



ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 180

[EPA-HQ-OPP-2015-0776 and EPA-HQ-OPP-2015-0831; FRL-9955-82]

Methyl Isobutyrate and Isobutyl Isobutyrate; 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 methyl isobutyrate (CAS Reg. No. 547-63-7) and for residues of isobutyl isobutyrate (CAS Reg. No. 97-85-8) when used as inert ingredients (solvents) applied to growing crops or raw agricultural commodities after harvest. Jeneil Biosurfactant Company submitted a petition to EPA under the Federal Food, Drug, and Cosmetic Act (FFDCA), requesting establishment of an exemption from the requirement of a tolerance. This regulation eliminates the need to establish a maximum permissible level for residues of methyl isobutyrate and isobutyl isobutyrate when used in accordance with the 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-2015-0776 and EPA-HQ-OPP-2015-0831, 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: Michael Goodis, 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-2015-0776 and EPA-HQ-OPP-2015-0831 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-2015-0776 and EPA-HQ-OPP-2015-0831, 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 March 16, 2016 (81 FR 14030) (FRL-9942-86), EPA issued a document pursuant to FFDCA section 408, 21 U.S.C. 346a, announcing the filing of two pesticide petitions (PP IN-10848 & PP IN-10850) by Jeneil Biosurfactant Company, 400 N. Dekora Woods Blvd., Saukville, WI 53080. The petitions requested that 40 CFR 180.910 be amended by establishing two exemptions from the requirement of a tolerance: one for residues of methyl isobutyrate (CAS Reg. No.547-63-7) (PP IN-10848) and one for isobutyl isobutyrate (CAS Reg. No. 97-85-8) (PP IN-10850), when used as inert ingredients (solvents) applied to growing crops or raw agricultural commodities after harvest. That document referenced a summary of each petition prepared by Jeneil Biosurfactant Company, the petitioner, which are available in the respective dockets (PP IN-10848 in docket ID number EPA-HQ-OPP-2015-0776 and PP IN-10850 in docket ID number EPA-HQ-OPP-2015-0831), <http://www.regulations.gov>. Comments were received in response to the notice of filing, requesting the denial of these petitions based only generally on a concern for the use of “toxic chemicals” in or on food. Because the commenters did not provide any information upon which to evaluate these specific inert ingredient tolerance

exemptions and because EPA has determined that such exemptions would be safe, EPA is not denying the petition as requested.

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 exemption is “safe.” Section 408(c)(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 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 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 methyl isobutyrate and isobutyl isobutyrate including exposure resulting from the exemption established by this action. EPA's assessment of exposures and risks associated with methyl isobutyrate and isobutyl isobutyrate 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 methyl isobutyrate and isobutyl isobutyrate 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.

Methyl isobutyrate and isobutyl isobutyrate are rapidly metabolized through hydrolysis to form an alcohol and carboxylic acid in the body. Many of the supporting data for methyl isobutyrate comes directly from the closely related and similarly metabolized compound isobutyl isobutyrate. Where separate information for methyl isobutyrate and isobutyl isobutyrate is available, the studies will be presented along with information for their common metabolite isobutanol.

An LD₅₀ value of 16,000 milligrams/kilogram body weight (mg/kg bw) was determined in rats for methyl isobutyrate. The LC₅₀ of methyl isobutyrate was 25.5 milligrams per Liter (mg/L) in mice. The acute oral LD₅₀ for isobutyl isobutyrate value in rats and mice was >6,400 mg/kg. The acute inhalation LC₅₀ (6 hour exposure duration) was between 3.88 and 31.94 mg/L isobutyl isobutyrate in rats. The dermal LD₅₀ value for isobutyl isobutyrate in guinea pigs was >8,550 mg/kg

No repeat-dose studies of methyl isobutyrate were identified in a search of the toxicological literature. In an 18-week oral gavage study in rats with isobutyl isobutyrate, there were no treatment related effects in hematology, clinical chemistry parameters, urinalysis, histological examination, behavior, appearance, body weight, or food/water consumption. The NOAEL was 1,000 mg/kg/day; the highest dose tested. In a 90-day oral toxicity study in rats with isobutanol, treatment related effects were seen only at 1,000 mg/kg bw/day, and included hypoactivity, which was significant during week one and decreased markedly after week 4, and lower body weight gain (18% below that of control rats) in males during week one. The NOAEL was 316 mg/kg bw/day.

In a 90-day study toxicity study in rats exposed to isobutanol in drinking water, no effects on body weight, food water consumption, and clinical signs of toxicity and organ weights (livers, kidneys, adrenal glands, and testes) were observed at doses up to 1,450 mg/kg/day. The NOAEL for isobutanol was 1,450 mg/kg/day.

In a 90-day isobutanol inhalation study, no differences were found in body weight, food consumption, ophthalmoscopic examination, clinical observation, clinical chemistry, neurobehavioral observations, organ weights, gross pathology, and histopathology. The NOAEL for repeat-dose effects including neurotoxicity was 2,500 ppm.

In two prenatal developmental toxicity studies via inhalation, female rats and Himalayan rabbits were exposed to vapor of isobutanol. In rats, no mortality or significant differences in clinical signs, body weight development, or gross pathology between controls and treated groups and no effects on development were noted. The maternal and developmental rat NOAELs were 3,030 ppm. In rabbits, no mortality or significant differences in clinical signs, body weight development, or gross pathology between controls and treated groups and no effects on development were noted. The maternal no observed adverse effect level (NOAEL) for rabbits was 758 ppm. Fetuses exhibited no signs of developmental changes in response to isobutanol. Therefore, the developmental NOAEL was 3,030 ppm, the highest dose.

In a 2-generation reproduction study in rats with isobutanol via inhalation, no exposure-related effects were observed on F0 and F1 parental survival or on F0 and F1 reproductive performance, body weights, food consumption and food efficiency in males or females. The NOAEL for isobutanol for parental systemic, reproductive and neonatal toxicity is 2,500 ppm (7,380 mg/m³ the maximum concentrations exposed).

There were no adequate studies on the carcinogenic potential of methyl isobutyrate or isobutanol isobutyrate. Methyl isobutyrate did not significantly induce chromosome loss in

mitotically growing *Saccharomyces cerevisiae*. The structurally similar isobutyl isobutyrate did not induce reverse mutations at concentrations as high as 5,000 microgram/milliliter (ug/mL). An evaluation of the structure of methyl isobutyrate for alerts to genotoxicity yields no identifiable structures of concern. Based on negative results in genotoxicity assays and an extensive history of exposure to isobutyl isobutyrate, carcinogenic potential of this compound is likely to be low. Methyl isobutyrate was not genotoxic in one study and it does not contain reactive substructures of concern and isobutyl isobutyrate was also negative in genotoxic assays and in extensive exposure history; therefore the carcinogenic potential of both compounds is low.

Metabolism of aliphatic esters such as methyl isobutyrate and isobutyl isobutyrate proceeds rapidly through hydrolysis to form an alcohol and carboxylic acid. These are reactions of the carboxylesterases or esterases, which predominate in hepatocytes but are present in most tissues throughout the body, including small intestine, colon, kidney, trachea and lung. Hydrolysis of methyl isobutyrate is extensive and will form methanol and isobutyric acid. Isobutyric acid is metabolized to propionic acid which, in turn, is converted to succinic acid and ultimately to glucose and glycogen. Methanol is oxidized and excreted ultimately as CO₂ and water. In male rats injected intravenously with isobutyl isobutyrate, the parent compound decreased rapidly in blood and was undetected after 166 seconds. The half-life was calculated at 11.1 seconds. Isobutanol and isobutyric acid levels increased rapidly, with the acid consistently higher than the alcohol, suggesting that the former is a metabolic product of the alcohol in addition to the parent compound. Isobutyric acid will be conjugated and excreted or will undergo β -oxidation in the fatty acid metabolic pathway.

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>.

EPA has not identified any toxicological points of departure for assessing methyl isobutyrate and isobutyl isobutyrate. On the basis of the metabolism of as methyl isobutyrate and isobutyl isobutyrate proceeding rapidly through hydrolysis to form an alcohol and carboxylic acid and ultimately to glucose and glycogen, low acute toxicity for animals via the dermal, inhalation, and oral routes of exposure, and low toxicity of the metabolite isobutyl alcohol, no adverse effect is expected from methyl isobutyrate and isobutyl isobutyrate as a result of exposure by any route.

C. Exposure Assessment

1. *Dietary exposure from food and feed uses.* In evaluating dietary exposure to methyl isobutyrate and isobutyl isobutyrate, EPA considered exposure under the proposed exemption

from the requirement of a tolerance. EPA assessed dietary exposures from methyl isobutyrate and isobutyl isobutyrate in food as follows:

Acute and chronic dietary assessments take into account exposure estimates from dietary consumption of food and drinking water. Because no adverse effects attributable to a single or repeat exposures to methyl isobutyrate and isobutyl isobutyrate were seen in the toxicity databases, quantitative dietary risk assessments are not appropriate. Due to expected use of methyl isobutyrate and isobutyl isobutyrate in pesticide formulations applied to growing crops and raw agricultural commodities after harvest, it is reasonable to expect that there will be some exposure to these substances from their use in pesticide products. In addition, FDA has approved the use of methyl isobutyrate and isobutyl isobutyrate as synthetic flavoring substances in food for direct human consumption (21 CFR 172.515), so there is expected to be additional dietary exposure to these substances from non-pesticidal sources.

2. *Dietary exposure from drinking water.* For the purpose of the screening level dietary risk assessment to support this request for an exemption from the requirement of a tolerance for methyl isobutyrate and isobutyl isobutyrate, a conservative drinking water concentration value would normally be included in dietary exposure screening level model. However, because no adverse effects attributable to a single or repeat exposures to methyl isobutyrate and isobutyl isobutyrate were seen in the toxicity databases, quantitative dietary risk assessments are not appropriate.

3. *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).

It is possible that methyl isobutyrate or isobutyl may be used as an inert ingredient in pesticide products that may result in residential exposures, although no residential uses are currently proposed.

4. *Cumulative effects from substances with a common mechanism of toxicity.* Section 408(b)(2)(D)(v) of FFDCFA requires that, when considering whether to establish, modify, or revoke a tolerance or exemption from 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.”

Because methyl isobutyrate and isobutyl isobutyrate do not have a toxic mode of action or a mechanism of toxicity, this provision does not apply.

D. Safety Factor for Infants and Children

1. *In general.* Section 408(b)(2)(C) of FFDCFA 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.

Because methyl isobutyrate and isobutyl isobutyrate do not have threshold effects and because of the lack of safety factors needed for this qualitative assessment, this provision does not apply to the assessment of methyl isobutyrate and isobutyl isobutyrate.

E. Aggregate Risks and Determination of Safety

Determination of safety section. Based on the lack of any endpoints of concern, EPA concludes that there is a reasonable certainty that no harm will result to the general population or to infants and children from aggregate exposure to methyl isobutyrate and isobutyl isobutyrate residues.

V. Analytical Enforcement Methodology

An analytical method is not required for enforcement purposes since the Agency is establishing an exemption from the requirement of a tolerance without any numerical limitation.

VI. Conclusions

Therefore, exemptions from the requirement of a tolerance are established under 40 CFR §180.910 for methyl isobutyrate (CAS Reg. No.547-63-7) and isobutyl isobutyrate (CAS Reg. No. 97-85-8) when used as inert ingredients (solvents) in pesticide formulations applied to growing crops or raw agricultural commodities after harvest.

VII. Statutory and Executive Order Reviews

This action establishes exemptions from the requirement of a tolerance under FFDC 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: December 15, 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 “Isobutyl isobutyrate (CAS Reg. No. 97-85-8)”; and “Methyl isobutyrate (CAS Reg. No. 547-63-7)” 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
* * * *	* *	*
Isobutyl isobutyrate (CAS Reg. No. 97-85-8)	None	Solvent
* * * *	* *	*
Methyl isobutyrate (CAS Reg. No. 547-63-7)	None	Solvent
* * * *	* *	*