OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

WASHINGTON, D.C. 20460

ADMINISTRATIVE ORDER

Exemption of Propionic Acid from the Human Health Requirements of the Endocrine Disruptor Screening Program

Pursuant to the requirements of Section 408(p)(1) of the Federal Food, Drug, and Cosmetic Act (FFDCA), EPA has developed an Endocrine Disruptor Screening Program (EDSP) to determine whether certain chemicals, such as pesticide active and inert ingredients, "*may have an effect in humans similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect as the Administrator may designate*." Section 408(p)(4) of the FFDCA authorizes EPA, by order, to exempt from the requirements of the endocrine screening program "*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 considers all information available and whether based on those data there is sufficient information to conclude that a chemical/substance is not anticipated to produce an effect in humans or wildlife similar to an effect produced by a naturally occurring estrogen, androgen or thyroid hormone. In a 1998 Federal Register notice, EPA 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 or targeted toxic

[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.

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)*;
- *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 Endangered Species Act obligations (See EPA's April 2022 ESA Workplan[14] and November 2022 ESA Workplan Update[15]). As a result, this exemption order is only applicable to human health at this time.

EPA has evaluated propionic acid (also referred to as propanoic acid), the pesticide active ingredient involved in registration review case #4078 (Docket IDs EPA-HQ-OPP-2008-0024 and EPA-HQ-OPP-2023-0037 available at www.regulations.gov). Based on the information that follows, EPA has determined that propionic acid is not anticipated to produce an effect in humans similar to an effect produced by naturally occurring estrogen, androgen, or thyroid hormones. This conclusion is based on limited toxic

[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.
[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

effects in the human health hazard database. The chemical has low to moderate acute toxicity (local irritation only) and no subchronic or chronic toxicity in mammalian studies up to the limit dose or at doses relevant to human exposure. Furthermore, exposures resulting from use of propionic acid as a pesticidal active ingredient are expected to be below levels of toxicological concern. Therefore, pursuant to FFDCA Section 408(p)(4), EPA hereby exempts the current pesticidal uses of propionic acid from the human health requirements of the EDSP.

Regulatory History

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 active ingredient as propanoic acid in sections (a) and (b), and as propanoic acid and propanoic sodium salt in section (c). In the 21 CFR §184.1081, all registered labels, and previous assessments refer to the active ingredient 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.[16] Propionic acid may be included as an active ingredient, and it may also be included as an inert ingredient[17] (*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").

Use and Usage

Propionic acid has both antimicrobial and conventional pesticidal uses in that is 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.

[16] Propionic Acid Registration Review Final Decision (2010), Docket ID EPA-HQ-OPP-2008-0024 in www.regulations.gov.
[17] https://www.epa.gov/pesticide-registration/inert-ingredients-overview-and-guidance

Surveys of pesticide use in food processing and animal production establishments were conducted in 2021.[18,19] 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.

Exposure

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[20]. 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.

Toxicity

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

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

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

[20] 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.

metabolite in mammals[21] 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.

Conclusion

The Endocrine Disruptor Science Policy Council (EDSPOC) met on March 5, 2024 to discuss the recommendation of the exemption of propionic acid from the requirements of the endocrine disruptor screening program. The EDSPOC recommended exempting propionic acid from the human health EDSP requirements.[22]

EPA has concluded that propionic acid has limited toxicity only at high dose levels, and is not anticipated to produce any effect similar to an effect produced by naturally occurring estrogen, androgen, or thyroid hormones, in humans, because of its low to moderate acute toxicity (with the exception of local irritation) and the absence of any adverse effects (including endocrine effects) in mammalian subchronic, chronic, or developmental toxicity studies at doses relevant to human risk assessment. Furthermore, exposures resulting from use as a pesticidal active ingredient are expected to be below levels of toxicological concern. EPA also notes that FDA has affirmed GRAS status of propionic acid as a direct food substance under certain good manufacturing practice conditions of use, including use as an antimicrobial agent and flavoring agent, and when used at levels that do not exceed current good manufacturing practice.

Based on the above information, EPA concludes that propionic acid has limited toxicity only at high dose levels that are not relevant for human health risk assessment and is not anticipated to produce in humans, any effect similar to an effect produced by naturally occurring estrogen, androgen, or thyroid hormones. Therefore, pursuant to FFDCA Section 408(p)(4), EPA hereby exempts propionic acid from the human health EDSP requirements. This recommendation may be revisited if new data become available for consideration that may impact the human health EDSP exemption.

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[21] 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.

[22] Memorandum: 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.