OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

WASHINGTON, D.C. 20460

MEMORANDUM

SUBJECT: Propionic Acid: Summary of Endocrine Disruptor Science Policy Council (EDSPOC) Meeting on March 5, 2024; Recommendations on the Exemption of Propionic Acid from the Human Health Requirements of the Endocrine Disruptor Screening Program.

PC Code: 077702
Case No.: 4078
CAS No.: 79-09-4

FROM: Endocrine Disruptor Science Policy Council (EDSPOC)
Ronnie Joe Bever, Co-Chair Bever, Ronnie Digitally signed by Bever, Ronnie Date: 2024.05.15 09:09:39 -04'00'
Brian Van Deusen, Co-Chair Brian Van Deusen Digitally signed by Brian Van Deusen Date: 2024.05.15 07:56:02 -04'00'
Office of Pesticide Programs

CC: REGULATORY CHEMICAL TEAM MEMBERS
Caleb Carr, Chemical Review Manager
Maryam Muhammad, Team Lead
Linda Arrington, Branch Chief
Pesticide Re-Evaluation Division
Office of Pesticide Programs

And

Erin Dandridge, Chemical Review Manager
Kendall Ziner, Acting Re-Evaluation Team Leader
Eric Miederhoff, Branch Chief
Antimicrobials Division
Office of Pesticide Programs

TO: Michal Freedhoff, Ph.D.
Assistant Administrator
Office of Chemical Safety and Pollution Prevention

MEETING ATTENDEES

EDSPOC Members: Joe Bever (co-chair), Brian Van Deusen (co-chair), Natalie Bray (executive secretary), Greg Akerman, Catherine Aubee, Lisa Austin, Julie Javier, Scott Lynn, Jacqueline Meadows, Monique Perron, Thomas Steeger, Nicholas Thomas

Presenter: Linnea Hansen

Other Attendees: Caleb Carr, Erin Dandridge, Jonathon Giordano, Colleen Rossmeisl, Christina Swartz, Kendall Ziner

1. PURPOSE OF MEETING

An Endocrine Disruptor Screening Program (EDSP) exemption memo has been prepared for propionic acid (also referred to as propanoic acid). Section 408(p)(4) of the Federal Food, Drug, and Cosmetic Act (FFDCA) authorizes the Environmental Protection Agency (EPA), by order, to exempt from the requirements of the endocrine screening program required by Section 408(p)(1) "a biologic substance or other substance if the Administrator determines that the substance is anticipated not to produce any effect in humans similar to an effect produced by a naturally occurring estrogen."

In determining whether to grant a FFDCA section 408(p)(4) exemption, EPA, a 1998 Federal Register notice, identified several examples of the types of chemicals that might warrant FFDCA section 408(p)(4) exemption orders. Included in that discussion are inert ingredients that are virtually non-toxic and strong mineral acids and bases, "*which would likely interact with tissue at the portal of entry giving rise to localized lesions rather than systemic effects.*"[1] Since that time, EPA has also issued FFDCA section 408(p)(4) exemption orders for pesticides with limited use patterns and therefore limited potential for exposure[2,3,4,5] and for chemicals with limited toxic effects.[6,7,8,9,10,11,12,13]

In 2023, EPA issued a Federal Register Notice (FRN) with near-term strategies for EPA to further its compliance with FFDCA Section 408(p). This FRN, entitled *Endocrine Disruptor Screening Program (EDSP): Near-Term Strategies for Implementation' Notice of Availability and Request for Comment* (88 FR 73841) is referred to here as EPA's EDSP Strategies Notice. EPA also published three documents supporting the strategies described in the Notice:

- *Use of Existing Mammalian Data to Address Data Needs and Decisions for Endocrine Disruptor Screening Program (EDSP) for Humans under FFDCA Section 408(p)*;

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[1] Endocrine Disruptor Screening Program; Proposed Statement of Policy, 63 Fed. Reg. 71542, 71564 (December 28, 1998).
[2] Exemption of Gonadotropin Releasing Hormones (GnRH) (9/21/20) (when used as an animal contraceptive vaccine) Docket ID EPA-HQ-OPP-2018-0798 available at www.regulations.gov.
[3] Exemption of Sodium Fluoroacetate (1/19/2023) (when used as an animal contraceptive vaccine) Docket ID EPA-HQ-OPP-2010-0753-1418 available at www.regulations.gov.
[4] Exemption of Acetaminophen (10/30/2014) (when used as a bait to control the brown tree snake) Docket ID EPA-HQ-OPP-2012-0145 available at www.regulations.gov.
[5] Exemption of Porcine Zona Pellucida (PZP) (9/14/2023) Docket EPA-HQ-OPP-2022-0153-0004 available at www.regulations.gov.
[6] Exemption of *Agrobacterium radiobacter* strains K84 and K1026 (June 2012) (naturally occurring soil bacterium present in many soils with limited potential for biological activity in nontarget organisms) Docket ID EPA-HQ-OPP-2009-0878 available at www.regulations.gov.
[7] Exemption of Dioctyl Sodium Sulfosuccinate (DSS) and Undecylenic Acid (UDA) (4/11/2014) (pet products "unlikely to interact with receptor binding sites at physiological pH") Docket ID EPA-HQ-OPP-2010-1006 available at www.regulations.gov.
[8] Exemption of Polybutene Resin (2014) (sticky, non-drying gel that acts as a tactile repellant, not biologically available to cause effects in whole organisms) Docket ID EPA-HQ-OPP-2009-0649 available at www.regulations.gov.
[9] Exemption of Kaolin (October 2015) (a natural substance/clay, considered chemically inert and without biological activity) Docket ID EPA-HQ-OPP-2014-0107 available at www.regulations.gov.
[10] Exemption of Citric Acid (1/19/2023) Docket ID EPA-HQ-OPP-2020-0558-0008 available at www.regulations.gov.
[11] Exemption of Linalool (1/19/2023) Docket ID EPA-HQ-OPP-2021-0423-0009 available at www.regulations.gov.
[12] Exemption of *Bacillus subtilis* (9/14/2023) Docket EPA-HQ-OPP-2022-0431 available at www.regulations.gov.
[13] Exemption of *Bacillus amyloliquefaciens* (9/14/2023) Docket EPA-HQ-OPP-2022-0159 available at www.regulations.gov.

- *List of Conventional Registration Review Chemicals for Which an FFDCA Section 408(p)(6) Determination is Needed*; and,
- *Status of Endocrine Disruptor Screening Program (EDSP) List 1 Screening Conclusions* (referred to here as List 1 Screening Conclusions).

The EDSP Strategies Notice and the support documents are available on www.regulations.gov in docket number EPA-HQ-OPP-2023-0474. As explained in these documents, EPA is prioritizing its screening for potential impacts to the estrogen, androgen, and thyroid systems in humans, focusing first on conventional active ingredients. Although EPA voluntarily expanded the scope of the EDSP to screening for potential impacts to the estrogen, androgen, and thyroid systems in wildlife, EPA announced that it is not addressing this discretionary component of the EDSP at this time, considering its current focus on developing a comprehensive, long-term approach to meeting its Endangered Species Act obligations (See EPA's April 2022 ESA Workplan[14] and November 2022 ESA Workplan Update[15]). As a result, this exemption memorandum is only applicable to human health at this time.

The exemption is based on limited toxic effects in the human health hazard database. The Endocrine Disruptor Science Policy Council (EDSPOC) met on March 5, 2024 to determine if this EDSP exemption specific to human health should be recommended to the Office of Chemical Safety and Pollution Prevention Assistant Administrator (OCSPP AA).

2. SUMMARY OF USE, EXPOSURE AND TOXICITY

Propionic acid (PC code 077702) was initially registered in 1972; the sodium and calcium salts of propionic acid (PC codes 077703 and 077701, respectively) are registered as inert ingredients. The 40 CFR §180.1023 refers to the ai as propanoic acid in sections (a) and (b), and as propanoic acid and propanoic sodium salt in section (c). The 21 CFR §184.1081, all registered labels, and previous assessments refer to the ai as propionic acid. As such, propionic acid and propanoic acid are the same active ingredient.

EPA exempted residues of propionic acid from the requirement of a tolerance on all crops when used as either an active or inert ingredient in pesticide formulations applied to growing crops, raw agricultural commodities before and after harvest, and animals (40 CFR 180.1023). Residues of propionic acid on livestock commodities are also exempt from the requirement of a tolerance when propionic acid is applied as a bactericide/fungicide to livestock drinking water, poultry litter, and storage areas for silage and grain (40 CFR 180.1023(b)). Propionic acid has also been exempted from the requirement of a tolerance when used as an active or inert ingredient in pesticide formulations applied to food-contact surfaces in public eating places, dairy-processing equipment, and food-processing equipment and utensils (40 CFR 180.940). Propionic acid is Generally Recognized As Safe (GRAS) (21 CFR 184.1081) by the United States Food and Drug Administration (FDA) for use in food under certain good manufacturing practice conditions of use. Historically, EPA has not considered propionic acid to pose a risk to humans or the environment. Propionic acid may be included as an

[14] https://www.epa.gov/system/files/documents/2022-04/balancing-wildlife-protection-and-responsible-pesticide-use_final.pdf
[15] https://www.epa.gov/system/files/documents/2022-11/esa-workplan-update.pdf

active ingredient, and it may also be included as an inert ingredient[16] (*i.e.*, "EPA has sufficient information to reasonably conclude that the current use pattern in pesticide products will not adversely affect public health or the environment").

Propionic acid has both antimicrobial and conventional pesticidal uses in that it serves as both a bactericide and as a fungicide. Antimicrobial products containing propionic acid as a bactericide are registered for use on the surfaces of, or in circulation through, food processing and dairy equipment and in drinking water for livestock and poultry. Antimicrobial products containing propionic acid are applied through immersion, circulation, or coarse spray, undiluted directly to drinking water (livestock and poultry) and diluted with water and applied directly to food processing surfaces. For conventional pesticidal products, propionic acid is registered for fungicidal and bactericidal use on stored grains for feed, silage, hay and haylage, in grain and silage storage areas, and on poultry litter. Conventional products are applied via broadcast applications using pressurized sprayers. There are no residential uses for products containing propionic acid.

Surveys of pesticide use in food processing and animal production establishments were conducted in 2021.[17,18] Use of propionic acid for sanitization of food processing and dairy equipment or in drinking water for livestock and poultry was not reported, suggesting little or no recent usage of the active ingredient for these uses. Currently, there are no available sources of data for the remaining registered uses of propionic acid upon which to generate nationally representative estimates of usage.

Humans may be exposed to propionic acid in food due to its registered post-harvest uses on crops, its use as a food additive, and as a naturally occurring component of animal and dairy products. Propionic acid is also a normal intermediary metabolite in mammals[19]. The Environmental Fate and Effects Division (EFED) provided estimated drinking water concentrations (EDWCs) for propionic acid based on its use as an inert ingredient and concluded that drinking water concentrations as a result of its use as an active ingredient are expected to be negligible (D279285, C. Jarvis, 2/14/2002). There are no registered residential uses; therefore, neither residential/non-occupational handler nor post-application exposures are anticipated. However, short- and intermediate-term occupational handler (dermal and inhalation) and post-application (dermal only) exposures are anticipated. Due to its low toxicity, points of departure were not established for propionic acid and a quantitative occupational assessment is not necessary.

Propionic acid is of moderate to low acute toxicity via the oral, dermal, and inhalation routes of exposure (Toxicity Category III) and is not a skin sensitizer (MRID 00247883). However, propionic acid is acutely toxic in eye and dermal irritation tests[20] (Toxicity Category I).

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[16] https://www.epa.gov/pesticide-registration/inert-ingredients-overview-and-guidance

[17]Nonagricultural Market Research Data (NMRD). 2022. Pest Control for Food-Handling Establishments 2021: United States Analysis and Opportunities. [Accessed January 2023].

[18]Nonagricultural Market Research Data (NMRD). 2022. Study of production animal health in 2021. [Accessed January 2023].

[19] Kagliwal, L.D., S.B. Jadhav, R.S. Singhal, and P.R. Kulkarni. 2014. Preservatives: Permitted Preservatives- Propionic Acid. In: Encyclopedia of Food Microbiology (Second Ed.) pp. 99-101. Academic Press.

[20] Clayton, G.D. and F.E. Clayton. 1982. Patty's Industrial Hygiene and Toxicology, 3rd Revised Ed., Vol. 2c. Wiley Interscience, NY.

Subchronic and chronic oral toxicity studies (rats and dogs) with propionic acid and/or its salts indicate local irritation as the primary effect. There were no adverse systemic effects seen up to the limit dose (1,000 mg/kg/day) set forth in the 870 Series Health Effects Test Guidelines. Adverse effects were only seen at doses substantially higher than the limit dose and the doses expected from the registered use patterns, thus these effects are not relevant for human health risk assessment.

Subchronic toxicity data are available for propionic acid as well as its calcium and sodium salts. Rats fed calcium or sodium propionate at one percent of the diet (equivalent to 750 mg/kg/day of propionic acid) for four weeks followed by three percent (equivalent to 1,200 mg/kg/day of propionic acid) for three weeks showed no adverse effects[21]. Rats fed five percent propionic acid in the diet (approximately 5,000 mg/kg/day or 5x the limit dose) for 110 days developed lesions of the forestomach[22]. Propionic acid was administered in the feed to dogs at rates equivalent to 220, 735, or 2,066 mg/kg/day for 90 days. Dogs in the high dose group (approximately 2x the limit dose) showed reduced food consumption, increased incidence of epithelial hyperplasia in the esophagus, and increased nitrite in the urine. These effects were no longer present in dogs held for a six-week recovery period (MRID 41338901). A limited study with calcium propionate in dogs for 90 days (MRID 41338902) showed vomiting and diarrhea in animals fed 2,523 mg/kg/day (approximately 2.5x the limit dose). Therefore, all the effects observed in subchronic studies occurred at doses exceeding the limit dose.

Adverse effects in chronic toxicity studies also occurred above the limit dose. Twenty male rats per group were fed four percent propionic acid in the diet for two years. Animals in the high dose group had hyperplasia and hyperplastic ulcers in the forestomach. Rats fed bread containing sodium propionate (4,000 mg/kg/day, or 4x the limit dose) for a year showed no adverse effects other than an initial depression of growth; rats fed a similar diet for 32 weeks exhibited no adverse effects[23,24].

Exposure to propionic acid did not show adverse effects in the developmental studies designed to assess the effects of exposure of the pregnant test animal on the developing fetus. No maternal or fetal effects were seen upon feeding calcium propionate to pregnant animals up to the highest doses tested (300 mg/kg/day for rats and mice or up to 400 mg/kg/day for hamsters and rabbits). There were no effects on fetal survival or growth, nor was there an increased incidence of fetal malformations or skeletal variations[25].

Additionally, in 2022 the Office of Pesticide Programs' Health Effects Division (HED) conducted a broad survey of the literature to identify studies that report toxicity following exposure to propionic acid via routes relevant to human health pesticide risk assessment not accounted for in the toxicology database. Following title/abstract and/or full text screening, no studies were identified as containing potentially relevant information (either quantitative or qualitative) for propionic acid human health risk assessment, including studies examining endocrine-sensitive endpoints.

[21] Harshbarger, K.E. 1942. Report of a study on the toxicity of several food preserving agents. J. Dairy Sci. 25:169-174.
[22] Lehninger, A.L. 1975. Biochemistry, 2nd ed., pp. 543-586. Worth Publishers, Inc., New York.
[23] Graham, W.D., H. Teed, and H.C. Grice. 1954. Chronic toxicity of bread additives to rats. J. Pharm. Pharmacol. 6:534-545.
[24] Graham, W.D., and H.C. Grice. 1955. Chronic toxicity of bread additives to rats. Part II. J. Pharm. Pharmacol. 7:126-134.
[25] Food and Drug Research Laboratories, Inc. 1972. Teratologic evaluation of FDA 71-36 (calcium propionate) in mice, rats, hamsters, and rabbits. Final report prepared under DHEW contract no. FDA 71-260. Maspeth, N.Y. 43 pp.

EPA considers all available information and whether based on those data there is sufficient information to conclude that a chemical/substance is anticipated not to produce an effect in humans or wildlife similar to an effect produced by a naturally occurring estrogen, androgen, or thyroid hormone. Propionic acid exhibits a lack of toxicity at doses relevant for human health risk assessment. Additionally, exposure from current uses is expected to be minimal. Propionic acid is Generally Recognized As Safe (GRAS) by the FDA for use in food, and EPA has sufficient information to reasonably conclude that the current use pattern in pesticide products will not adversely affect public health. Subchronic and chronic oral toxicity studies (rats and dogs) with propionic acid and/or its salts indicate local irritation as the primary effect. There were no adverse systemic effects seen up to the limit dose (1,000 mg/kg/day). Exposure to propionic acid did not show adverse effects in the developmental studies up to the highest doses tested (300 mg/kg/day for rats and mice or up to 400 mg/kg/day for hamsters and rabbits). Endpoints are assessed in the subchronic, chronic, and developmental FIFRA studies that may be influenced by changes in estrogen, androgen, and thyroid levels, yet there were no indications of toxicity. Following published literature review screening, no studies were identified as containing potentially relevant information (either quantitative or qualitative) for propionic acid human health risk assessment, including studies examining endocrine-sensitive endpoints. Thus, all evidence suggests that propionic acid should be considered as safe from endocrine and non-endocrine adverse toxicological effects. Regarding exposure, propionic acid is also a normal intermediary metabolite in mammals[1] and is a naturally occurring component of animal and dairy products. Added exposure to humans may result from exposure to propionic acid in food due to its registered post-harvest uses on crops, and its use as a food additive. There are no registered residential uses; therefore, neither residential/non-occupational handler nor post-application exposures are anticipated. However, short- and intermediate-term occupational handler (dermal and inhalation) and post-application (dermal only) exposures are anticipated. Due to its low toxicity (local irritation only), points of departure were not established for propionic acid and a quantitative occupational assessment was considered unnecessary.

3. EDSPOC RECOMMENDATION

The EDSPOC recommends exempting propionic acid from the human health EDSP requirements. Propionic acid has limited toxicity only at high dose levels and is not anticipated to result in exposure that would produce an effect in humans similar to an effect produced by a naturally occurring estrogen, androgen or thyroid hormone. This recommendation may be revisited if new data become available for consideration that may impact the human health EDSP exemption.

4. OCSPP AA APPROVAL AND SIGNATURE

This Administrative Order exempting propionic acid from EDSP can only be issued if approved by the OCSPP AA in accordance with the Administrator's FFDCA 408(p)(4) delegation.

Deadline

There is no court ordered/judicial deadline associated with this action. The Registration Review Final Decision for propionic acid will be completed after the human health EDSP exemption is approved.

[1] Kagliwal, L.D., S.B. Jadhav, R.S. Singhal, and P.R. Kulkarni. 2014. Preservatives: Permitted Preservatives- Propionic Acid. In: Encyclopedia of Food Microbiology (Second Ed.) pp. 99-101. Academic Press.

Peer Review
OPP followed the Agency's Peer Review policies with respect to the underlying major scientific and technical products supporting this action.

Scientific Integrity
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/system/files/documents/2023-12/scientific_integrity_policy_2012_accessible.pdf.
The 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.

Plain Language
This notice complies with the Agency's guidelines on the use of plain English. Whenever possible, EPA wrote the exemption order in an active voice, with simplified language and displayed data in tables to make it easier for the public to read and understand.

Anticipated Public Reaction
No unusual public reaction is anticipated on the registration review process for propionic acid, nor its exemption from the human health requirements of the EDSP.

Staff Contact
For further information regarding the exemption order, please let us know, or have your staff contact Emily Rogers by email at rogers.emily@epa.gov or by phone at (202) 566-1895.