose groups
	Metric 12:	Exposure Route and Method	High	Animals were dosed via gavage, which is an acceptable route of exposure for the test substance.

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Study Citation:	Kawashima, K., Tanaka, S., Nakaura, S., Nagao, S., Endo, T., Onoda, K., Takanaka, A., Omori, Y. (1983). [Effect of oral administration of tris(2-chloroethyl) phosphate to pregnant rats on prenatal and postnatal development]. Eisei Shikenjo Hokoku / Bulletin of the National Institute of Hygienic Sciences (101):55-61.
Health Outcome(s):	Renal/Kidney
Reported Health Effect(s):	Dam absolute and relative kidney weight
Duration:	Reproductive/Developmental GD 7-15
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	4992702

Domain	Metric		Rating	Comments
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	Medium	The test animal species, strain, source, sex, and age were reported and were appropriate. Starting body weights were not specified in the study text, but means could be extracted from a figure provided.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	High	Animal husbandry conditions including the number of animals per cage, temperature, humidity, light/dark cycle, food and water availability, and room ventilation frequencies were reported and were appropriate. Conditions were consistent across groups.
	Metric 15:	Number of Animals per Group	Medium	The number of animals per group was appropriate for the outcomes of interest.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	Medium	The methods did not include this outcome; it was only noted in the study text that dam kidney weights were also measured. Kidney weights alone in the absence of clinical chemistry, and gross and microscopic examinations are not the most sensitive measure of kidney effects, particularly when the authors noted the kidney as a possible target organ.
	Metric 17:	Consistency of Outcome Assessment	High	Based on the available figures and text, there is no indication that there were any inconsistencies between groups in the outcome assessments.
	Metric 18:	Sampling Adequacy	High	Sampling was adequate
	Metric 19:	Blinding of Assessors	N/A	Blinding is not required for the outcomes of interest.
	Metric 20:	Negative Control Response	High	Data for negative control responses were reported and were acceptable.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	The study reported all information to determine confounding. Decreases in maternal feed consumption and maternal body weights were recorded in the high-dose group. No differences in body weight were reported and any decreases in feed consumption were not expected to substantially influence the hazard outcomes.
	Metric 22:	Health Outcomes Unrelated to Exposure	Medium	The only mortalities observed were at the high dose. The study authors did not detail the causes of death but believed them to be exposure-related.
	Metric 23:	Data Presentation and Analysis	High	The methods of statistical analysis were provided and were appropriate for the data sets.
	Metric 24:	Reporting of Data	High	quantitative absolute and relative organ weights were reported for all groups.

Overall Quality Determination — High

Study Citation:	Kawashima, K., Tanaka, S., Nakaura, S., Nagao, S., Endo, T., Onoda, K., Takanaka, A., Omori, Y. (1983). [Effect of oral administration of tris(2-chloroethyl) phosphate to pregnant rats on prenatal and postnatal development]. Eisei Shikenjo Hokoku / Bulletin of the National Institute of Hygienic Sciences (101):55-61.
Health Outcome(s):	Nutritional/Metabolic
Reported Health Effect(s):	Maternal body weight and food consumption
Duration:	Reproductive/Developmental GD 7-15
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	4992702

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was identified definitively by name.
	Metric 2:	Test Substance Source	Low	The source other than the manufacturer (Tokyo Chemical Industry Co., Ltd) was cited and it was not analytically verified.
	Metric 3:	Test Substance Purity	Low	The test substance purity was not provided in the study report. Current TCEP products have a purity of >93% but it is not clear whether the products are the same as a product used when the toxicology study was published.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	Low	A concurrent negative control group was included, but the nature of the controls was not explicitly stated (e.g., untreated or vehicle). A 4% olive oil vehicle was used in the study.
	Metric 5:	Positive Controls	N/A	Positive controls are not necessary for the study type.
	Metric 6:	Randomized Allocation of Animals	Low	The study did not report how dams were allocated into study groups, or whether they were distributed based on body weight. Randomization was specified later in the experiment for the selection of dams and pups for sacrifice and pups used for behavioral tests.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Medium	The preparation of the test solution was reported. The test substance was suspended in 4% olive oil using an ultrasonic crusher. Storage conditions (whether in a sealed container, room temperature conditions, in the dark) were not reported but are not likely to have a large impact on the stability/volatility of TCEP.
	Metric 8:	Consistency of Exposure Administration	Low	Animals from all groups were dosed once daily. The time of day of dosing and the dose volume was not reported. This missing information may have a substantial impact on the study results.
	Metric 9:	Reporting of Doses/Concentrations	Medium	The doses were clearly reported without ambiguity; however, there is no indication that dosing was analytically verified.
	Metric 10:	Exposure Frequency and Duration	Low	The dosing frequency and duration were appropriate for the maternal endpoints evaluated. However, the study specified the desire to expose animals during organogenesis and dosing occurred during GD 7-15, rather than GD 5-15 as per OECD guidelines.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	Medium	The number and spacing of doses seemed reasonable but the publication lacked a justification for the chosen doses and the percent of dams (23%) dying at the top dose was excessive for a study with three dose groups.
	Metric 12:	Exposure Route and Method	High	Animals were dosed via gavage, which is an acceptable route of exposure for the test substance.

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Study Citation:	Kawashima, K., Tanaka, S., Nakaura, S., Nagao, S., Endo, T., Onoda, K., Takanaka, A., Omori, Y. (1983). [Effect of oral administration of tris(2-chloroethyl) phosphate to pregnant rats on prenatal and postnatal development]. Eisei Shikenjo Hokoku / Bulletin of the National Institute of Hygienic Sciences (101):55-61.
Health Outcome(s):	Nutritional/Metabolic
Reported Health Effect(s):	Maternal body weight and food consumption
Duration:	Reproductive/Developmental GD 7-15
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	4992702

Domain	Metric		Rating	Comments
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	Medium	The test animal species, strain, source, sex, and age were reported and were appropriate. Starting body weights were not specified in the study text, but means could be extracted from a figure provided.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	High	Animal husbandry conditions including the number of animals per cage, temperature, humidity, light/dark cycle, food and water availability, and room ventilation frequencies were reported and were appropriate. Conditions were consistent across groups.
	Metric 15:	Number of Animals per Group	Medium	The number of animals per group was appropriate for the outcomes of interest.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	Medium	Limited details of the outcome assessment methodology were provided (e.g., the frequency of maternal measurements was not reported in the study text); however, the frequency can be gleaned from some data figures, and the missing information is unlikely to have a substantial impact on the results.
	Metric 17:	Consistency of Outcome Assessment	High	Based on the available figures and text, there is no indication that there were any inconsistencies between groups in the outcome assessments.
	Metric 18:	Sampling Adequacy	Medium	Sampling was not adequately described in the study methods and the number of animals sampled (n) was not included in the data figures. It is assumed that all dams were monitored.
	Metric 19:	Blinding of Assessors	N/A	Blinding is not required for the outcomes of interest.
	Metric 20:	Negative Control Response	High	Data for negative control responses were reported and were acceptable.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	High	The study reported all information to determine confounding. Decreases in maternal feed consumption and maternal body weights were recorded in the high-dose group. No differences in body weight were reported and any decreases in feed consumption were not expected to substantially influence the hazard outcomes.
	Metric 22:	Health Outcomes Unrelated to Exposure	Medium	The only mortalities observed were at the high dose. The study authors did not detail the causes of death but believed them to be exposure-related.
	Metric 23:	Data Presentation and Analysis	High	The methods of statistical analysis were provided and were appropriate for the data sets.
	Metric 24:	Reporting of Data	Medium	Maternal body weight and food consumption data were reported in figures as means with no measures of variance, and no ”n” was specified. Statistical significance was not noted in the figures but was described in the study text.

Overall Quality Determination — High

Study Citation:	Kawashima, K., Tanaka, S., Nakaura, S., Nagao, S., Endo, T., Onoda, K., Takanaka, A., Omori, Y. (1983). [Effect of oral administration of tris(2-chloroethyl) phosphate to pregnant rats on prenatal and postnatal development]. Eisei Shikenjo Hokoku / Bulletin of the National Institute of Hygienic Sciences (101):55-61.
Health Outcome(s):	Mortality
Reported Health Effect(s):	Dam mortality
Duration:	Reproductive/Developmental GD 7-15
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	4992702

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was identified definitively by name.
	Metric 2:	Test Substance Source	Low	The source other than the manufacturer (Tokyo Chemical Industry Co., Ltd) was cited and it was not analytically verified.
	Metric 3:	Test Substance Purity	Low	The test substance purity was not provided in the study report. Current TCEP products have a purity of >93% but it is not clear whether the products are the same as a product used when the toxicology study was published.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	Low	A concurrent negative control group was included, but the nature of the controls was not explicitly stated (e.g., untreated or vehicle). A 4% olive oil vehicle was used in the study.
	Metric 5:	Positive Controls	N/A	Positive controls are not necessary for the study type.
	Metric 6:	Randomized Allocation of Animals	Low	The study did not report how dams were allocated into study groups, or whether they were distributed based on body weight. Randomization was specified later in the experiment for the selection of dams and pups for sacrifice and pups used for behavioral tests.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Medium	The preparation of the test solution was reported. The test substance was suspended in 4% olive oil using an ultrasonic crusher. Storage conditions (whether in a sealed container, room temperature conditions, in the dark) were not reported but are not likely to have a large impact on the stability/volatility of TCEP.
	Metric 8:	Consistency of Exposure Administration	Low	Animals from all groups were dosed once daily. The time of day of dosing and the dose volume was not reported. This missing information may have a substantial impact on the study results.
	Metric 9:	Reporting of Doses/Concentrations	Medium	The doses were clearly reported without ambiguity; however, there is no indication that dosing was analytically verified.
	Metric 10:	Exposure Frequency and Duration	Medium	The dosing frequency and duration were appropriate for the maternal endpoints evaluated. However, the study specified the desire to expose animals during organogenesis and dosing occurred during GD 7-15, rather than GD 5-15 as per OECD guidelines.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	Medium	The number and spacing of doses seemed reasonable but the publication lacked a justification for the chosen doses and the percent of dams (23%) dying at the top dose was excessive for a study with three dose groups.
	Metric 12:	Exposure Route and Method	High	Animals were dosed via gavage, which is an acceptable route of exposure for the test substance.

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Study Citation:	Kawashima, K., Tanaka, S., Nakaura, S., Nagao, S., Endo, T., Onoda, K., Takanaka, A., Omori, Y. (1983). [Effect of oral administration of tris(2-chloroethyl) phosphate to pregnant rats on prenatal and postnatal development]. Eisei Shikenjo Hokoku / Bulletin of the National Institute of Hygienic Sciences (101):55-61.
Health Outcome(s):	Mortality
Reported Health Effect(s):	Dam mortality
Duration:	Reproductive/Developmental GD 7-15
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	4992702

Domain	Metric		Rating	Comments
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	Medium	The test animal species, strain, source, sex, and age were reported and were appropriate. Starting body weights were not specified in the study text, but means could be extracted from a figure provided.
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	High	Animal husbandry conditions including the number of animals per cage, temperature, humidity, light/dark cycle, food and water availability, and room ventilation frequencies were reported and were appropriate. Conditions were consistent across groups.
	Metric 15:	Number of Animals per Group	Medium	The number of animals per group was appropriate for the outcomes of interest.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	Medium	Limited details of the outcome assessment methodology were provided (e.g., the frequency of maternal measurements was not reported in the study text); however, the frequency can be gleaned from some data figures, and the missing information is unlikely to have a substantial impact on the results.
	Metric 17:	Consistency of Outcome Assessment	High	Based on the available figures and text, there is no indication that there were any inconsistencies between groups in the outcome assessments.
	Metric 18:	Sampling Adequacy	High	All animals were monitored for mortality
	Metric 19:	Blinding of Assessors	N/A	Blinding is not required for the outcome of interest.
	Metric 20:	Negative Control Response	High	Data for negative control responses were reported and were acceptable.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	High	The study reported all information to determine confounding. Decreases in maternal feed consumption and maternal body weights were recorded in the high-dose group. No differences in body weight were reported and any decreases in feed consumption were not expected to substantially influence the hazard outcomes.
	Metric 22:	Health Outcomes Unrelated to Exposure	Medium	The only mortalities observed were at the high dose. The study authors did not detail the causes of death but believed them to be exposure-related.
	Metric 23:	Data Presentation and Analysis	High	The methods of statistical analysis were provided and were appropriate for the data sets.
	Metric 24:	Reporting of Data	Medium	Mortality data were clearly reported for all dose groups. The general timing of death was noted, but no cause of death was specified.

Overall Quality Determination — High

Study Citation:	Moser, V. C., Phillips, P. M., Hedge, J. M., McDaniel, K. L. (2015). Neurotoxicological and thyroid evaluations of rats developmentally exposed to tris(1,3-dichloro-2-propyl)phosphate (TDCIPP) and tris(2-chloro-2-ethyl)phosphate (TCEP). Neurotoxicology and Teratology 52(Pt B):236-247.
Health Outcome(s):	Reproductive/Developmental; Reproductive/Developmental;
Reported Health Effect(s):	Reproductive/Developmental: Resorptions (nonpregnant dams); viability, litter size, and litter weight, male:female ratio; in F1 and F2 offspring: body weight/body weight gain; Reproductive/Developmental: Resorptions (nonpregnant dams); viability, litter size, and litter weight, male:female ratio; in F1 and F2 offspring: body weight/body weight gain;
Duration:	Reproductive/Developmental From gestation day 10 and through weaning
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	3008543

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	All Outcomes: The test substance was definitively identified as TCEP. The CASRN was provided.
	Metric 2:	Test Substance Source	High	All Outcomes: The test substance source was specified (Sigma-Aldrich).
	Metric 3:	Test Substance Purity	Medium	All Outcomes: The purity of the test substance was 97%. The identity of any impurities was not reported.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	All Outcomes: The study specified that corn oil was the vehicle control.
	Metric 5:	Positive Controls	N/A	All Outcomes: Not required by study type.
	Metric 6:	Randomized Allocation of Animals	Low	All Outcomes: The study stated that dam weights on gestation day (GD) 9 were stratified and dose groups assigned so that the average weight for each dose group was comparable. Pups were not directly dosed; however, it was not indicated how they were allocated to specific (behavioral) testing schedules. The method of culling offspring was not stated.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Medium	All Outcomes: Minimal information about test substance preparation and storage conditions were reported. The study stated that TCEP was dissolved in corn oil and made fresh every 3-4 days.
	Metric 8:	Consistency of Exposure Administration	High	All Outcomes: Dosing was described; it appeared that doses were administered consistently across study groups. The gavage volume was 0.5 mL/kg.
	Metric 9:	Reporting of Doses/Concentrations	High	All Outcomes: The doses administered were reported without ambiguity. The study noted that the highest dose tested for TCEP started out as 125 mg/kg-day; however, owing to toxicity, the highest dose was reduced to 90 mg/kg-day after 5 days of dosing.
	Metric 10:	Exposure Frequency and Duration	High	All Outcomes: The dosing period was appropriate to assess developmental toxicity; dosing of dams occurred from GD 10 through weaning (encompassing the period of pup growth/development).
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	All Outcomes: Three dose groups plus the control were used. The dose groups were justified by the study authors; they were based on a pilot study in non-pregnant females to determine doses that did not produce overt toxicity. The highest dose used at the start of the study was lowered owing to overt toxicity. The highest dose used thereafter was high enough to induce some toxicity in dams (e.g., increased liver weight).

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Study Citation:	Moser, V. C., Phillips, P. M., Hedge, J. M., McDaniel, K. L. (2015). Neurotoxicological and thyroid evaluations of rats developmentally exposed to tris(1,3-dichloro-2-propyl)phosphate (TDCIPP) and tris(2-chloro-2-ethyl)phosphate (TCEP). Neurotoxicology and Teratology 52(Pt B):236-247.
Health Outcome(s):	Reproductive/Developmental; Reproductive/Developmental;
Reported Health Effect(s):	Reproductive/Developmental: Resorptions (nonpregnant dams); viability, litter size, and litter weight, male:female ratio; in F1 and F2 offspring: body weight/body weight gain; Reproductive/Developmental: Resorptions (nonpregnant dams); viability, litter size, and litter weight, male:female ratio; in F1 and F2 offspring: body weight/body weight gain;
Duration:	Reproductive/Developmental From gestation day 10 and through weaning
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	3008543

Domain	Metric		Rating	Comments
	Metric 12:	Exposure Route and Method	High	All Outcomes: The route and method were suited to the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	Medium	All Outcomes: The study indicated that Long-Evans rats were obtained from a commercial source (Charles River Laboratories) on GD 2. Although ages were not stated, the dams' pregnancy status identified them as mature. Starting body weights were shown graphically (Figure 1).
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	High	All Outcomes: Husbandry conditions, including temperature, humidity, light-dark cycle, and diet and water availability were reported in adequate detail.
	Metric 15:	Number of Animals per Group	Low	All Outcomes: The number of dams per group ("n" was presumably 14 based on the indication that 56 animals were used in the study and there were 3 dose groups plus controls) is below the number typically recommended for prenatal developmental toxicity studies (typically about 20).
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	All Outcomes: The endpoints evaluated the outcomes of interest (the study was especially interested in evaluating thyrotoxicity and developmental neurotoxicity). Information on endpoints evaluated in the offspring are described: Developmental parameters and growth - Two dams that did not deliver were evaluated for resorptions; litter endpoints evaluated included litter size and litter weight on postnatal day (PND)2, male:female ratio of pups, pup viability, and pup body weights pre- and post-weaning. Liver - absolute and relative organ weights. Thyrotoxicity - serum T3 and T4; Developmental neurotoxicity - brain weight, serum and brain acetylcholintesterase (AchE) activity in the serum and brain, neurobehavior (righting relflex in pre-weaning pups, standard locomotor activity in pre- and post-weaning pups and adult offspring, locomotor activity including a lighting change, elevated zero maze, and modified functional observational battery (FOB) in post-weaning pups and adult offspring, and Morris maze in adult offspring.
	Metric 17:	Consistency of Outcome Assessment	High	All Outcomes: The timing of outcome assessments appeared to be consistent across groups. For developmental neurobehavior, a table (Table 1) was included indicating testing sequence/timing of testing for the various types of tests. Organ weight data for offspring (body, brain, and liver weights) were shown for the same time points (e.g., PND6, PND22). With respect to offspring body weights, the study authors noted that, post-weaning, pups were allocated to different testing timelines; data were interpolated to common weigh days and combined within litter.

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Study Citation:	Moser, V. C., Phillips, P. M., Hedge, J. M., McDaniel, K. L. (2015). Neurotoxicological and thyroid evaluations of rats developmentally exposed to tris(1,3-dichloro-2-propyl)phosphate (TDCIPP) and tris(2-chloro-2-ethyl)phosphate (TCEP). Neurotoxicology and Teratology 52(Pt B):236-247.
Health Outcome(s):	Reproductive/Developmental; Reproductive/Developmental;
Reported Health Effect(s):	Reproductive/Developmental: Resorptions (nonpregnant dams); viability, litter size, and litter weight, male:female ratio; in F1 and F2 offspring: body weight/body weight gain; Reproductive/Developmental: Resorptions (nonpregnant dams); viability, litter size, and litter weight, male:female ratio; in F1 and F2 offspring: body weight/body weight gain;
Duration:	Reproductive/Developmental From gestation day 10 and through weaning
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	3008543

Domain	Metric		Rating	Comments
	Metric 18:	Sampling Adequacy	Medium	All Outcomes: Endpoints in offspring were evaluated in all the animals allocated to specific groups. Litter parameters (e.g., litter size and litter weight) were evaluated in all pups on PND2, righting reflex was measured in all pups prior to culling (PNDs 2-4), organ weights were recorded in all animals scheduled for sacrifice (e.g., all culled pups on PND6, the 10/sex/group pups sacrificed at weaning and as adults). Behavioral tests were typically conducted using 1 male and 1 female from each litter (the "n" was relatively low because fewer than the recommended number of dams/group was used to start the study).
	Metric 19:	Blinding of Assessors	Medium	All Outcomes: Blinding is not required for many outcomes (organ weights, serum and brain measurements of AchE activity, offspring body weights). Neurobehavioral tests typically require blinding. The study indicated that for the FOB and elevated zero maze, the observer was unaware of treatment group (i.e., blinded) and testing over the days was counterbalanced across dose groups and sex. For the Morris water maze, swimming was monitored by video and digitized for computer analysis. There was no mention of blinding for righting reflex or motor activity measurements (however, the manner in which these endpoints were measured were likely less subjective).
	Metric 20:	Negative Control Response	Medium	All Outcomes: Developmental parameters and growth - data for litter size, litter weight, male:female ratio of pups, and pup viability were not provided; offspring body weights in controls were shown graphically in Figure 2. Liver - Liver weights were shown for all groups including controls in Table 2. Thyroid - Thyroid hormone levels were shown for all groups including controls in Supplemental Figure 1. Developmental neurotoxicity - Brain weights for all groups including controls were shown in Table 2; brain AchE data (but not serum AchE data) for controls was provided in the text. For behavioral tests, data were typically shown for controls for any effects in which there was a potential treatment-related effects; results for controls were not included for all tests that reported negative results.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	All Outcomes: Not all information to determine confounding was provided; however, reported information did not identify differences.
	Metric 22:	Health Outcomes Unrelated to Exposure	Medium	All Outcomes: Information neither supported nor dismissed the suggestion that were differences among dose groups with respect to outcomes unrelated to exposure.
	Metric 23:	Data Presentation and Analysis	High	All Outcomes: Statistical analyses were described in adequate detail. The litter was the unit for statistical analyses.

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Study Citation:	Moser, V. C., Phillips, P. M., Hedge, J. M., McDaniel, K. L. (2015). Neurotoxicological and thyroid evaluations of rats developmentally exposed to tris(1,3-dichloro-2-propyl)phosphate (TDCIPP) and tris(2-chloro-2-ethyl)phosphate (TCEP). Neurotoxicology and Teratology 52(Pt B):236-247.
Health Outcome(s):	Reproductive/Developmental; Reproductive/Developmental;
Reported Health Effect(s):	Reproductive/Developmental: Resorptions (nonpregnant dams); viability, litter size, and litter weight, male:female ratio; in F1 and F2 offspring: body weight/body weight gain; Reproductive/Developmental: Resorptions (nonpregnant dams); viability, litter size, and litter weight, male:female ratio; in F1 and F2 offspring: body weight/body weight gain;
Duration:	Reproductive/Developmental From gestation day 10 and through weaning
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	3008543

Domain	Metric	Rating	Comments
	Metric 24: Reporting of Data	Medium	All Outcomes: In general, negative results were reported qualitatively in the text; other results (including any result that was potentially treatment-related) were reported by exposure group and sex (when applicable). Developmental parameters and growth - negative results (litter size and weight, male:female ratio, viability) were reported qualitatively; offspring body weights were presented graphically in Figure 2; Liver - Liver weights (PNDs 6 and 22) were provided in Table 2; Thyroid - T3 and T4 levels were provided in Supplemental Table 1; Developmental neurotoxicity - Brain weight data were reported in Table 2; brain and serum AchE activity reported in the text; for neurobehavioral tests, negative results were qualitatively; endpoints within tests that examined potential effects were provided in more quantitative formats (e.g., latency to leave closed arm in elevated zero maze test, hindlimb strength).

Overall Quality Determination High

Study Citation:	Moser, V. C., Phillips, P. M., Hedge, J. M., McDaniel, K. L. (2015). Neurotoxicological and thyroid evaluations of rats developmentally exposed to tris(1,3-dichloro-2-propyl)phosphate (TDCIPP) and tris(2-chloro-2-ethyl)phosphate (TCEP). Neurotoxicology and Teratology 52(Pt B):236-247.
Health Outcome(s):	Nutritional/Metabolic
Reported Health Effect(s):	Maternal body weights
Duration:	Reproductive/Developmental From gestation day 10 and through weaning
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	3008543

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was definitively identified as TCEP. The CASRN was provided.
	Metric 2:	Test Substance Source	High	The test substance source was specified (Sigma-Aldrich).
	Metric 3:	Test Substance Purity	Medium	The purity of the test substance was 97%. The identity of any impurities was not reported.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	The study specified that corn oil was the vehicle control.
	Metric 5:	Positive Controls	N/A	Not required by study type.
	Metric 6:	Randomized Allocation of Animals	Medium	The study stated that dam weights on gestation day (GD) 9 were stratified and dose groups assigned so that the average weight for each dose group was comparable.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Medium	Minimal information about test substance preparation and storage conditions were reported. The study stated that TCEP was dissolved in corn oil and made fresh every 3-4 days.
	Metric 8:	Consistency of Exposure Administration	High	Dosing was described; it appeared that doses were administered consistently across study groups. The gavage volume was 0.5 mL/kg.
	Metric 9:	Reporting of Doses/Concentrations	High	The doses administered were reported without ambiguity. The study noted that the highest dose tested for TCEP started out as 125 mg/kg-day; however, owing to toxicity, the highest dose was reduced to 90 mg/kg-day after 5 days of dosing.
	Metric 10:	Exposure Frequency and Duration	High	The dosing period was appropriate to assess developmental toxicity; dosing of dams occurred from GD 10 through weaning (encompassing the period of pup growth/development).
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	Three dose groups plus the control were used. The dose groups were justified by the study authors; they were based on a pilot study in non-pregnant females to determine doses that did not produce overt toxicity. The highest dose used at the start of the study was lowered owing to overt toxicity. The highest dose used thereafter was high enough to induce toxicity in dams (e.g., increased liver weight).
	Metric 12:	Exposure Route and Method	High	The route and method were suited to the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	Medium	The study indicated that Long-Evans rats were obtained from a commercial source (Charles River Laboratories) on GD 2. Although ages were not stated, the dams' pregnancy status identified them as mature. Starting body weights were shown graphically (Figure 1).

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Health Outcome(s):	Nutritional/Metabolic
Reported Health Effect(s):	Maternal body weights
Duration:	Reproductive/Developmental From gestation day 10 and through weaning
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	3008543

Domain	Metric		Rating	Comments
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	High	Husbandry conditions, including temperature, humidity, light-dark cycle, and diet and water availability were reported in adequate detail.
	Metric 15:	Number of Animals per Group	Low	The number of females per group (”n” was presumably 14 based on the indication that 56 animals were used in the study and there were 3 dose groups plus controls) is below the number typically recommended for prenatal developmental toxicity studies (n - 20).
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	The study indicated that dams were weighed twice weekly and more frequently around birth.
	Metric 17:	Consistency of Outcome Assessment	High	Based on the data (presented graphically in Figure 1), it appears that body weights were assessed consistently across group (i.e., measured at the same time points for all dose groups, including controls).
	Metric 18:	Sampling Adequacy	Medium	Although not stated, body weights were presumably assessed in all dams.
	Metric 19:	Blinding of Assessors	N/A	Blinding is not required for this outcome.
	Metric 20:	Negative Control Response	Medium	Body weight data for controls were presented graphically in Figure 1.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	Not all information to determine confounding was provided; however, reported information did not identify differences.
	Metric 22:	Health Outcomes Unrelated to Exposure	Medium	Information neither supported nor dismissed the suggestion that were differences among dose groups with respect to outcomes unrelated to exposure.
	Metric 23:	Data Presentation and Analysis	N/A	Statistical analyses were not necessary/not required (negative results across groups; a 10% change from controls could be used as a benchmark for a biologically significant effect).
	Metric 24:	Reporting of Data	Medium	The study presented body weight data for dams graphically (Figure 1), In the text, the study authors indicated that there were no differences in body weight throughout dosing.

Overall Quality Determination — High

Study Citation:	Moser, V. C., Phillips, P. M., Hedge, J. M., McDaniel, K. L. (2015). Neurotoxicological and thyroid evaluations of rats developmentally exposed to tris(1,3-dichloro-2-propyl)phosphate (TDCIPP) and tris(2-chloro-2-ethyl)phosphate (TCEP). Neurotoxicology and Teratology 52(Pt B):236-247.
Health Outcome(s):	Thyroid
Reported Health Effect(s):	Serum T3 and T4 in dams; F1 offspring: thyroid endpoints (T3 and T4 levels)
Duration:	Reproductive/Developmental From gestation day 10 and through weaning
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	3008543

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was definitively identified as TCEP. The CASRN was provided.
	Metric 2:	Test Substance Source	High	The test substance source was specified (Sigma-Aldrich).
	Metric 3:	Test Substance Purity	Medium	The purity of the test substance was 97%. The identity of any impurities was not reported.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	The study specified that corn oil was the vehicle control.
	Metric 5:	Positive Controls	N/A	Not required by study type.
	Metric 6:	Randomized Allocation of Animals	Medium	The study stated that dam weights on gestation day (GD) 9 were stratified and dose groups assigned so that the average weight for each dose group was comparable.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Medium	Minimal information about test substance preparation and storage conditions were reported. The study stated that TCEP was dissolved in corn oil and made fresh every 3-4 days.
	Metric 8:	Consistency of Exposure Administration	High	Dosing was described; it appeared that doses were administered consistently across study groups. The gavage volume was 0.5 mL/kg.
	Metric 9:	Reporting of Doses/Concentrations	High	The doses administered were reported without ambiguity. The study noted that the highest dose tested for TCEP started out as 125 mg/kg-day; however, owing to toxicity, the highest dose was reduced to 90 mg/kg-day after 5 days of dosing.
	Metric 10:	Exposure Frequency and Duration	High	The dosing period was appropriate to assess developmental toxicity; dosing of dams occurred from GD 10 through weaning (encompassing the period of pup growth/development).
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	Three dose groups plus the control were used. The dose groups were justified by the study authors; they were based on a pilot study in non-pregnant females to determine doses that did not produce overt toxicity. The highest dose used at the start of the study was lowered owing to overt toxicity. The highest dose used thereafter was high enough to induce toxicity in dams (e.g., increased liver weight).
	Metric 12:	Exposure Route and Method	High	The route and method were suited to the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	Medium	The study indicated that Long-Evans rats were obtained from a commercial source (Charles River Laboratories) on GD 2. Although ages were not stated, the dams' pregnancy status identified them as mature. Starting body weights were shown graphically (Figure 1).

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Study Citation:	Moser, V. C., Phillips, P. M., Hedge, J. M., McDaniel, K. L. (2015). Neurotoxicological and thyroid evaluations of rats developmentally exposed to tris(1,3-dichloro-2-propyl)phosphate (TDCIPP) and tris(2-chloro-2-ethyl)phosphate (TCEP). Neurotoxicology and Teratology 52(Pt B):236-247.
Health Outcome(s):	Thyroid
Reported Health Effect(s):	Serum T3 and T4 in dams; F1 offspring: thyroid endpoints (T3 and T4 levels)
Duration:	Reproductive/Developmental From gestation day 10 and through weaning
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	3008543

Domain	Metric		Rating	Comments
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	High	Husbandry conditions, including temperature, humidity, light-dark cycle, and diet and water availability were reported in adequate detail.
	Metric 15:	Number of Animals per Group	Low	The number of females per group (”n” was presumably 14 based on the indication that 56 animals were used in the study and there were 3 dose groups plus controls) is below the number typically recommended for prenatal developmental toxicity studies (n - 20).
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	Medium	The study evaluated serum T3 and T4; thyroid weights and thyroid histology were not assessed.
	Metric 17:	Consistency of Outcome Assessment	High	Serum T3 and T4 levels were measured in dams from all groups sacrificed on postnatal day (PND) 23.
	Metric 18:	Sampling Adequacy	Medium	Although not explicitly stated, the study language suggest liver weights were assessed in all dams.
	Metric 19:	Blinding of Assessors	N/A	Blinding is not required for this outcome.
	Metric 20:	Negative Control Response	High	Thyroid hormone data for controls were provided (Supplemental Table 1). The study also noted that control values for this study were similar to control values for another study that was conducted in tandem.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	Not all information to determine confounding was provided; however, reported information did not identify differences.
	Metric 22:	Health Outcomes Unrelated to Exposure	Medium	Information neither supported nor dismissed the suggestion that were differences among dose groups with respect to outcomes unrelated to exposure.
	Metric 23:	Data Presentation and Analysis	High	Statistical analyses were described in adequate detail.
	Metric 24:	Reporting of Data	High	Serum thyroid hormone data were reported by dose group (Supplemental Table 1). The study authors indicated that TCEP treatment did not alter T3 or T4 levels in dams.

Overall Quality Determination High

Study Citation:	Moser, V. C., Phillips, P. M., Hedge, J. M., McDaniel, K. L. (2015). Neurotoxicological and thyroid evaluations of rats developmentally exposed to tris(1,3-dichloro-2-propyl)phosphate (TDCIPP) and tris(2-chloro-2-ethyl)phosphate (TCEP). Neurotoxicology and Teratology 52(Pt B):236-247.
Health Outcome(s):	Hepatic/Liver
Reported Health Effect(s):	Liver weights in dams; F1 offspring: liver weight
Duration:	Reproductive/Developmental From gestation day 10 and through weaning
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	3008543

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was definitively identified as TCEP. The CASRN was provided.
	Metric 2:	Test Substance Source	High	The test substance source was specified (Sigma-Aldrich).
	Metric 3:	Test Substance Purity	Medium	The purity of the test substance was 97%. The identity of any impurities was not reported.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	The study specified that corn oil was the vehicle control.
	Metric 5:	Positive Controls	N/A	Not required by study type.
	Metric 6:	Randomized Allocation of Animals	Medium	The study stated that dam weights on gestation day (GD) 9 were stratified and dose groups assigned so that the average weight for each dose group was comparable.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Medium	Minimal information about test substance preparation and storage conditions were reported. The study stated that TCEP was dissolved in corn oil and made fresh every 3-4 days.
	Metric 8:	Consistency of Exposure Administration	High	Dosing was described; it appeared that doses were administered consistently across study groups. The gavage volume was 0.5 mL/kg.
	Metric 9:	Reporting of Doses/Concentrations	High	The doses administered were reported without ambiguity. The study noted that the highest dose tested for TCEP started out as 125 mg/kg-day; however, owing to toxicity, the highest dose was reduced to 90 mg/kg-day after 5 days of dosing.
	Metric 10:	Exposure Frequency and Duration	High	The dosing period was appropriate to assess developmental toxicity; dosing of dams occurred from GD 10 through weaning (encompassing the period of pup growth/development).
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	Three dose groups plus the control were used. The dose groups were justified by the study authors; they were based on a pilot study in non-pregnant females to determine doses that did not produce overt toxicity. The highest dose used at the start of the study was lowered owing to overt toxicity. The highest dose used thereafter was high enough to induce toxicity in dams (e.g., increased liver weight).
	Metric 12:	Exposure Route and Method	High	The route and method were suited to the test substance.
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	Medium	The study indicated that Long-Evans rats were obtained from a commercial source (Charles River Laboratories) on GD 2. Although ages were not stated, the dams' pregnancy status identified them as mature. Starting body weights were shown graphically (Figure 1).

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Study Citation:	Moser, V. C., Phillips, P. M., Hedge, J. M., McDaniel, K. L. (2015). Neurotoxicological and thyroid evaluations of rats developmentally exposed to tris(1,3-dichloro-2-propyl)phosphate (TDCIPP) and tris(2-chloro-2-ethyl)phosphate (TCEP). Neurotoxicology and Teratology 52(Pt B):236-247.
Health Outcome(s):	Hepatic/Liver
Reported Health Effect(s):	Liver weights in dams; F1 offspring: liver weight
Duration:	Reproductive/Developmental From gestation day 10 and through weaning
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	3008543

Domain	Metric		Rating	Comments
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	High	Husbandry conditions, including temperature, humidity, light-dark cycle, and diet and water availability were reported in adequate detail.
	Metric 15:	Number of Animals per Group	Low	The number of females per group (”n” was presumably 14 based on the indication that 56 animals were used in the study and there were 3 dose groups plus controls) is below the number typically recommended for prenatal developmental toxicity studies (n - 20).
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	Medium	The study evaluated liver weights; no other liver endpoints (clinical chemistry changes indicative of liver toxicity, liver histology) were assessed.
	Metric 17:	Consistency of Outcome Assessment	High	Liver weights were measured in dams from all dose groups after sacrifice on postnatal day (PND) 23.
	Metric 18:	Sampling Adequacy	Medium	Although not stated, body weights were presumably assessed in all dams.
	Metric 19:	Blinding of Assessors	N/A	Blinding is not required for this outcome.
	Metric 20:	Negative Control Response	High	Liver weight data for controls were provided (Table 2).
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	Not all information to determine confounding was provided; however, reported information did not identify differences.
	Metric 22:	Health Outcomes Unrelated to Exposure	Medium	Information neither supported nor dismissed the suggestion that were differences among dose groups with respect to outcomes unrelated to exposure.
	Metric 23:	Data Presentation and Analysis	High	Statistical analyses were described in adequate detail.
	Metric 24:	Reporting of Data	Medium	Absolute and relative liver weight data were reported by dose group (Table 2). The study authors indicated that absolute and relative liver were increased by treatment; absolute liver weight was not statistically significantly increased and relative liver weight was significantly increased at the highest dose (p = 0.0249).

Overall Quality Determination — High

Study Citation:	Moser, V. C., Phillips, P. M., Hedge, J. M., McDaniel, K. L. (2015). Neurotoxicological and thyroid evaluations of rats developmentally exposed to tris(1,3-dichloro-2-propyl)phosphate (TDCIPP) and tris(2-chloro-2-ethyl)phosphate (TCEP). Neurotoxicology and Teratology 52(Pt B):236-247.
Health Outcome(s):	Mortality; Neurological/Behavioral;
Reported Health Effect(s):	Mortality: Mortality in dams; Neurological/Behavioral: Serum AchE in dams; F1 offspring: righting reflex, motor activity, modified FOB, anxiety behaviors, cognitive learning, AchE activity, brain weight;
Duration:	Reproductive/Developmental From gestation day 10 and through weaning
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	3008543

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	All Outcomes: The test substance was definitively identified as TCEP. The CASRN was provided.
	Metric 2:	Test Substance Source	High	All Outcomes: The test substance source was specified (Sigma-Aldrich).
	Metric 3:	Test Substance Purity	Medium	All Outcomes: The purity of the test substance was 97%. The identity of any impurities was not reported.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	All Outcomes: The study specified that corn oil was the vehicle control.
	Metric 5:	Positive Controls	N/A	All Outcomes: Not required by study type.
	Metric 6:	Randomized Allocation of Animals	Medium	All Outcomes: The study stated that dam weights on gestation day (GD) 9 were stratified and dose groups assigned so that the average weight for each dose group was comparable.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	Medium	All Outcomes: Minimal information about test substance preparation and storage conditions were reported. The study stated that TCEP was dissolved in corn oil and made fresh every 3-4 days.
	Metric 8:	Consistency of Exposure Administration	High	All Outcomes: Dosing was described; it appeared that doses were administered consistently across study groups. The gavage volume was 0.5 mL/kg.
	Metric 9:	Reporting of Doses/Concentrations	High	All Outcomes: The doses administered were reported without ambiguity. The study noted that the highest dose tested for TCEP started out as 125 mg/kg-day; however, owing to toxicity, the highest dose was reduced to 90 mg/kg-day after 5 days of dosing.
	Metric 10:	Exposure Frequency and Duration	High	All Outcomes: The dosing period was appropriate to assess developmental toxicity; dosing of dams occurred from GD 10 through weaning (encompassing the period of pup growth/development).
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	All Outcomes: Three dose groups plus the control were used. The dose groups were justified by the study authors; they were based on a pilot study in non-pregnant females to determine doses that did not produce overt toxicity. The highest dose used at the start of the study was lowered owing to overt toxicity. The highest dose used thereafter was high enough to induce toxicity in dams (e.g., increased liver weight).
	Metric 12:	Exposure Route and Method	High	All Outcomes: The route and method were suited to the test substance.
Domain 4: Test Animals				

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Study Citation:	Moser, V. C., Phillips, P. M., Hedge, J. M., McDaniel, K. L. (2015). Neurotoxicological and thyroid evaluations of rats developmentally exposed to tris(1,3-dichloro-2-propyl)phosphate (TDCIPP) and tris(2-chloro-2-ethyl)phosphate (TCEP). Neurotoxicology and Teratology 52(Pt B):236-247.
Health Outcome(s):	Mortality; Neurological/Behavioral;
Reported Health Effect(s):	Mortality: Mortality in dams; Neurological/Behavioral: Serum AchE in dams; F1 offspring: righting reflex, motor activity, modified FOB, anxiety behaviors, cognitive learning, AchE activity, brain weight;
Duration:	Reproductive/Developmental From gestation day 10 and through weaning
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	3008543

Domain	Metric		Rating	Comments
	Metric 13:	Test Animal Characteristics	Medium	All Outcomes: The study indicated that Long-Evans rats were obtained from a commercial source (Charles River Laboratories) on GD 2. Although ages were not stated, the dams' pregnancy status identified them as mature. Starting body weights were shown graphically (Figure 1).
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	High	All Outcomes: Husbandry conditions, including temperature, humidity, light-dark cycle, and diet and water availability were reported in adequate detail.
	Metric 15:	Number of Animals per Group	Low	All Outcomes: The number of females per group ("n" was presumably 14 based on the indication that 56 animals were used in the study and there were 3 dose groups plus controls) is below the number typically recommended for prenatal developmental toxicity studies (n - 20).
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	Medium	Mortality: The outcome (mortality) was presumably evaluated via active monitoring of the animals.; Neurological/Behavioral: The study evaluated clinical signs of toxicity and serum acetylcholinesterase (AchE) activity; no other neurological endpoints (e.g., brain histology) were assessed.
	Metric 17:	Consistency of Outcome Assessment	Medium	Mortality: The timing of assessments of mortality was not explicitly specified (presumably animals were observed at the time of dosing).; Neurological/Behavioral: Serum AChE activity was measured in dams from all dose groups after sacrifice on postnatal day (PND) 23. Clinical signs were presumably assessed consistently across groups.
	Metric 18:	Sampling Adequacy	Medium	All Outcomes: Although not explicitly stated, the study language suggest liver weights were assessed in all dams.
	Metric 19:	Blinding of Assessors	N/A	All Outcomes: Blinding is not required for this outcome.
	Metric 20:	Negative Control Response	Medium	Mortality: It was not explicitly stated that no mortality occurred in controls; however, the study reported that there was evidence of toxicity at the highest dose of TCEP and once the highest dose was lowered, no toxicity was observed thereafter (presumably in any dose group).; Neurological/Behavioral: Based on the information provided in the study report, controls likely showed no toxic signs of toxicity. Serum AChE activity in controls was reported in the text.
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	All Outcomes: Not all information to determine confounding was provided; however, reported information did not identify differences.
	Metric 22:	Health Outcomes Unrelated to Exposure	Medium	All Outcomes: Information neither supported nor dismissed the suggestion that were differences among dose groups with respect to outcomes unrelated to exposure.

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Study Citation:	Moser, V. C., Phillips, P. M., Hedge, J. M., McDaniel, K. L. (2015). Neurotoxicological and thyroid evaluations of rats developmentally exposed to tris(1,3-dichloro-2-propyl)phosphate (TDCIPP) and tris(2-chloro-2-ethyl)phosphate (TCEP). Neurotoxicology and Teratology 52(Pt B):236-247.
Health Outcome(s):	Mortality; Neurological/Behavioral;
Reported Health Effect(s):	Mortality: Mortality in dams; Neurological/Behavioral: Serum AchE in dams; F1 offspring: righting reflex, motor activity, modified FOB, anxiety behaviors, cognitive learning, AchE activity, brain weight;
Duration:	Reproductive/Developmental From gestation day 10 and through weaning
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	3008543

Domain	Metric		Rating	Comments
	Metric 23:	Data Presentation and Analysis	High	Mortality: Statistical analyses were not reported. Findings were considered negative across groups; the sacrifice of 2/14 animals at the highest dose compared to a presumed incidence of 0/14 in controls is not statistically significant (based on Fisher's test performed for this review).; Neurological/Behavioral: Statistical analyses were described in adequate detail.
	Metric 24:	Reporting of Data	Medium	Mortality: The study indicated that two dams in the highest dose group at the start of the study (125 mg/kg-day) were sacrificed moribund after about 3 days of dosing; mortality in this group was presumably 2/14 compared to 0/14 for controls (but this was not explicitly specified).; Neurological/Behavioral: The study reported neurological signs of toxicity (tremors) in two rats treated at the highest dose of TCEP initially tested (125 mg/kg-day for the first 5 days) and indicated that there was no toxicity observed after the dose was reduced (presumably in any group). With respect to AChE activity, quantitative data were not provided; however, it was indicated in the text that AChE levels in all dose groups were within 97%-104% of control values.

Overall Quality Determination High

Study Citation:	NTP, (1991). Final report on the reproductive toxicity of tris(2-chloroethyl) phosphate in CD-1 Swiss mice.
Health Outcome(s):	Mortality
Reported Health Effect(s):	Mortality
Duration:	Reproductive/Developmental About 35 weeks
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	10603716

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was identified definitively: nomenclature: tris(2-chloroethyl)phosphate and CASRN: 115-96-8. The compound was also identified as TCEP by gas chromatography.
	Metric 2:	Test Substance Source	High	The source of the test substance was a manufacturer (Aldrich); a batch/lot number was indicated (HT0090787).
	Metric 3:	Test Substance Purity	High	TCEP was comprehensively analyzed to determine the purity of the test chemical, which was indicated to be >98% pure. Observed effects were likely due to the test substance itself.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	An appropriate control group was used throughout the study (i.e., control mice were administered the corn oil vehicle only).
	Metric 5:	Positive Controls	N/A	Positive controls were not required by study type.
	Metric 6:	Randomized Allocation of Animals	Low	The study did not indicate how animals were allocated to study groups. It was mentioned that animals were randomly paired for some phases of the experiment.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	The test substance was mixed in corn oil; each dose level was independently formulated. Aliquots of each formulation (including the control) were sent for analysis at various time points during the study. The stock concentration was 8 mg/mL. Formulation analyses showed that TCEP mixed at this concentration was stable for 3 weeks at room temperature; dose formulations were prepared at least every three weeks.
	Metric 8:	Consistency of Exposure Administration	Medium	Appendix I notes that the time of gavage dosing varied up to 1 hr among doses (one exception occurred). Other details of exposure administration are incompletely reported (e.g., gavage volume). Any missing information is unlikely to have a substantial impact on results (especially since a published protocol that complied to GLP standards was used).
	Metric 9:	Reporting of Doses/Concentrations	High	Doses in mg/kg-day were reported without ambiguity.
	Metric 10:	Exposure Frequency and Duration	High	The study frequency/duration was adequate to detect effects pertaining to the outcome of interest.

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Study Citation:	NTP, (1991). Final report on the reproductive toxicity of tris(2-chloroethyl) phosphate in CD-1 Swiss mice.
Health Outcome(s):	Mortality
Reported Health Effect(s):	Mortality
Duration:	Reproductive/Developmental About 35 weeks
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	10603716

Domain	Metric		Rating	Comments
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	The dose range-finding (Task 1) and continuous breeding (Task 3) phases of the study utilized at least 3 dose levels and a concurrent control; the dose intervals were typically two-fold. The offspring assessment (Task 4) included two dose levels plus the control owing to there being too few offspring to analyze at the high-dose. Doses were initially selected (based on the dose range-finding study) to induce some systemic toxicity without severe toxicity/death at the high-dose (and to allow for the identification of a NOAEL).
	Metric 12:	Exposure Route and Method	High	The study used a route of exposure (oral) that was considered appropriate (i.e., applicable to humans). Analyses of dosing formulations confirmed that the method of exposure was suited to the test substance (i.e., the test substance was stably mixed with corn oil for administration via gavage).
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	Medium	Based on OECD guidelines, the rat is the preferred species for most assessments of reproductive toxicity (e.g., based on guidelines for one- and two-generation toxicity tests, combined repeated-dose with reproductive/developmental toxicity); a rationale should have been provided for the use of mice in this study. The species and strain (VAF Crl: Swiss CD-1 [ICR]BR outbred albino mice), sex (both), age (e.g., 8 weeks at the start of Task 1 and 11 weeks at the start of Task 2), and starting body weights of the animals on the study were reported. Mice were purchased from a commercial source (Charles River Breeding Laboratories, Inc.).
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	High	The following husbandry conditions were reported: temperature, light-dark cycle (14 hours light/10 hours dark), and food and water availability and were similar for treated groups of mice and controls. Humidity was not reported.
	Metric 15:	Number of Animals per Group	Medium	The number of animals per group was in line with the numbers usually used for studies of this type. Reproduction studies typically aim to achieve about 20 successful pregnancies per dose group; for some tasks in this study, there were 20 pairs/treatment group, which resulted in fewer than 20 pregnancies per group (e.g., fertility was 18-19 out of 20 during Task 2). The number of animals per group was adequate to evaluate the outcome of interest.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	The outcome analysis (monitoring of mortality, presumably daily but not explicitly specified) was an appropriate method to evaluate the outcome of interest.
	Metric 17:	Consistency of Outcome Assessment	High	Outcomes were assessed consistently across study groups.
	Metric 18:	Sampling Adequacy	High	Mortality was evaluated in all animals.
	Metric 19:	Blinding of Assessors	N/A	Blinding is not applicable to this outcome (which is not subjective).

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Study Citation:	NTP, (1991). Final report on the reproductive toxicity of tris(2-chloroethyl) phosphate in CD-1 Swiss mice.
Health Outcome(s):	Mortality
Reported Health Effect(s):	Mortality
Duration:	Reproductive/Developmental About 35 weeks
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	10603716

Domain	Metric		Rating	Comments
	Metric 20:	Negative Control Response	High	The biological response of the negative control group was adequate (little to no mortality occurred in controls depending on the phase of the study).
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	The study did not report all information to determine confounding, but the information reported did not identify differences. In general, the body weights of treated animals were similar to controls throughout the study.
	Metric 22:	Health Outcomes Unrelated to Exposure	High	Details on outcomes unrelated to exposure were reported. The study indicated that, during quarantine, representative animals were sacrificed and evaluated for antibodies against mouse viruses and parasites. The health status of sentinel animals maintained in the same room as treated animals were monitored as well (tested for viral antibodies). Animals tested negative for infections throughout the study.
	Metric 23:	Data Presentation and Analysis	High	Appropriate statistical analyses were performed (or could be performed) for all end-points.
	Metric 24:	Reporting of Data	High	The number of animals that died was reported by phase of the study and by group.

Overall Quality Determination High

Study Citation:	NTP, (1991). Final report on the reproductive toxicity of tris(2-chloroethyl) phosphate in CD-1 Swiss mice.
Health Outcome(s):	Nutritional/Metabolic
Reported Health Effect(s):	Body weight and water consumption
Duration:	Reproductive/Developmental About 35 weeks
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	10603716

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was identified definitively: nomenclature: tris(2-chloroethyl)phosphate and CASRN: 115-96-8. The compound was also identified as TCEP by gas chromatography.
	Metric 2:	Test Substance Source	High	The source of the test substance was a manufacturer (Aldrich); a batch/lot number was indicated (HT0090787).
	Metric 3:	Test Substance Purity	High	TCEP was comprehensively analyzed to determine the purity of the test chemical, which was indicated to be >98% pure. Observed effects were likely due to the test substance itself.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	An appropriate control group was used throughout the study (i.e., control mice were administered the corn oil vehicle only).
	Metric 5:	Positive Controls	N/A	Positive controls were not required by study type.
	Metric 6:	Randomized Allocation of Animals	Low	The study did not indicate how animals were allocated to study groups. It was mentioned that animals were randomly paired for some phases of the experiment.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	The test substance was mixed in corn oil; each dose level was independently formulated. Aliquots of each formulation (including the control) were sent for analysis at various time points during the study. The stock concentration was 8 mg/mL. Formulation analyses showed that TCEP mixed at this concentration was stable for 3 weeks at room temperature; dose formulations were prepared at least every three weeks.
	Metric 8:	Consistency of Exposure Administration	Medium	Appendix I notes that the time of gavage dosing varied up to 1 hr among doses (one exception occurred). Other details of exposure administration are incompletely reported (e.g., gavage volume). Any missing information is unlikely to have a substantial impact on results (especially since a published protocol that complied to GLP standards was used).
	Metric 9:	Reporting of Doses/Concentrations	High	Doses in mg/kg-day were reported without ambiguity.
	Metric 10:	Exposure Frequency and Duration	High	The study frequency/duration was adequate to detect effects pertaining to the outcome of interest.
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	The dose range-finding (Task 1) and continuous breeding (Task 3) phases of the study utilized at least 3 dose levels and a concurrent control; the dose intervals were typically two-fold. The offspring assessment (Task 4) included two dose levels plus the control owing to there being too few offspring to analyze at the high-dose. Doses were initially selected (based on the dose range-finding study) to induce some systemic toxicity without severe toxicity/death at the high-dose (and to allow for the identification of a NOAEL).

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Study Citation:	NTP, (1991). Final report on the reproductive toxicity of tris(2-chloroethyl) phosphate in CD-1 Swiss mice.
Health Outcome(s):	Nutritional/Metabolic
Reported Health Effect(s):	Body weight and water consumption
Duration:	Reproductive/Developmental About 35 weeks
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	10603716

Domain	Metric		Rating	Comments
	Metric 12:	Exposure Route and Method	High	The study used a route of exposure (oral) that was considered appropriate (i.e., applicable to humans). Analyses of dosing formulations confirmed that the method of exposure was suited to the test substance (i.e., the test substance was stably mixed with corn oil for administration via gavage).
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	Medium	Based on OECD guidelines, the rat is the preferred species for most assessments of reproductive toxicity (e.g., based on guidelines for one- and two-generation toxicity tests, combined repeated-dose with reproductive/developmental toxicity); a rationale should have been provided for the use of mice in this study. The species and strain (VAF Crl: Swiss CD-1 [ICR]BR outbred albino mice), sex (both), age (e.g., 8 weeks at the start of Task 1 and 11 weeks at the start of Task 2), and starting body weights of the animals on the study were reported. Mice were purchased from a commercial source (Charles River Breeding Laboratories, Inc.).
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	High	The following husbandry conditions were reported: temperature, light-dark cycle (14 hours light/10 hours dark), and food and water availability and were similar for treated groups of mice and controls. Humidity was not reported.
	Metric 15:	Number of Animals per Group	Medium	The number of animals per group was in line with the numbers usually used for studies of this type. Reproduction studies typically aim to achieve about 20 successful pregnancies per dose group; for some tasks in this study, there were 20 pairs/treatment group, which resulted in fewer than 20 pregnancies per group (e.g., fertility was 18-19 out of 20 during Task 2). The number of animals per group was adequate to evaluate the outcome of interest.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	The outcome analysis was an appropriate method to evaluate the outcome of interest. In Task 1, body weights were evaluated at days 0, 7, and 14 and water consumption was evaluated during weeks 1 and 2. In Task 2, body weights were evaluated during weeks 1 (pre-cohabitation), 2 (first week of continuous breeding), 3, 6, 10, and 14; water consumption was evaluated during weeks 2, 6, 10, and 14. Terminal body weights and water consumption in the week after cohabitation were measured in Task 3. Body weights of animals in the final litter from Task 2 were measured on postnatal days (PNDs) 0, 4, 7, 14, and 21; terminal body weights and water consumption were also recorded in Task 4.
	Metric 17:	Consistency of Outcome Assessment	High	Outcomes were assessed consistently across study groups.
	Metric 18:	Sampling Adequacy	Medium	Body weight was evaluated in all animals. Water consumption was measured for males and females combined during periods in which they shared a cage (e.g., weeks 6, 10, and 14 of Task 2 and week of Task 4). During cohabitation, the amount of water consumed was estimated by dividing the total consumption by the number of animals per cage (assumed equal among sexes).

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Study Citation:	NTP, (1991). Final report on the reproductive toxicity of tris(2-chloroethyl) phosphate in CD-1 Swiss mice.
Health Outcome(s):	Nutritional/Metabolic
Reported Health Effect(s):	Body weight and water consumption
Duration:	Reproductive/Developmental About 35 weeks
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	10603716

Domain	Metric		Rating	Comments
	Metric 19:	Blinding of Assessors	N/A	Blinding is not applicable to this outcome (which is not subjective).
	Metric 20:	Negative Control Response	High	The biological response of the negative control group was adequate (the controls gained weight and appeared to drink appropriate amounts of water).
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	The study did not report all information to determine confounding, but the information reported did not identify differences.
	Metric 22:	Health Outcomes Unrelated to Exposure	High	Details on outcomes unrelated to exposure were reported. The study indicated that, during quarantine, representative animals were sacrificed and evaluated for antibodies against mouse viruses and parasites. The health status of sentinel animals maintained in the same room as treated animals were monitored as well (tested for viral antibodies). Animals tested negative for viral antibodies throughout the study.
	Metric 23:	Data Presentation and Analysis	High	Appropriate statistical analyses were performed at all measured time points.
	Metric 24:	Reporting of Data	High	Body weight and water consumption data were provided in data tables in the body of the report and/or in the appendices. Data for individual animals (body weight) were reported in the appendices for some time points (initial and final body weights for Task 2, and at necropsy for tasks 3 and 4).

Overall Quality Determination High

Study Citation:	NTP, (1991). Final report on the reproductive toxicity of tris(2-chloroethyl) phosphate in CD-1 Swiss mice.
Health Outcome(s):	Reproductive/Developmental
Reported Health Effect(s):	mating, pregnancy, and fertility, cumulative days to litter, dam weight, mean litters/pair, live pups/litter, proportion of pups born alive, sex of pups, pup weights, pup survival, estrous cyclicity, sperm parameters (concentration, motility, abnormal sperm), reproductive organ weights (epididymis, testis, cauda epididymis, prostate, seminal vesicles, ovary) and histology (epididymis, testis, ovary)
Duration:	Reproductive/Developmental About 35 weeks
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	10603716

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was identified definitively: nomenclature: tris(2-chloroethyl)phosphate and CASRN: 115-96-8. The compound was also identified as TCEP by gas chromatography.
	Metric 2:	Test Substance Source	High	The source of the test substance was a manufacturer (Aldrich); a batch/lot number was indicated (HT0090787).
	Metric 3:	Test Substance Purity	High	TCEP was comprehensively analyzed to determine the purity of the test chemical, which was indicated to be >98% pure. Observed effects were likely due to the test substance itself.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	An appropriate control group was used throughout the study (i.e., control mice were administered the corn oil vehicle only).
	Metric 5:	Positive Controls	N/A	Positive controls were not required by study type.
	Metric 6:	Randomized Allocation of Animals	Low	The study did not indicate how animals were allocated to study groups. It was mentioned that animals were randomly paired for some phases of the experiment.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	The test substance was mixed in corn oil; each dose level was independently formulated. Aliquots of each formulation (including the control) were sent for analysis at various time points during the study. The stock concentration was 8 mg/mL. Formulation analyses showed that TCEP mixed at this concentration was stable for 3 weeks at room temperature; dose formulations were prepared at least every three weeks.
	Metric 8:	Consistency of Exposure Administration	Medium	Appendix I notes that the time of gavage dosing varied up to 1 hr among doses (one exception occurred). Other details of exposure administration are incompletely reported (e.g., gavage volume). Any missing information is unlikely to have a substantial impact on results (especially since a published protocol that complied to GLP standards was used).
	Metric 9:	Reporting of Doses/Concentrations	High	Doses in mg/kg-day were reported without ambiguity.
	Metric 10:	Exposure Frequency and Duration	High	The study frequency/duration was adequate to detect effects pertaining to the outcome of interest. The exposure protocols (duration/timing of exposure) were specifically designed to evaluate reproductive/developmental outcomes.

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Study Citation:	NTP, (1991). Final report on the reproductive toxicity of tris(2-chloroethyl) phosphate in CD-1 Swiss mice.
Health Outcome(s):	Reproductive/Developmental
Reported Health Effect(s):	mating, pregnancy, and fertility, cumulative days to litter, dam weight, mean litters/pair, live pups/litter, proportion of pups born alive, sex of pups, pup weights, pup survival, estrous cyclicity, sperm parameters (concentration, motility, abnormal sperm), reproductive organ weights (epididymis, testis, cauda epididymis, prostate, seminal vesicles, ovary) and histology (epididymis, testis, ovary)
Duration:	Reproductive/Developmental About 35 weeks
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	10603716

Domain	Metric		Rating	Comments
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	The dose range-finding (Task 1) and continuous breeding (Task 3) phases of the study utilized at least 3 dose levels and a concurrent control; the dose intervals were typically two-fold. The offspring assessment (Task 4) included two dose levels plus the control owing to there being too few offspring to analyze at the high-dose. Doses were initially selected (based on the dose range-finding study) to induce some systemic toxicity without severe toxicity/death at the high-dose (and to allow for the identification of a NOAEL).
	Metric 12:	Exposure Route and Method	High	The study used a route of exposure (oral) that was considered appropriate (i.e., applicable to humans). Analyses of dosing formulations confirmed that the method of exposure was suited to the test substance (i.e., the test substance was stably mixed with corn oil for administration via gavage).
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	Medium	Based on OECD guidelines, the rat is the preferred species for most assessments of reproductive toxicity (e.g., based on guidelines for one- and two-generation toxicity tests, combined repeated-dose with reproductive/developmental toxicity); a rationale should have been provided for the use of mice in this study. The species and strain (VAF Crl: Swiss CD-1 [ICR]BR outbred albino mice), sex (both), age (e.g., 8 weeks at the start of Task 1 and 11 weeks at the start of Task 2), and starting body weights of the animals on the study were reported. Mice were purchased from a commercial source (Charles River Breeding Laboratories, Inc.).
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	High	The following husbandry conditions were reported: temperature, light-dark cycle (14 hours light/10 hours dark), and food and water availability and were similar for treated groups of mice and controls. Humidity was not reported.
	Metric 15:	Number of Animals per Group	Medium	The number of animals per group was in line with the numbers usually used for studies of this type. Reproduction studies typically aim to achieve about 20 successful pregnancies per dose group; for some tasks in this study, there were 20 pairs/treatment group, which resulted in fewer than 20 pregnancies per group (e.g., fertility was 18-19 out of 20 during Task 2). The number of animals per group was adequate to evaluate the outcome of interest.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	High	The outcome analysis was an appropriate method to evaluate the outcome of interest. A large number of reproductive/developmental parameters were evaluated in Tasks 2, 3, and 4; the endpoints evaluated were specifically selected to identify sensitive effects pertaining to this outcome of interest.
	Metric 17:	Consistency of Outcome Assessment	High	Outcomes were assessed consistently across study groups.

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Study Citation:	NTP, (1991). Final report on the reproductive toxicity of tris(2-chloroethyl) phosphate in CD-1 Swiss mice.
Health Outcome(s):	Reproductive/Developmental
Reported Health Effect(s):	mating, pregnancy, and fertility, cumulative days to litter, dam weight, mean litters/pair, live pups/litter, proportion of pups born alive, sex of pups, pup weights, pup survival, estrous cyclicity, sperm parameters (concentration, motility, abnormal sperm), reproductive organ weights (epididymis, testis, cauda epididymis, prostate, seminal vesicles, ovary) and histology (epididymis, testis, ovary)
Duration:	Reproductive/Developmental About 35 weeks
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	10603716

Domain	Metric		Rating	Comments
	Metric 18:	Sampling Adequacy	Medium	Reproductive/developmental parameters were evaluated in all animals that were assigned to each task of the study.
	Metric 19:	Blinding of Assessors	High	Blinding is not applicable to many of the outcomes (numbers of pups, pup weights, etc.); however, the study explicitly stated that vaginal cytology and sperm parameters (evaluated in Tasks 3 and 4) were scored randomly and without knowledge of treatment group (i.e., blinded). As per guidelines, blinding is not required for initial histology evaluations.
	Metric 20:	Negative Control Response	High	The biological response of the negative control group was adequate (low incidence of lesions in controls; high fertility in controls, etc.).
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	The study did not report all information to determine confounding, but the information reported did not identify differences. In general, the body weights of treated animals were similar to controls throughout the study.
	Metric 22:	Health Outcomes Unrelated to Exposure	High	Details on outcomes unrelated to exposure were reported. The study indicated that, during quarantine, representative animals were sacrificed and evaluated for antibodies against mouse viruses and parasites. The health status of sentinel animals maintained in the same room as treated animals were monitored as well (tested for viral antibodies). Animals tested negative for viral antibodies throughout the study.
	Metric 23:	Data Presentation and Analysis	High	Appropriate statistical analyses were performed at all measured time points.
	Metric 24:	Reporting of Data	High	Reproductive/developmental data (summarized and for individual animals) were provided in the body of the report and/or the appendices.

Overall Quality Determination High

Study Citation:	NTP, (1991). Final report on the reproductive toxicity of tris(2-chloroethyl) phosphate in CD-1 Swiss mice.
Health Outcome(s):	Hepatic/Liver; Renal/Kidney; Ocular/Sensory; Immune/Hematological;
Reported Health Effect(s):	Hepatic/Liver: Liver weight and histology (F0 and F1 animals during phases 3 and 4, respectively).; Renal/Kidney: Kidney weight and histology (F0 and F1 animals during phases 3 and 4, respectively).; Ocular/Sensory: Eye histology (F1 animals in phase 4); Immune/Hematological: Spleen and axillary lymph nodes histology (F1 animals in phase 4);
Duration:	Reproductive/Developmental About 35 weeks
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	10603716

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	All Outcomes: The test substance was identified definitively: nomenclature: tris(2-chloroethyl)phosphate and CASRN: 115-96-8. The compound was also identified as TCEP by gas chromatography.
	Metric 2:	Test Substance Source	High	All Outcomes: The source of the test substance was a manufacturer (Aldrich); a batch/lot number was indicated (HT0090787).
	Metric 3:	Test Substance Purity	High	All Outcomes: TCEP was comprehensively analyzed to determine the purity of the test chemical, which was indicated to be >98% pure. Observed effects were likely due to the test substance itself.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	All Outcomes: An appropriate control group was used throughout the study (i.e., control mice were administered the corn oil vehicle only).
	Metric 5:	Positive Controls	N/A	All Outcomes: Positive controls were not required by study type.
	Metric 6:	Randomized Allocation of Animals	Low	All Outcomes: The study did not indicate how animals were allocated to study groups. It was mentioned that animals were randomly paired for some phases of the experiment.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	All Outcomes: The test substance was mixed in corn oil; each dose level was independently formulated. Aliquots of each formulation (including the control) were sent for analysis at various time points during the study. The stock concentration was 8 mg/mL. Formulation analyses showed that TCEP mixed at this concentration was stable for 3 weeks at room temperature; dose formulations were prepared at least every three weeks.
	Metric 8:	Consistency of Exposure Administration	Medium	All Outcomes: Appendix I notes that the time of gavage dosing varied up to 1 hr among doses (one exception occurred). Other details of exposure administration are incompletely reported (e.g., gavage volume). Any missing information is unlikely to have a substantial impact on results (especially since a published protocol that complied to GLP standards was used).
	Metric 9:	Reporting of Doses/Concentrations	High	All Outcomes: Doses in mg/kg-day were reported without ambiguity.
	Metric 10:	Exposure Frequency and Duration	High	All Outcomes: The study frequency/duration was adequate to detect effects pertaining to the outcome of interest.

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Study Citation:	NTP, (1991). Final report on the reproductive toxicity of tris(2-chloroethyl) phosphate in CD-1 Swiss mice.
Health Outcome(s):	Hepatic/Liver; Renal/Kidney; Ocular/Sensory; Immune/Hematological;
Reported Health Effect(s):	Hepatic/Liver: Liver weight and histology (F0 and F1 animals during phases 3 and 4, respectively).; Renal/Kidney: Kidney weight and histology (F0 and F1 animals during phases 3 and 4, respectively).; Ocular/Sensory: Eye histology (F1 animals in phase 4); Immune/Hematological: Spleen and axillary lymph nodes histology (F1 animals in phase 4);
Duration:	Reproductive/Developmental About 35 weeks
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	10603716

Domain	Metric		Rating	Comments
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	All Outcomes: The dose range-finding (Task 1) and continuous breeding (Task 3) phases of the study utilized at least 3 dose levels and a concurrent control; the dose intervals were typically two-fold. The offspring assessment (Task 4) included two dose levels plus the control owing to there being too few offspring to analyze at the high-dose. Doses were initially selected (based on the dose range-finding study) to induce some systemic toxicity without severe toxicity/death at the high-dose (and to allow for the identification of a NOAEL).
	Metric 12:	Exposure Route and Method	High	All Outcomes: The study used a route of exposure (oral) that was considered appropriate (i.e., applicable to humans). Analyses of dosing formulations confirmed that the method of exposure was suited to the test substance (i.e., the test substance was stably mixed with corn oil for administration via gavage).
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	Medium	All Outcomes: Based on OECD guidelines, the rat is the preferred species for most assessments of reproductive toxicity (e.g., based on guidelines for one- and two-generation toxicity tests, combined repeated-dose with reproductive/developmental toxicity); a rationale should have been provided for the use of mice in this study. The species and strain (VAF Crl: Swiss CD-1 [ICR]BR outbred albino mice), sex (both), age (e.g., 8 weeks at the start of Task 1 and 11 weeks at the start of Task 2), and starting body weights of the animals on the study were reported. Mice were purchased from a commercial source (Charles River Breeding Laboratories, Inc.).
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	High	All Outcomes: The following husbandry conditions were reported: temperature, light-dark cycle (14 hours light/10 hours dark), and food and water availability and were similar for treated groups of mice and controls. Humidity was not reported.
	Metric 15:	Number of Animals per Group	Medium	All Outcomes: The number of animals per group was in line with the numbers usually used for studies of this type. Reproduction studies typically aim to achieve about 20 successful pregnancies per dose group; for some tasks in this study, there were 20 pairs/treatment group, which resulted in fewer than 20 pregnancies per group (e.g., fertility was 18-19 out of 20 during Task 2). The number of animals per group was adequate to evaluate the outcome of interest.
Domain 5: Outcome Assessment				

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Study Citation:	NTP, (1991). Final report on the reproductive toxicity of tris(2-chloroethyl) phosphate in CD-1 Swiss mice.
Health Outcome(s):	Hepatic/Liver; Renal/Kidney; Ocular/Sensory; Immune/Hematological;
Reported Health Effect(s):	Hepatic/Liver: Liver weight and histology (F0 and F1 animals during phases 3 and 4, respectively).; Renal/Kidney: Kidney weight and histology (F0 and F1 animals during phases 3 and 4, respectively).; Ocular/Sensory: Eye histology (F1 animals in phase 4); Immune/Hematological: Spleen and axillary lymph nodes histology (F1 animals in phase 4);
Duration:	Reproductive/Developmental About 35 weeks
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	10603716

Domain	Metric		Rating	Comments
	Metric 16:	Outcome Assessment Methodology	Medium	Hepatic/Liver: The outcome analysis partially addressed the outcome of interest. Liver weight and histology were evaluated in F0 and F1 animals at the end of Tasks 3 and 4, respectively (only high-dose animals and controls in Task 4). No other (potentially more sensitive) measures of liver toxicity (e.g., hematology or clinical chemistry parameters) were evaluated in the study.; Renal/Kidney: The outcome analysis partially addressed the outcome of interest. Kidney weight and histology were evaluated in F0 and F1 animals at the end of Tasks 3 and 4, respectively (only high-dose animals and controls in Task 4). No other (potentially more sensitive) measures of renal toxicity (e.g., clinical chemistry or urinalysis parameters) were evaluated in the study.; Ocular/Sensory: The outcome analysis partially addressed the outcome of interest. Eye histology was evaluated in F1 animals at the end of Task 4 (only high-dose animals and controls). No other measures of ocular toxicity were evaluated in the study, and the eyes of F0 animals sacrificed at the end of Task 3 were also not evaluated histologically.; Immune/Hematological: The outcome analysis partially addressed the outcome of interest. Spleen/lymph node histology was evaluated in F1 animals at the end of Task 4 (only high-dose animals and controls). No other measures of immunotoxicity were evaluated in the study, and the spleen/lymph nodes of F0 animals sacrificed at the end of Task 3 were also not evaluated histologically.
	Metric 17:	Consistency of Outcome Assessment	High	All Outcomes: Outcomes were assessed consistently across study groups.
	Metric 18:	Sampling Adequacy	High	Hepatic/Liver: Liver weight was assessed in all animals on the study; liver histology was assessed in all animals in Task 3 and in control and high-dose animals in Task 4.; Renal/Kidney: Kidney weight was assessed in all animals on the study; kidney histology was assessed in all animals in Task 3 and in control and high-dose animals in Task 4.; Ocular/Sensory: Eye histology was assessed in control and high-dose animals in Task 4.; Immune/Hematological: Spleen/axillary lymph nodes histology was assessed in control and high-dose animals in Task 4.
	Metric 19:	Blinding of Assessors	N/A	Hepatic/Liver: Blinding is not applicable to liver weight (which is not subjective); guidelines indicate that blinding is not required for initial histological evaluations.; Renal/Kidney: Blinding is not applicable to kidney weight (which is not subjective); guidelines indicate that blinding is not required for initial histological evaluations.; Ocular/Sensory: Guidelines indicate that blinding is not required for initial histological evaluations.; Immune/Hematological: Guidelines indicate that blinding is not required for initial histological evaluations.
	Metric 20:	Negative Control Response	High	All Outcomes: The biological response of the negative control group was adequate (e.g., the incidence of lesions was low in controls) .

Domain 6: Confounding / Variable Control

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Study Citation:	NTP, (1991). Final report on the reproductive toxicity of tris(2-chloroethyl) phosphate in CD-1 Swiss mice.
Health Outcome(s):	Hepatic/Liver; Renal/Kidney; Ocular/Sensory; Immune/Hematological;
Reported Health Effect(s):	Hepatic/Liver: Liver weight and histology (F0 and F1 animals during phases 3 and 4, respectively).; Renal/Kidney: Kidney weight and histology (F0 and F1 animals during phases 3 and 4, respectively).; Ocular/Sensory: Eye histology (F1 animals in phase 4); Immune/Hematological: Spleen and axillary lymph nodes histology (F1 animals in phase 4);
Duration:	Reproductive/Developmental About 35 weeks
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	10603716

Domain	Metric		Rating	Comments
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	All Outcomes: The study did not report all information to determine confounding, but the information reported did not identify differences. In general, the body weights of treated animals were similar to controls throughout the study.
	Metric 22:	Health Outcomes Unrelated to Exposure	High	All Outcomes: Details on outcomes unrelated to exposure were reported. The study indicated that, during quarantine, representative animals were sacrificed and evaluated for antibodies against mouse viruses and parasites. The health status of sentinel animals maintained in the same room as treated animals were monitored as well (tested for viral antibodies). Animals tested negative for viral antibodies throughout the study.
	Metric 23:	Data Presentation and Analysis	High	All Outcomes: Appropriate statistical analyses were performed (or could be performed) at all measured time points.
	Metric 24:	Reporting of Data	High	Hepatic/Liver: Liver data were provided in the study report. Liver data for individual animals were also reported in the appendices.; Renal/Kidney: Kidney data were provided in the study report. Kidney data for individual animals were also reported in the appendices.; Ocular/Sensory: Eye histology data (summarized and for individual animals) were provided in the study report and/or appendices.; Immune/Hematological: Spleen/lymph nodes histology data (summarized and for individual animals) were provided in the study report and/or appendices.

Overall Quality Determination High

Study Citation:	NTP, (1991). Final report on the reproductive toxicity of tris(2-chloroethyl) phosphate in CD-1 Swiss mice.
Health Outcome(s):	Neurological/Behavioral
Reported Health Effect(s):	Brain histology (F0 and F1 animals during phases 3 and 4, respectively).
Duration:	Reproductive/Developmental About 35 weeks
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	10603716

Domain	Metric		Rating	Comments
Domain 1: Test Substance				
	Metric 1:	Test Substance Identity	High	The test substance was identified definitively: nomenclature: tris(2-chloroethyl)phosphate and CASRN: 115-96-8. The compound was also identified as TCEP by gas chromatography.
	Metric 2:	Test Substance Source	High	The source of the test substance was a manufacturer (Aldrich); a batch/lot number was indicated (HT0090787).
	Metric 3:	Test Substance Purity	High	TCEP was comprehensively analyzed to determine the purity of the test chemical, which was indicated to be >98% pure. Observed effects were likely due to the test substance itself.
Domain 2: Test Design				
	Metric 4:	Negative and Vehicle Controls	High	An appropriate control group was used throughout the study (i.e., control mice were administered the corn oil vehicle only).
	Metric 5:	Positive Controls	N/A	Positive controls were not required by study type.
	Metric 6:	Randomized Allocation of Animals	Low	The study did not indicate how animals were allocated to study groups. It was mentioned that animals were randomly paired for some phases of the experiment.
Domain 3: Exposure Characterization				
	Metric 7:	Preparation and Storage of Test Substance	High	The test substance was mixed in corn oil; each dose level was independently formulated. Aliquots of each formulation (including the control) were sent for analysis at various time points during the study. The stock concentration was 8 mg/mL. Formulation analyses showed that TCEP mixed at this concentration was stable for 3 weeks at room temperature; dose formulations were prepared at least every three weeks.
	Metric 8:	Consistency of Exposure Administration	Medium	Appendix I notes that the time of gavage dosing varied up to 1 hr among doses (one exception occurred). Other details of exposure administration are incompletely reported (e.g., gavage volume). Any missing information is unlikely to have a substantial impact on results (especially since a published protocol that complied to GLP standards was used).
	Metric 9:	Reporting of Doses/Concentrations	High	Doses in mg/kg-day were reported without ambiguity.
	Metric 10:	Exposure Frequency and Duration	Medium	The study frequency/duration was generally adequate to detect effects pertaining to the outcome of interest but because the test substance has an effect on cholinesterase, the study would have been more robust if it tested animals postnatally for this activity.

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Study Citation:	NTP, (1991). Final report on the reproductive toxicity of tris(2-chloroethyl) phosphate in CD-1 Swiss mice.
Health Outcome(s):	Neurological/Behavioral
Reported Health Effect(s):	Brain histology (F0 and F1 animals during phases 3 and 4, respectively).
Duration:	Reproductive/Developmental About 35 weeks
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	10603716

Domain	Metric		Rating	Comments
	Metric 11:	Number of Exposure Groups and Dose/Concentration Spacing	High	The dose range-finding (Task 1) and continuous breeding (Task 3) phases of the study utilized at least 3 dose levels and a concurrent control; the dose intervals were typically two-fold. The offspring assessment (Task 4) included two dose levels plus the control owing to there being too few offspring to analyze at the high-dose. Doses were initially selected (based on the dose range-finding study) to induce some systemic toxicity without severe toxicity/death at the high-dose (and to allow for the identification of a NOAEL).
	Metric 12:	Exposure Route and Method	High	The study used a route of exposure (oral) that was considered appropriate (i.e., applicable to humans). Analyses of dosing formulations confirmed that the method of exposure was suited to the test substance (i.e., the test substance was stably mixed with corn oil for administration via gavage).
Domain 4: Test Animals				
	Metric 13:	Test Animal Characteristics	Medium	Based on OECD guidelines, the rat is the preferred species for most assessments of reproductive toxicity (e.g., based on guidelines for one- and two-generation toxicity tests, combined repeated-dose with reproductive/developmental toxicity); a rationale should have been provided for the use of mice in this study. The species and strain (VAF Crl: Swiss CD-1 [ICR]BR outbred albino mice), sex (both), age (e.g., 8 weeks at the start of Task 1 and 11 weeks at the start of Task 2), and starting body weights of the animals on the study were reported. Mice were purchased from a commercial source (Charles River Breeding Laboratories, Inc.).
	Metric 14:	Adequacy and Consistency of Animal Husbandry Conditions	High	The following husbandry conditions were reported: temperature, light-dark cycle (14 hours light/10 hours dark), and food and water availability and were similar for treated groups of mice and controls. Humidity was not reported.
	Metric 15:	Number of Animals per Group	Medium	The number of animals per group was in line with the numbers usually used for studies of this type. Reproduction studies typically aim to achieve about 20 successful pregnancies per dose group; for some tasks in this study, there were 20 pairs/treatment group, which resulted in fewer than 20 pregnancies per group (e.g., fertility was 18-19 out of 20 during Task 2). The number of animals per group was adequate to evaluate the outcome of interest.
Domain 5: Outcome Assessment				
	Metric 16:	Outcome Assessment Methodology	Medium	The outcome analysis partially addressed the outcome of interest. Brain histology was evaluated in F0 and F1 animals at the end of Tasks 3 and 4, respectively (only high-dose animals and controls in Task 4). No other measures of neurotoxicity were evaluated in the study. In particular brain weights were not evaluated nor were changes in serum cholinesterase.
	Metric 17:	Consistency of Outcome Assessment	High	Outcomes were assessed consistently across study groups.

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Study Citation:	NTP, (1991). Final report on the reproductive toxicity of tris(2-chloroethyl) phosphate in CD-1 Swiss mice.
Health Outcome(s):	Neurological/Behavioral
Reported Health Effect(s):	Brain histology (F0 and F1 animals during phases 3 and 4, respectively).
Duration:	Reproductive/Developmental About 35 weeks
Chemical:	Tris(2-chloroethyl) phosphate (TCEP)- Parent compound
HERO ID:	10603716

Domain	Metric		Rating	Comments
	Metric 18:	Sampling Adequacy	High	Brain histology was assessed in all animals in Task 3 and in control and high-dose animals in Task 4.
	Metric 19:	Blinding of Assessors	N/A	Guidelines indicate that blinding is not required for initial histological evaluations.
	Metric 20:	Negative Control Response	High	The biological response of the negative control group was adequate (e.g., the incidence of lesions was low in controls).
Domain 6: Confounding / Variable Control				
	Metric 21:	Confounding Variables in Test Design and Procedures	Medium	The study did not report all information to determine confounding, but the information reported did not identify differences. In general, the body weights of treated animals were similar to controls throughout the study.
	Metric 22:	Health Outcomes Unrelated to Exposure	High	Details on outcomes unrelated to exposure were reported. The study indicated that, during quarantine, representative animals were sacrificed and evaluated for antibodies against mouse viruses and parasites. The health status of sentinel animals maintained in the same room as treated animals were monitored as well (tested for viral antibodies). Animals tested negative for viral antibodies throughout the study.
	Metric 23:	Data Presentation and Analysis	High	Appropriate statistical analyses were performed (or could be performed) at all measured time points.
	Metric 24:	Reporting of Data	High	Brain histology data (summarized and for individual animals) were provided in the study report and/or appendices.

Overall Quality Determination High