

Note to Reader: The following provides a basic overview and explanation of the document entitled *Approach for Evaluating Developmental Neurotoxicity Potential for the Organophosphate Pesticides*

Organophosphate (OP) pesticides are currently undergoing Registration Review, which is a process under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) that requires EPA to reevaluate pesticides every 15 years to ensure that as science advances and as policies and practices change, pesticides continue to meet the statutory standard of causing no unreasonable adverse effects on human health or the environment.

OPs have been extensively studied for decades and share the ability to cause neurotoxicity through binding of an enzyme, called acetylcholinesterase, that is responsible for breaking down the neurotransmitter acetylcholine. Neurotransmitters are chemical messengers that transmit messages across the nervous system and to parts of the body. When exposure to an OP occurs, the acetylcholinesterase enzyme becomes unable to perform its role in breaking down acetylcholine. At high levels of OP exposure, the resulting build-up of acetylcholine can cause a suite of neurological effects, such as tremors, fatigue, and nausea. The Office of Pesticide Programs (OPP) has a long history of using changes in acetylcholinesterase as a health-protective endpoint, or the adverse effect that forms the basis for OP risk assessments.

In addition to requirements under FIFRA, the Food Quality Protection Act (FQPA) amended the Federal Food, Drug, and Cosmetic Act (FFDCA) to require EPA to assess the risk to human health in a manner that includes an additional tenfold margin of safety. This is called the “FQPA safety factor” and it adds additional protections when EPA assesses risks of pesticides to infants and children such that EPA takes into account potential toxicity and completeness of data. The FQPA amendments to FFDCA also permit EPA to apply a different safety factor in lieu of the default 10X factor when there is reliable data that demonstrate that such a factor would be protective of infants and children.

In 2015 (with updates in 2016), EPA performed a review of available epidemiological, laboratory animal, and *in vitro* studies to evaluate the potential for OPs to produce neurodevelopmental effects, and the review identified uncertainties associated with the doses at which these potential effects may occur. Despite recognizing several limitations and inconsistencies in the available studies, EPA assumed at that time that all the OPs cause similar neurodevelopmental effects and retained the default 10X FQPA safety factor for all OP pesticides. This meant that the 10X safety factor was applied to all individual OPs without consideration of chemical-specific differences.

Since 2016, the Agency has been working with stakeholders and international regulatory counterparts to better understand the potential for OPs to cause developmental neurotoxicity (DNT) and the doses that may be associated with these potential effects. An international effort spanning more than a decade led to the development of a battery of *in vitro* tests that evaluate key neurodevelopmental processes. In 2020, this DNT battery was reviewed favorably by the Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (FIFRA SAP) for use in a weight of evidence (WOE) evaluation for DNT hazard potential (which means data from the battery can reliably be used with other sources of information EPA uses to make regulatory decisions with respect to DNT). Additionally, guidance on the use of the DNT battery was approved and released by the Organization of Economic Cooperation and Development (OECD) in June 2023.

The DNT battery provides high quality data for individual OP compounds that were not available at the time of the Agency's 2016 review. The new data demonstrate that differences exist across OP chemicals with respect to their potential to elicit neurodevelopmental effects, with exposures to some OPs having much higher potential to cause adverse neurodevelopmental outcomes than others. Such differences were also previously seen in epidemiological studies and laboratory animal studies for the OPs, and the new data corroborate those findings. As a result, the currently available data do not support the assumption that all OP compounds have the same potential to elicit neurodevelopmental outcomes or that these potential outcomes would have similar quantitative relationships with acetylcholinesterase changes (i.e., how close or far apart are the doses that elicit potential DNT and acetylcholinesterase changes). This has prompted EPA to reevaluate its approach to assessing the DNT potential of the OPs. As a result, the Agency has determined, based on the best available science, that the DNT potential of OPs should be evaluated on a chemical-by-chemical basis, not as a group.

Moving forward, as with all pesticides subject to FQPA, EPA will continue to retain a default 10X safety factor as required under the FFDCA to protect infants and children, unless reliable data exists to support a different safety factor. This document, entitled *Approach for Evaluating Developmental Neurotoxicity Potential for the Organophosphate Pesticides*, provides further details regarding EPA's decision to evaluate OPs on a chemical-by-chemical basis, including information on the development, review, and acceptance of the DNT battery in WOE evaluations. In determining an appropriate FQPA safety factor for each OP, OPP intends to perform a WOE evaluation for DNT potential using high quality, chemical-specific data, when appropriate. In this WOE evaluation, EPA will first evaluate whether the chemical has the potential to elicit neurodevelopmental outcomes based on all of the data from three primary lines of evidence – epidemiological studies, bioassays performed with laboratory animals, and the DNT battery. This will include relevant chemical-specific studies that are identified as part of updated literature searches performed to support human health risk assessments. For chemicals where there is evidence of DNT potential, the Agency will further examine the available *in vitro* and *in vivo* data, where exposures are better controlled and quantified, to evaluate anticipated doses that may be associated with potential DNT effects and how these doses relate to those eliciting acetylcholinesterase changes. EPA will account for this examination as part of its analysis to determine whether reliable data exists to support a different FQPA safety factor than the default 10x. This approach for the OPs is consistent with how EPA determines appropriate FQPA safety factors for all pesticides subject to FQPA.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460



OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

Date: April 10, 2023

SUBJECT: Approach for Evaluating Developmental Neurotoxicity Potential for the Organophosphate Pesticides

PC Code: See table below

Decision No.: 591082

Petition No.: NA

Risk Assessment Type: NA

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Regulatory Action: NA

Case No.: NA

CAS No.: See table below

40 CFR: See table below

FROM: Monique Perron, Senior Science Advisor
Immediate Office
Office of Pesticide Programs

Monique Perron

THROUGH: Ed Messina, Director
Immediate Office
Office of Pesticide Programs

Ed Messina

TO: Anna Romanovsky, Chemical Review Manager
Kelly Sherman, Branch Supervisor
Elissa Reaves, Director
Pesticide Reevaluation Division
Office of Pesticide Programs

Chemical	PC Code	CAS No.	40 CFR
Acephate	103301	30560-19-1	§180.108
Bensulide	009801	741-58-2	§180.241
Cadusafos	128864	95465-99-9	§180.461
Chlorethoxyfos	129006	54593-83-8	§180.486
Chlorpyrifos	059101	2921-88-2	§180.342
Chlorpyrifos-methyl*	059102	5598-13-0	§180.419
Coumaphos	036501	56-72-4	§180.189
Dichlorvos (DDVP)	084001	62-73-7	§180.235
Diazinon	057801	333-41-5	§180.153
Dicrotophos	035201	141-66-2	§180.299
Dimethoate	035001	60-51-5	§180.204
Ethoprop	041101	13194-48-4	§180.262
Fenamiphos	100601	22224-92-6	§180.349
Fenitrothion	105901	122-14-5	§180.540
Fosthiazate	129022	98886-44-3	§180.596
Malathion	057701	121-75-5	§180.111
Naled	034401	300-76-5	§180.215
Phorate	057201	298-02-2	§180.206
Phosmet	059201	732-11-6	§ 180.261
Phostebupirim (Tebupirimiphos)	129086	96182-53-5	NA
Pirimiphos-methyl	108102	29232-93-7	§ 180.409
Profenofos	111401	41198-08-7	§180.404
Terbufos	105001	13071-79-9	§ 180.352
Tetrachlorvinphos (TCVP)	083701	961-11-5	§ 180.252
Tribufos	074801	78-48-8	§180.272
Trichlorfon	057901	52-68-6	§ 180.198

* Currently undergoing voluntary cancellation

The conclusions conveyed in this assessment were developed in full compliance with *EPA Scientific Integrity Policy for Transparent and Objective Science*, and EPA Scientific Integrity Program's *Approaches for Expressing and Resolving Differing Scientific Opinions*. The full text of *EPA Scientific Integrity Policy for Transparent and Objective Science*, as updated and approved by the Scientific Integrity Committee and EPA Science Advisor can be found here: https://www.epa.gov/sites/default/files/201402/documents/scientific_integrity_policy_2012.pdf. The full text of the EPA Scientific Integrity Program's *Approaches for Expressing and Resolving Differing Scientific Opinions* can be found here: <https://www.epa.gov/scientific-integrity/approaches-expressing-and-resolving-differing-scientific-opinions>

Executive Summary

The Food Quality Protection Act (FQPA) instructs EPA, in making its “reasonable certainty of no harm” finding, that in “the case of threshold effects, an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and postnatal toxicity and completeness of data with respect to exposure and toxicity to infants and children.” Section 408 (b)(2)(C) further states that “the Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children”. Based on an EPA review on neurodevelopmental effects, the 10X FQPA safety factor (SF) for organophosphates (OPs) was retained for the population subgroups that include infants, children, youths, and women of childbearing age for all exposure scenarios. In recent years, high quality data on critical neurodevelopmental processes have become available, prompting the Office of Pesticide Programs (OPP) to reevaluate its approach to evaluating developmental neurotoxicity (DNT) potential and determining the FQPA SFs for OPs. Based on the best available science, OPP has determined that DNT potential for OPs should be evaluated on a chemical-by-chemical basis, not as a group. Consequently, chemical-specific data and information will be used in a weight of evidence (WOE) evaluation of DNT potential for individual OPs to inform appropriate FQPA SF determinations.

Introduction

In 2015, EPA released a literature review on neurodevelopmental effects and FQPA Safety Factor (SF) determination for the OP pesticides (A. Lowit, D331251, 15-SEP-2015). The review was then updated in 2016 to incorporate additional studies and address public comments (A. Aldridge *et al.*, 29-DEC-2016, D437043). For the FQPA determination, data from three primary lines of evidence – epidemiological studies, studies in laboratory animals, and *in vitro* assays – were evaluated in a weight-of-evidence (WOE) approach to assess the DNT potential of OPs. Although the mode of action/adverse outcome pathway (MOA/AOP) has not been established for any potential developmental neurotoxic outcomes, OPP took a conservative approach by performing the 2015/2016 review for the OPs as a group based on the assumption that, like acetylcholinesterase (AChE) inhibition and subsequent neurotoxicity, developmental neurotoxic outcomes would share a common MOA/AOP. Based on the 2015/2016 review, the 10X FQPA SF for OPs was retained for the population subgroups that include infants, children, youths, and women of childbearing age for all exposure scenarios due to uncertainties in the human dose-response relationship for potential neurodevelopmental outcomes and its quantitative relationship to AChE inhibition. Similarly, a 10X database uncertainty factor was applied for occupational risk assessments. To address this uncertainty, EPA recognized the need to pursue approaches for quantitative or semi-quantitative comparisons between AChE inhibition and neurodevelopmental outcomes.

Much of the concern related to neurodevelopmental outcomes from OP exposures is largely based on the extensive chlorpyrifos dataset comprised of epidemiological studies (some directly measuring chlorpyrifos), over 30 *in vivo* toxicity studies (including the guideline DNT study), and numerous *in vitro* studies published in the literature. In contrast, for the remaining OPs the epidemiological evidence was generally limited to studies using non-specific biomarkers that

make it difficult to causally or quantitatively link exposure of individual OPs to the investigated outcomes¹, to a few *in vivo* studies, and to little to no *in vitro* data. For most of these chemicals, *in vivo* guideline DNT studies are available and none provided a more sensitive endpoint than AChE inhibition, which is the basis for endpoints used in current OP human health risk assessments. As a result, the 2015/2016 review was heavily reliant upon chlorpyrifos studies. However, since that time, high quality data from a battery of *in vitro* assays that evaluate critical neurodevelopmental processes have become available for numerous OP compounds. No consistent pattern has emerged to suggest that all OP compounds share a common pathway for potential DNT, indicating that DNT potential of OPs should be evaluated on a chemical-by-chemical basis, rather than as a group. This has prompted the OPP to reevaluate its approach to evaluating DNT potential and determining the FQPA SFs for OPs based on the best available science and human relevant information.

DNT NAM Battery

Since the 2015/2016 review, high quality data on underlying biological processes of neurodevelopment have become available as a result of an international effort for over a decade to develop new approach methodologies (NAMs) for DNT. This international effort recognized limitations of available DNT studies and, through a series of meetings with scientists, regulators, and stakeholders (e.g., Lein et al., 2007; Coecke et al., 2007; Crofton et al., 2011; Bal-Price et al., 2012; Aschner et al., 2017; Fritsche et al., 2017; Fritsche et al., 2018a; Fritsche et al., 2018b; Sachana et al. 2019), led to the development of a battery of *in vitro* assays (referred to hereafter as DNT NAM battery; Sachana et al., 2021) that assess processes critical to development of the nervous system and provide chemical-specific evaluation of DNT potential. The current DNT NAM battery consists of multiple *in vitro* assays that utilize either human or rat neural cell models. Assays in the DNT NAM battery were developed by the US EPA Office of Research and Development (ORD) and international collaborators². The battery measures critical neurodevelopmental processes *in vitro* including proliferation of neuroprogenitor cells, differentiation of neuroprogenitor cells into glial and neuronal subtypes, apoptosis, migration of neurons and oligodendrocytes, neurite outgrowth, synaptogenesis, and neural network formation.

When development of the DNT NAM battery was initiated, it was recognized that brain development is complex and occurs with different timelines in different brain regions, involving many different cell types. The concept of evaluating key neurodevelopmental processes was designed to address this issue, given that these processes must take place across all brain regions and neurotransmitter types for proper nervous system development, and the mechanisms underlying these processes are well conserved. By focusing on critical biological processes that are the underpinnings of the apical endpoints, the DNT NAM battery can provide relevant information regarding DNT potential of individual chemicals related to critical processes of neurodevelopment and evaluate early perturbations that are difficult to obtain or evaluate *in vivo*.

¹ The majority of epidemiology studies in the 2015/2016 review used non-specific biomarkers of OP exposure, with urinary dialkyl phosphates (DAPs) as the most commonly measured biomarker. DAPs are considered non-toxic metabolites and each DAP is a breakdown product from multiple OPs making it impossible to separate exposure and associated effects for individual, specific OPs.

² <https://www.regulations.gov/document/EPA-HQ-OPP-2020-0263-0006>
<https://www.oecd.org/env/ehs/testing/guidance-evaluation-of-data-developmental-neurotoxicity-in-vitro-testing.pdf>

It is paramount, however, to recognize that the presence of bioactivity in these assays provides evidence of potential to disrupt DNT processes, but it should not be construed as evidence that a tested chemical is a developmental neurotoxicant *in vivo*. Although activity may be observed in the battery, it may not necessarily represent an adverse change that is typically linked to tissue-level or apical effects in a MOA/AOP. As described in the “*Toxicity Testing in the 21st Century*” report³, to develop an AOP, not only is it necessary to establish plausible relationships among the key events, but quantitative relationships also need to be established. In other words, how much of a change in one key event is needed to result in an adverse effect at the next level of biological organization? Thus, certain exposures to a chemical may impact normal physiological responses in a way that may not necessarily be adverse. Consequently, the AOP concept requires an understanding of adaptive/homeostatic capacity of biological systems and their limits, relative to concentration and duration of exposure. At this time, OPP is assuming that observed activity in the battery is associated with adversity, which is a conservative approach for utilizing the data.

International Peer Review and Acceptance

The assays in the DNT NAM battery have been extensively characterized and reviewed. The methods, data from positive control and reference chemical testing, and the readiness of these assays have been evaluated and published in the peer-reviewed literature (Bal-Price et al., 2018; Sachana et al., 2021). For example, during development of the Network Formation Assay, data from positive and negative control chemicals were first published for the assay in 2016 (Brown et al., 2016), and this was followed by publication of results with reference chemicals (Frank et al., 2017) that demonstrated or lacked putative evidence of DNT *in vivo*⁴, and then by screening of larger sets of chemicals (Shafer et al., 2019). A similar approach was followed for all the other assays in the current DNT NAM battery, and the primary literature for each battery is summarized in Sachana et al. (2021).

In 2020, EPA convened a Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panels (SAP) to review the DNT NAM battery with the OPs as a case study⁵. The Agency’s Issue Paper supporting the SAP review provides additional characterization of the assays developed by EPA, including information on coefficients of variation, metrics of assay performance, and intralaboratory reproducibility. Overall, the SAP agreed that the current DNT NAM battery reflects, if not directly models, critical processes for neurodevelopment and that data from the battery can be used as part of a WOE evaluation, but also noted several processes and cell types that were believed to be missing in the battery. As discussed in the Agency’s response to the SAP⁶, the current battery is not entirely lacking these processes and cell types and/or these perceived limitations could be addressed by utilizing information from other available studies. The panel recommended the DNT battery “be a living and evolving process that can be revised and improved with new technology, assays, information on validity and reliability and *in vivo* translation”; however, the panel also noted that “this is not

³ http://www.nap.edu/catalog.php?record_id=11970

⁴ Note: Some chemicals were tested using doses and/or exposure routes that are not relevant for human health risk assessment.

⁵ <https://www.regulations.gov/document/EPA-HQ-OPP-2020-0263-0006>

⁶ <https://www.regulations.gov/document/EPA-HQ-OPP-2020-0263-0057>

meant to preclude the ability of the Agency to utilize all valid and relevant data in their efforts to determine risks for human health”.

International review and acceptance of the battery has also progressed since the 2020 SAP. Some organizations, such as European Food Safety Authority (EFSA) and European Chemicals Agency (ECHA), currently consider data from the DNT NAM battery as part of their evaluations. Further, an Expert Group on DNT was convened by the Organization of Economic Cooperation and Development (OECD) to develop a guidance document that describes the use of the battery as part of an Integrated Approach for Testing and Assessment (IATA) for DNT⁷. This guidance has been through two rounds of review by OECD member states and partners (e.g. non-governmental organizations (NGOs) and industry), and will be considered for approval by the OECD Working Group of the National Coordinators for the Test Guidelines Programme (WNT) at its meeting in April 2023. This guidance includes several case-studies for application of the battery to DNT decision-making. In addition, the guidance includes additional technical characterization of the assays, as it contains appendices that contain a “ToxTemp” form for each assay (Krebs et al., 2019). These “Toxtemp” forms contain information regarding the biological/human relevance, technical performance, appropriate assay positive controls and domains of applicability for each assay.

Approach for Evaluating DNT Potential and Use in Risk Assessment

Data from the DNT NAM battery have the ability to inform the uncertainty in the human dose-response relationship for potential neurodevelopmental outcomes and AChE inhibition for OPs. Through the use of kinetic models, such as high-throughput toxicokinetic (HTTK) or refined physiologically-based pharmacokinetic (PBPK) models, the *in vitro* concentration that is associated with activity observed in the DNT NAM battery assay can be directly compared with an internal dose metric (e.g., average blood concentration) associated with the points of departure (PODs) based on other toxicological endpoints. For OPs, such comparison evaluates the relative sensitivity of activity in the DNT NAM battery to AChE inhibition given that the PODs for OP human health risk assessments are based on 10% AChE inhibition. This quantitative comparison between bioactivity in the DNT NAM battery and AChE inhibition provides a more scientifically robust, data-driven basis for evaluating DNT potential and its quantitative relationship to AChE inhibition to determine the appropriate FQPA SF on a chemical-by-chemical basis.

As previously discussed, the data from the DNT battery for individual OP compounds demonstrate that the DNT potential for OPs should be evaluated on a chemical-by-chemical basis, not as a group. No consistent pattern (e.g., differences in degree of activity/inactivity; activity in different assays that represent different critical processes) has emerged to suggest that all OPs share a common pathway for potential DNT⁸. Therefore, OPP will utilize chemical-specific data and information in its WOE evaluation of DNT potential for each OP to inform the FQPA SF determination. EPA is not making any judgements at this time on the FQPA SFs that will be applied in future OP risk assessments. In determining an appropriate FQPA SF for each individual OP risk assessment, OPP will consider high quality, chemical-specific data from the

⁷ <https://www.oecd.org/env/ehs/testing/guidance-evaluation-of-data-developmental-neurotoxicity-in-vitro-testing.pdf>

⁸ <https://www.regulations.gov/document/EPA-HQ-OPP-2020-0263-0006>

primary lines of evidence – epidemiological studies, studies in laboratory animals, and *in vitro* assays –in the WOE evaluations for DNT potential in conjunction with other FQPA SF considerations, such as completeness of the toxicological database, evidence of neurotoxicity, evidence of sensitivity/susceptibility, and residual uncertainty in the exposure database. These determinations will be summarized in future risk assessments for each OP accompanied by supporting documentation that will provide details of each chemical-specific WOE evaluation of DNT potential.

References:

Aschner et al. (2017) Reference compounds for alternative test methods to indicate developmental neurotoxicity (DNT) potential of chemicals: example lists and criteria for their selection and use. ALTEX. 34(1):49-74. <https://doi.org/10.14573/altex.1604201>

Bal-Price et al. (2012) Advancing the science of developmental neurotoxicity (DNT): testing for better safety evaluation. ALTEX 29(2):202-15. <https://doi.org/10.14573/altex.2012.2.202>

Bal-Price et al. (2018). Recommendation on test readiness criteria for new approach methods in toxicology: Exemplified for developmental neurotoxicity. ALTEX. 35(3):306-352. <https://pubmed.ncbi.nlm.nih.gov/29485663/>

Brown et al. (2016) Editor's Highlight: Evaluation of a Microelectrode Array-Based Assay for Neural Network Ontogeny Using Training Set Chemicals. Toxicol. Sci. 154(1):126-139. <https://doi.org/10.1093/toxsci/kfw147>

Chen et al. (2012) Preformed biomarkers including dialkylphosphates (DAPs) in produce may confound biomonitoring in pesticide exposure and risk assessment. J Agric Food Chem. 60(36):9342-51. <https://doi.org/10.1021/jf303116p>

Coecke et al. (2007) Workgroup report: incorporating *in vitro* alternative methods for developmental neurotoxicity into international hazard and risk assessment strategies. Environ. Health Perspect. 115(6):924-931. <https://doi.org/10.1289/ehp.9427>

Crofton et al. (2011) Developmental neurotoxicity testing: recommendations for developing alternative methods for the screening and prioritization of chemicals. ALTEX. 28(1):9-15. <https://pubmed.ncbi.nlm.nih.gov/21311847/>

Fritsche et al. (2017) OECD/EFSA workshop on developmental neurotoxicity (DNT): The use of non-animal test methods for regulatory purposes. ALTEX. 34(2):311-315. <https://doi.org/10.14573/altex.1701171>

Fritsche et al. (2018a) Consensus statement on the need for innovation, transition and implementation of developmental neurotoxicity (DNT) testing for regulatory purposes. 354:3-6. <https://doi.org/10.1016/j.taap.2018.02.004>

Fritsche et al. (2018b) Development of the Concept for Stem Cell-Based Developmental Neurotoxicity Evaluation. *Toxicol Sci.* 165(1):14-20. doi: 10.1093/toxsci/kfy175.
<https://pubmed.ncbi.nlm.nih.gov/29982725/>

Frank et al. (2017) From the Cover: Developmental Neurotoxicants Disrupt Activity in Cortical Networks on Microelectrode Arrays: Results of Screening 86 Compounds During Neural Network Formation. *Toxicol. Sci.* 160(1):121-135. <https://doi.org/10.1093/toxsci/kfx169>

Krebs et al. (2019) Template for the description of cell-based toxicological test methods to allow evaluation and regulatory use of the data. *ALTEX* 36(4):682-699.
<https://doi.org/10.14573/altex.1909271>

Lein et al. (2007) Meeting report: alternatives for developmental neurotoxicity testing. *Environ Health Perspect.* 115(5):764-8. <https://doi.org/10.1289/ehp.9841>

Sachana et al. (2019) International Regulatory and Scientific Effort for Improved Developmental Neurotoxicity Testing. *Toxicol. Sci.* 167(1):45-57. <https://doi.org/10.1093/toxsci/kfy211>

Sachana et al. (2021) Toward a Better Testing Paradigm for Developmental Neurotoxicity: OECD Efforts and Regulatory Considerations. 10(2):86.
<https://doi.org/10.3390/biology10020086>

Shafer et al. (2019) Evaluation of Chemical Effects on Network Formation in Cortical Neurons Grown on Microelectrode Arrays. *Toxicol Sci.* 169(2):436-455.
<https://doi.org/10.1093/toxsci/kfz052>

Zhang et al. (2008) Dialkylphosphates (DAPs) in fruits and vegetables may confound biomonitoring in organophosphorus insecticide exposure and risk assessment. *J Agric Food Chem.* 56(22):10638-45. <https://doi.org/10.1021/jf8018084>