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ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 180

[EPA-HQ-OPP-2015-0719; FRL-9949-49]

n-Butyl 3-hydroxybutyrate and Isopropyl 3-hydroxybutyrate; Exemption from the Requirement of a Tolerance

AGENCY: Environmental Protection Agency (EPA).

ACTION: Final rule.

SUMMARY: This regulation establishes exemptions from the requirement of a tolerance for residues of n-butyl 3-hydroxybutyrate (CAS Reg. No. 53605-94-0) and isopropyl 3-hydroxybutyrate (CAS Reg. No. 54074-94-1) when used as inert ingredients (solvents) in pesticide formulations applied to growing crops or raw agricultural commodities after harvest; to animals; and to food contact surfaces in public eating places, dairy-processing equipment, and food-processing equipment and utensils. Steptoe and Johnson, on behalf of Eastman Chemical Company, submitted a petition to EPA under the Federal Food, Drug, and Cosmetic Act (FFDCA), requesting establishment of these exemptions from the requirement of a tolerance. This regulation eliminates the need to establish a maximum permissible level for residues of n-butyl 3-hydroxybutyrate and isopropyl 3-hydroxybutyrate when applied or used under these conditions.

DATES: This regulation is effective *[insert date of publication in the Federal Register]*.

Objections and requests for hearings must be received on or before *[insert date 60 days after date of publication in the Federal Register]*, and must be filed in accordance with the instructions provided in 40 CFR part 178 (see also Unit I.C. of the **SUPPLEMENTARY INFORMATION**).

ADDRESSES: The docket for this action, identified by docket identification (ID) number EPA-HQ-OPP-2015-0719, is available at <http://www.regulations.gov> or at the Office of Pesticide Programs Regulatory Public Docket (OPP Docket) in the Environmental Protection Agency Docket Center (EPA/DC), West William Jefferson Clinton Bldg., Rm. 3334, 1301 Constitution Ave., NW., Washington, DC 20460-0001. The Public Reading Room is open from 8:30 a.m. to 4:30 p.m., Monday through Friday, excluding legal holidays. The telephone number for the Public Reading Room is (202) 566-1744, and the telephone number for the OPP Docket is (703) 305-5805. Please review the visitor instructions and additional information about the docket available at <http://www.epa.gov/dockets>.

FOR FURTHER INFORMATION CONTACT: Susan Lewis, Registration Division (7505P), Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460-0001; main telephone number: (703) 305-7090; email address: RDfRNotices@epa.gov.

SUPPLEMENTARY INFORMATION:

I. General Information

A. Does this Action Apply to Me?

You may be potentially affected by this action if you are an agricultural producer, food manufacturer, or pesticide manufacturer. The following list of North American Industrial Classification System (NAICS) codes is not intended to be exhaustive, but rather provides a guide to help readers determine whether this document applies to them. Potentially affected entities may include:

- Crop production (NAICS code 111).
- Animal production (NAICS code 112).
- Food manufacturing (NAICS code 311).

- Pesticide manufacturing (NAICS code 32532).

B. How Can I Get Electronic Access to Other Related Information?

You may access a frequently updated electronic version of 40 CFR part 180 through the Government Printing Office's e-CFR site at http://www.ecfr.gov/cgi-bin/text-idx?&c=ecfr&tpl=/ecfrbrowse/Title40/40tab_02.tpl.

C. How Can I File an Objection or Hearing Request?

Under FFDCA section 408(g), 21 U.S.C. 346a, any person may file an objection to any aspect of this regulation and may also request a hearing on those objections. You must file your objection or request a hearing on this regulation in accordance with the instructions provided in 40 CFR part 178. To ensure proper receipt by EPA, you must identify docket ID number EPA-HQ-OPP-2015-0719 in the subject line on the first page of your submission. All objections and requests for a hearing must be in writing, and must be received by the Hearing Clerk on or before *[insert date 60 days after date of publication in the **Federal Register**]*. Addresses for mail and hand delivery of objections and hearing requests are provided in 40 CFR 178.25(b).

In addition to filing an objection or hearing request with the Hearing Clerk as described in 40 CFR part 178, please submit a copy of the filing (excluding any Confidential Business Information (CBI)) for inclusion in the public docket. Information not marked confidential pursuant to 40 CFR part 2 may be disclosed publicly by EPA without prior notice. Submit the non-CBI copy of your objection or hearing request, identified by docket ID number EPA-HQ-OPP-2015-0719, by one of the following methods:

- *Federal eRulemaking Portal:* <http://www.regulations.gov>. Follow the online instructions for submitting comments. Do not submit electronically any information you consider to be CBI or other information whose disclosure is restricted by statute.

- *Mail*: OPP Docket, Environmental Protection Agency Docket Center (EPA/DC), (28221T), 1200 Pennsylvania Ave., NW., Washington, DC 20460-0001.

- *Hand Delivery*: To make special arrangements for hand delivery or delivery of boxed information, please follow the instructions at <http://www.epa.gov/dockets/contacts.html>. Additional instructions on commenting or visiting the docket, along with more information about dockets generally, is available at <http://www.epa.gov/dockets>.

II. Petition for Exemption

In the **Federal Register** of November 23, 2015 (80 FR 72941) (FRL-9936-73), EPA issued a document pursuant to FFDCA section 408, 21 U.S.C. 346a, announcing the filing of a pesticide petition (PP IN-10841) by Steptoe and Johnson LLP (1330 Connecticut Avenue, NW, Washington, DC 20036-1795) on behalf of the Eastman Chemical Company (200 South Wilcox Drive, Kingsport, TN 37660-5280). The petition requested that 40 CFR 180.910, 180.930, and 180.940 be amended to establish exemptions from the requirement of a tolerance for residues of n-butyl 3-hydroxybutyrate (CAS Reg. No. 53605-94-0); and isopropyl 3-hydroxybutyrate (CAS Reg. No. 54074-94-1) when used as inert ingredients (solvents) in pesticide formulations applied to pre- and post-harvest crops under 40 CFR 180.910; to animals under 40 CFR 180.930; and to food contact surface sanitizing solutions under 40 CFR 180.940(a). That document referenced a summary of the petition prepared by Steptoe and Johnson on behalf of Eastman Chemical Company, the petitioner, which is available in the docket, <http://www.regulations.gov>. Comments were received on the notice of filing. EPA's response to these comments is discussed in Unit V.B.

III. Inert Ingredient Definition

Inert ingredients are all ingredients that are not active ingredients as defined in 40 CFR 153.125 and include, but are not limited to, the following types of ingredients (except when

they have a pesticidal efficacy of their own): Solvents such as alcohols and hydrocarbons; surfactants such as polyoxyethylene polymers and fatty acids; carriers such as clay and diatomaceous earth; thickeners such as carrageenan and modified cellulose; wetting, spreading, and dispersing agents; propellants in aerosol dispensers; microencapsulating agents; and emulsifiers. The term “inert” is not intended to imply nontoxicity; the ingredient may or may not be chemically active. Generally, EPA has exempted inert ingredients from the requirement of a tolerance based on the low toxicity of the individual inert ingredients.

IV. Aggregate Risk Assessment and Determination of Safety

Section 408(c)(2)(A)(i) of FFDCA allows EPA to establish an exemption from the requirement for a tolerance (the legal limit for a pesticide chemical residue in or on a food) only if EPA determines that the tolerance is “safe.” Section 408(b)(2)(A)(ii) of FFDCA defines “safe” to mean that “there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information.” This includes exposure through drinking water and in residential settings, but does not include occupational exposure. Section 408(b)(2)(C) of FFDCA requires EPA to give special consideration to exposure of infants and children to the pesticide chemical residue in establishing a tolerance and to “ensure that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure to the pesticide chemical residue....”

EPA establishes exemptions from the requirement of a tolerance only in those cases where it can be clearly demonstrated that the risks from aggregate exposure to pesticide chemical residues under reasonably foreseeable circumstances will pose no appreciable risks to human health. In order to determine the risks from aggregate exposure to pesticide inert ingredients, the Agency considers the toxicity of the inert in conjunction with possible exposure

to residues of the inert ingredient through food, drinking water, and through other exposures that occur as a result of pesticide use in residential settings. If EPA is able to determine that a finite tolerance is not necessary to ensure that there is a reasonable certainty that no harm will result from aggregate exposure to the inert ingredient, an exemption from the requirement of a tolerance may be established.

Consistent with FFDCA section 408(c)(2)(A), and the factors specified in FFDCA section 408(c)(2)(B), EPA has reviewed the available scientific data and other relevant information in support of this action. EPA has sufficient data to assess the hazards of and to make a determination on aggregate exposure for n-butyl 3-hydroxybutyrate and isopropyl 3-hydroxybutyrate including exposure resulting from the exemption established by this action. EPA's assessment of exposures and risks associated with n-butyl 3-hydroxybutyrate and isopropyl 3-hydroxybutyrate follows.

A. Toxicological Profile

EPA has evaluated the available toxicity data and considered their validity, completeness, and reliability as well as the relationship of the results of the studies to human risk. EPA has also considered available information concerning the variability of the sensitivities of major identifiable subgroups of consumers, including infants and children. Specific information on the studies received and the nature of the adverse effects caused by n-butyl 3-hydroxybutyrate and isopropyl 3-hydroxybutyrate as well as the no-observed-adverse-effect-level (NOAEL) and the lowest-observed-adverse-effect-level (LOAEL) from the toxicity studies are discussed in this unit.

n-Butyl-3-hydroxybutyrate and isopropyl-3-hydroxybutyrate are structurally similar chemical entities differing only in one methyl group (CH₃). Therefore the toxicity of these two

chemicals is expected to be similar. Since there are no adequate data available for each one individually, the Agency utilizes read-across data to fill data gaps.

n-Butyl-3-hydroxybutyrate and isopropyl-3-hydroxybutyrate both exhibit very low levels of acute oral, dermal and inhalation toxicity each with LD₅₀ values > 5,000 mg/kg. n-Butyl-3-hydroxybutyrate is moderately irritating to the rabbit eye and is slightly irritating to rabbit skin. Isopropyl-3-hydroxybutyrate is not irritating to rabbit skin. n-Butyl-3-hydroxybutyrate and isopropyl-3-hydroxybutyrate are not dermal sensitizers.

In a 28-day subchronic feeding study in rats which included a reproduction/developmental screening assessment, exposure to isopropyl-3-hydroxybutyrate resulted in no adverse test item-related toxicological effects on clinical observations, no adverse effects seen in FOB assessments, no adverse effects on motor activity evaluations, no adverse effects seen in gross necropsy observations, male or female reproductive performance, or neurobehavioral parameters. The no-observed-adverse-effect-level (NOAEL) for reproductive toxicity was 1,000 mg/kg/day. The NOAEL for systemic toxicity was 1,000 mg/kg/day. In the absence of effects on the general physical condition of F₁ pups, the NOAEL for neonatal toxicity was 1,000 mg/kg/day.

n-Butyl-3-hydroxybutyrate and isopropyl-3-hydroxybutyrate were negative in reverse gene mutation assays. Isopropyl-3-hydroxybutyrate was negative in a chromosome aberration assay and a gene mutation assay.

There were no neurotoxicity or immunotoxicity studies available. However, there was no evidence of adverse neurotoxic effects noted during the FOB evaluations and the motor activity evaluations. There was no evidence of immunotoxicity in the available database.

Based on the negative responses seen in the genotoxicity and lack of systemic toxicity in the reproductive and developmental screening study, n-butyl-3-hydroxybutyrate and isopropyl-3-hydroxybutyrate are considered unlikely to be carcinogenic.

n-Butyl-3-hydroxybutyrate and isopropyl-3-hydroxybutyrate both have a low solubility; therefore, it is unlikely that either material will be absorbed by the body and become systemically bioavailable. Both compounds are expected to hydrolyze quickly and completely *in vivo*, and the resulting hydrolysis products are very close in structure or are the same, depending on the specific hydrolysis product. The available *in vitro* data suggests that isopropyl-3-hydroxybutyrate can undergo fast hydrolysis by enzymes in the plasma and liver to produce n-butyl-3-hydroxybutyrate, which is perhaps further metabolized. Isopropyl-3-hydroxybutyrate concentration decreased from approximately 70µM to below the limit of detection (<6.68 µM) in plasma within 2 hours and in rat liver S9 fraction within 30 minutes. Although stable in phosphate buffer, isopropyl-3-hydroxybutyrate concentration levels decreased from 70 µM to below the LOD within 30 minutes with ONLY slight increases in beta-hydroxybutyrate levels indicating that either it is formed in small quantity (minor pathway) and/or rapidly metabolized and removed from the circulation.

B. Toxicological Points of Departure/Levels of Concern

Once a pesticide's toxicological profile is determined, EPA identifies toxicological points of departure (POD) and levels of concern to use in evaluating the risk posed by human exposure to the pesticide. For hazards that have a threshold below which there is no appreciable risk, the toxicological POD is used as the basis for derivation of reference values for risk assessment. PODs are developed based on a careful analysis of the doses in each toxicological study to determine the dose at which no adverse effects are observed (the NOAEL) and the lowest dose at which adverse effects of concern are identified (the LOAEL). Uncertainty/safety factors are

used in conjunction with the POD to calculate a safe exposure level - generally referred to as a population-adjusted dose (PAD) or a reference dose (RfD) - and a safe margin of exposure (MOE). For non-threshold risks, the Agency assumes that any amount of exposure will lead to some degree of risk. Thus, the Agency estimates risk in terms of the probability of an occurrence of the adverse effect expected in a lifetime. For more information on the general principles EPA uses in risk characterization and a complete description of the risk assessment process, see <http://www.epa.gov/pesticides/factsheets/riskassess.htm>.

An acute effect was not found in the database therefore an acute dietary assessment is not necessary. In the 28-day subchronic oral toxicity study in rats with neurotoxicity measurements, no toxicity was observed at doses up to 1,000 mg/kg/day. Therefore, the Agency concluded that it is not necessary to conduct a quantitative risk assessment.

C. Exposure Assessment

1. *Dietary exposure from food, feed uses and drinking water.* In evaluating dietary exposure to n-butyl-3-hydroxybutyrate and isopropyl-3-hydroxybutyrate, EPA considered exposure under the proposed exemption from the requirement of a tolerance. EPA assessed dietary exposures from n-butyl-3-hydroxybutyrate and isopropyl-3-hydroxybutyrate in food and drinking water as follows:

Dietary exposure can occur from eating foods or ingesting drinking water containing residues of n-butyl-3-hydroxybutyrate and isopropyl-3-hydroxybutyrate. Because no hazard endpoint of concern was identified for the acute and chronic dietary assessment (food, feed and drinking water uses, a quantitative dietary exposure risk assessment was not conducted

2. *From non-dietary exposure.* The term “residential exposure” is used in this document to refer to non-occupational, non-dietary exposure (e.g., textiles (clothing and diapers), carpets, swimming pools, and hard surface disinfection on walls, floors, tables).

n-Butyl-3-hydroxybutyrate and isopropyl-3-hydroxybutyrate may be used in inert ingredients in products that are registered for specific uses that may result in residential exposure, such as pesticides used in and around the home. However, since no endpoint of concern identified in the available database, it is not necessary to conduct a quantitative residential exposure assessment.

3. *Cumulative effects from substances with a common mechanism of toxicity.* Section 408(b)(2)(D)(v) of FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider “available information” concerning the cumulative effects of a particular pesticide's residues and “other substances that have a common mechanism of toxicity.”

EPA has not found n-butyl-3-hydroxybutyrate and isopropyl-3-hydroxybutyrate to share a common mechanism of toxicity with any other substances, and n-butyl-3-hydroxybutyrate and isopropyl-3-hydroxybutyrate does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has assumed that n-butyl-3-hydroxybutyrate and isopropyl-3-hydroxybutyrate does not have a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see EPA's website at <http://www.epa.gov/pesticides/cumulative>.

D. Safety Factor for Infants and Children

1. *In general.* Section 408(b)(2)(C) of FFDCA provides that EPA shall apply an additional tenfold (10X) margin of safety for infants and children in the case of threshold effects to account for prenatal and postnatal toxicity and the completeness of the database on toxicity and exposure unless EPA determines based on reliable data that a different margin of safety will be safe for infants and children. This additional margin of safety is commonly referred to as the

FQPA Safety Factor (SF). In applying this provision, EPA either retains the default value of 10X, or uses a different additional safety factor when reliable data available to EPA support the choice of a different factor.

As part of its qualitative assessment, EPA evaluated the available toxicity and exposure data on n-butyl-3-hydroxybutyrate and isopropyl-3-hydroxybutyrate and considered its validity, completeness, and reliability, as well as the relationship of this information to human risk. EPA considers the toxicity database to be sufficient to evaluate risk and has identified no residual uncertainty with regard to prenatal and postnatal toxicity or exposure. No hazard was identified based on the available studies; therefore, EPA concludes that there are no threshold effects of concern to infants, children, or adults from n-butyl-3-hydroxybutyrate and isopropyl-3-hydroxybutyrate. As a result, EPA concludes that no additional margin of exposure (safety) is necessary.

E. Aggregate Risks and Determination of Safety

Because no toxicological endpoints of concern were identified, EPA concludes that aggregate exposure to residues of n-butyl-3-hydroxybutyrate and isopropyl-3-hydroxybutyrate will not pose a risk to the U.S. population, including infants and children, and that there is a reasonable certainty that no harm will result to the general population, or to infants and children from aggregate exposure to n-butyl-3-hydroxybutyrate and isopropyl-3-hydroxybutyrate residues.

V. Other Considerations

A. Analytical Enforcement Methodology

An analytical method is not required for enforcement purposes since the Agency is not establishing a numerical tolerance for residues of n-butyl-3-hydroxybutyrate and isopropyl-3-hydroxybutyrate in or on any food commodities. EPA is not establishing a limitation on the

amount of n-butyl-3-hydroxybutyrate and isopropyl-3-hydroxybutyrate that may be used in pesticide formulations applied to growing crops.

B. Comments

Two generic comments objecting to the use of chemicals in food were submitted to the docket for this action. Neither of the comments contained any specific information bearing on the Agency's safety finding for these chemicals. The Agency understands the commenters' concerns and recognizes that some individuals believe that pesticides should be banned on agricultural crops. However, the existing legal framework provided by section 408 of the Federal Food, Drug and Cosmetic Act (FFDCA) states that tolerances may be set when persons seeking such tolerances or exemptions have demonstrated that the pesticide meets the safety standard imposed by that statute. The comment appears to be directed at the underlying statute and not EPA's implementation of it; the citizen has made no contention that EPA has acted in violation of the statutory framework.

VI. Conclusions

Therefore, exemptions from the requirement of a tolerance are established under 40 CFR 180.910, 40 CFR 180.930, and 40 CFR 180.940(a) for n-butyl-3-hydroxybutyrate (CAS Reg. No. 53605-94-0) and isopropyl-3-hydroxybutyrate (CAS Reg. No. 54074-94-1) when used as inert ingredients (solvents) in pesticide formulations applied to growing crops or raw agricultural commodities after harvest (40 CFR 180.910); to animals (40 CFR 180.930); or to food contact surfaces in public eating places, dairy-processing equipment, and food-processing equipment and utensils (40 CFR 180.940(a)).

VII. Statutory and Executive Order Reviews

This action establishes exemptions from the requirement of a tolerance under FFDCA section 408(d) in response to a petition submitted to the Agency. The Office of Management

and Budget (OMB) has exempted these types of actions from review under Executive Order 12866, entitled “Regulatory Planning and Review” (58 FR 51735, October 4, 1993). Because this action has been exempted from review under Executive Order 12866, this action is not subject to Executive Order 13211, entitled “Actions Concerning Regulations That Significantly Affect Energy Supply, Distribution, or Use” (66 FR 28355, May 22, 2001) or Executive Order 13045, entitled “Protection of Children from Environmental Health Risks and Safety Risks” (62 FR 19885, April 23, 1997). This action does not contain any information collections subject to OMB approval under the Paperwork Reduction Act (PRA) (44 U.S.C. 3501 *et seq.*), nor does it require any special considerations under Executive Order 12898, entitled “Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations” (59 FR 7629, February 16, 1994).

Since tolerances and exemptions that are established on the basis of a petition under FFDCA section 408(d), such as the exemptions in this final rule, do not require the issuance of a proposed rule, the requirements of the Regulatory Flexibility Act (RFA) (5 U.S.C. 601 *et seq.*), do not apply.

This action directly regulates growers, food processors, food handlers, and food retailers, not States or tribes, nor does this action alter the relationships or distribution of power and responsibilities established by Congress in the preemption provisions of FFDCA section 408(n)(4). As such, the Agency has determined that this action will not have a substantial direct effect on States or tribal governments, on the relationship between the national government and the States or tribal governments, or on the distribution of power and responsibilities among the various levels of government or between the Federal Government and Indian tribes. Thus,

the Agency has determined that Executive Order 13132, entitled “Federalism” (64 FR 43255, August 10, 1999) and Executive Order 13175, entitled “Consultation and Coordination with Indian Tribal Governments” (65 FR 67249, November 9, 2000) do not apply to this action. In addition, this action does not impose any enforceable duty or contain any unfunded mandate as described under Title II of the Unfunded Mandates Reform Act (UMRA) (2 U.S.C. 1501 *et seq.*).

This action does not involve any technical standards that would require Agency consideration of voluntary consensus standards pursuant to section 12(d) of the National Technology Transfer and Advancement Act (NTTAA) (15 U.S.C. 272 note).

VIII. Congressional Review Act

Pursuant to the Congressional Review Act (5 U.S.C. 801 *et seq.*), EPA will submit a report containing this rule and other required information to the U.S. Senate, the U.S. House of Representatives, and the Comptroller General of the United States prior to publication of the rule in the **Federal Register**. This action is not a “major rule” as defined by 5 U.S.C. 804(2).

List of Subjects in 40 CFR Part 180

Environmental protection, Administrative practice and procedure, Agricultural commodities, Pesticides and pests, Reporting and recordkeeping requirements.

Dated: July 25, 2016.

Daniel J. Rosenblatt,
Acting Director, Registration Division, Office of Pesticide Programs.

Therefore, 40 CFR chapter I is amended as follows:

PART 180--[AMENDED]

1. The authority citation for part 180 continues to read as follows:

Authority: 21 U.S.C. 321(q), 346a and 371.

2. In §180.910, add alphabetically the inert ingredients to the table to read as follows:

§ 180.910 Inert ingredients used pre- and post-harvest; exemptions from the requirement of a tolerance.

* * * * *

Inert ingredients	Limits	Uses
* * * * *	* * * * *	* * *
n-Butyl-3-hydroxybutyrate (CAS Reg. No.53605-94-0)		Solvent
* * * * *	* * * * *	* * *
Isopropyl-3-hydroxybutyrate (CAS Reg. No. 54074-94-1)		Solvent
* * * * *	* * * * *	* * *

3. In §180.930, add alphabetically the inert ingredients to the table to read as follows:

§ 180.930 Inert ingredients applied to animals; exemptions from the requirement of a tolerance.

* * * * *

Inert ingredients	Limits	Uses
* * * * *	* * * * *	* * *
n-Butyl-3-hydroxybutyrate (CAS Reg. No. 53605-94-0)		Solvent
* * * * *	* * * * *	* * *
Isopropyl-3-hydroxybutyrate (CAS Reg. No. 54074-94-1)		Solvent
* * * * *	* * * * *	* * *

4. In §180.940(a), add alphabetically the inert ingredients to the table in paragraph (a)

to read as follows:

§ 180.940 Tolerance exemptions for active and inert ingredients for use in antimicrobial formulations (Food-contact surface sanitizing solutions).

* * * *

(a) * * *

Pesticide Chemical	CAS Reg. No.	Limits
* *	* *	* * *
n-Butyl-3-hydroxybutyrate	53605-94-0	Solvent
* *	* *	* * *
Isopropyl-3-hydroxybutyrate	54074-94-1	Solvent
* *	* *	* * *

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