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

OFFICE OF PREVENTION,
PESTICIDES, AND TOXIC SUBSTANCES

DATE: July 31, 2006

ACTION MEMORANDUM

SUBJECT: Inert Reassessment—Isobornyl Acetate (CAS Reg. No. 125-12-2)

FROM: Pauline Wagner, Chief Pauline Wagner 7/28/06
Inert Ingredient Assessment Branch
Registration Division (7505P)

TO: Lois A. Rossi, Director
Registration Division (7505P)

I. FQPA REASSESSMENT ACTION

Action: Reassessment of the exemption from the requirement of a tolerance for isobornyl acetate. The one tolerance exemption is being reassessed and maintained as-is.

Chemicals: Isobornyl Acetate

CFR: 40 CFR 180.920

CAS #: 125-12-2 (isobornyl acetate)

Use Summary: Isobornyl acetate is important as a flavoring agent and in industries where scenting is necessary (e.g., manufacture of toiletries) as it provides a pine-needle odor. As an inert ingredient in pesticide formulations, isobornyl acetate is used as a solvent in pesticide products that are used on agricultural crops.

List Reclassification Determination: The current List Classification for isobornyl acetate is List 3. Because EPA has determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to isobornyl acetate used as an inert ingredient in pesticide formulations, the List Classification will change from List 3 to List 4B.

II. MANAGEMENT CONCURRENCE

I concur with the reassessment of the exemption from the requirement of a tolerance for the inert ingredient isobornyl acetate (CAS Reg. No. 125-12-2) and with the List reclassification determination, as described above. I consider the exemption established in 40 CFR 180.920 to be reassessed for purposes of FFDCA's section 408(q) as of the date of my signature, below. A *Federal Register* Notice regarding this tolerance exemption reassessment decision will be published in the near future.

Lois Rossi

Lois A. Rossi, Director
Registration Division

July 31, 2006

Date:

cc: Debbie Edwards, SRRD
Joe Nevola, SRRD

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OFFICE OF PREVENTION,
PESTICIDES, AND TOXIC SUBSTANCES

July 31, 2006

MEMORANDUM

SUBJECT: Reassessment of the Exemption from the Requirement of a Tolerance for Isobornyl Acetate (CAS Reg. No. 125-12-2)

FROM: Kathleen Martin, Chemist
Inert Ingredient Assessment Branch
Registration Division (7505P)

TO: Pauline Wagner, Chief
Inert Ingredient Assessment Branch
Registration Division (7505P)

BACKGROUND

Attached is the science assessment for isobornyl acetate. The purpose of this document is to reassess the existing exemption from the requirement of tolerance for residues of isobornyl acetate as required under the Food Quality Protection Act (FQPA). This reassessment summarizes available information on the use, physical/chemical properties, toxicological effects, exposure profile, environmental fate, and ecotoxicity of isobornyl acetate.

EXECUTIVE SUMMARY

Isobornyl acetate is cyclic acetate with the odor of pine-needles; it is used as a flavoring and scenting agent. As an inert ingredient, isobornyl acetate is a solvent in pesticide products that are used on agricultural crops. Its exemption from the requirement of a tolerance is under 40 CFR 180.920—ingredients in pesticide formulations applied to growing crops only. In assessing the risk of isobornyl acetate, an important source of data was the comprehensive monograph on the monocyclic and bicyclic secondary alcohols, ketones, and related esters (which includes isobornyl acetate) which was recently prepared by the Joint WHO/FAO Expert Committee on Food Additives (JEFCA 2006).

Isobornyl acetate has low oral and dermal acute toxicity (Toxicity Category IV). In a subchronic oral study, the "principal untoward effect of [isobornyl acetate] was on the kidney, especially in male animals;" nephrotoxicity was seen as low as 90 mg/kg/day (Gaunt et al 1971). The kidney effects were only seen in the male rats. A possible explanation for the nephrotoxic effects in males but not females is the accumulation of alpha-2u-globulin, a protein in the male rat kidney that appears to lead to renal tubule tumor formation (US EPA 1991). Female rats and other laboratory mammals administered the same chemicals do not accumulate it in the kidney and they do not develop renal tubule tumors (US EPA 1991). The no effect level reported from this subchronic study—15 mg/kg/day—is a dose much greater than would be expected from any potential food or drinking water exposure. Developmental toxicity data are not available for isobornyl acetate, *per se*. However, the developmental toxicity data for camphor—a closely related chemical—show no effects in the offspring, even at doses where effects were seen in the maternal animals (i.e., no increased sensitivity).

JEFCA (2006) estimates that daily exposure from isobornyl acetate as a food additive is 4 µg/kg bw/day. And, individuals are exposed to isobornyl acetate naturally; it has been detected in a wide variety of foods. JEFCA (2006) reports that any consumed isobornyl acetate is expected to readily metabolize to innocuous products. In 2004 JEFCA (2005b) determined that there is no "safety concern at current levels of intake when [isobornyl acetate is] used as a flavouring agent." Considering the low toxicity, physical-chemical properties, and rapid biodegradation in the environment, exposures of concern are not anticipated from the use of isobornyl acetate as an inert ingredient in pesticide products applied to growing crops.

Taking into consideration all available information on isobornyl acetate, EPA has determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to isobornyl acetate when used as an inert ingredient in pesticide products when considering dietary (i.e., food and water) exposure and all other nonoccupational sources of pesticide exposure for which there is reliable information. Overall exposure due to the use of isobornyl acetate as an inert ingredient in pesticide products is expected to result in human exposure below any dose level that would produce any adverse effect. This is based on available animal toxicity studies and the use pattern of isobornyl acetate. Therefore, it is recommended that the exemption from the requirement of tolerance established for residues of isobornyl acetate can be considered reassessed as safe under section 408(q) of FFDCA.

I. INTRODUCTION

This report provides a qualitative assessment for isobornyl acetate, an inert ingredient in pesticide formulations exempted from the requirement of tolerance when applied to growing crops (40 CFR 180.920). It is important as a flavoring agent and in industries where scenting is important (e.g., manufacture of toiletries) as it provides a pine-needle odor.

Isobornyl acetate has not been identified as meeting the criteria of EPA's High Production Volume (HPV) Challenge Program nor is it being sponsored by the Organization for Economic Cooperation and Development's (OECD) SIDS (Screening Information Data Set) Program. However, the European Chemicals Bureau (ECB) has compiled an IUCLID (International Uniform Chemical Information Database) report on this chemical.[1]

II. USE INFORMATION

A. Pesticides

Isobornyl acetate is used as an inert ingredient only. There are currently no registered pesticide products containing isobornyl acetate as an active ingredient. As an inert ingredient, isobornyl acetate is a solvent in pesticide products that are used: on agricultural crops; as household disinfectant sprays; and in human and pet insect repellants. The exemption from the requirement of a tolerance for isobornyl acetate is provided in Table 1 below.

Table 1. Tolerance Exemptions Being Reassessed in this Document

CFR Citation				CAS Registry Number and 9CI Name
40 CFR 180	Inert Ingredient	Limits	Uses	
.920[a]	Isobornyl acetate	(none)	solvent	125-12-2 Bicyclo[2.2.1]heptan-2-ol, 1,7,7-trimethyl-, acetate, (1R,2R,4R)-rel-

[a]Residues listed in 40 CFR 180.920 are exempted from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to growing crops only.

[1]The ECB, which is a unit under the auspices of the European Union, is the focal point for data and the assessment procedure on dangerous chemicals. IUCLID is the basic tool for the data collection and evaluation in the frame of the European Risk Assessment Programme on Existing Substances. http://ecb.jrc.it/

B. Other Uses

Isobornyl acetate is used in compounding pine-needle odors, toilet waters, bath preparations, antiseptics, theater sprays, soaps, making synthetic camphor, and as a flavoring agent (Lewis 2002). Its U.S. Food and Drug Administration (FDA)-approved direct food additive use is listed in Table 2.

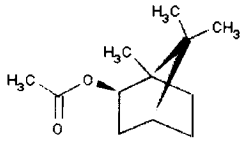
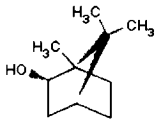
Table 2. FDA Direct Food Additive Uses for Isobornyl Acetate

Name	21 CFR	Use Pattern
Isobornyl acetate	172.515	Synthetic flavoring substances and adjuvants. They are used in the minimum quantity required to produce their intended effect.

III. PHYSICAL AND CHEMICAL PROPERTIES

Some of the physical and chemical characteristics of isobornyl acetate, along with its structure and nomenclature, are provided in Table 3. Because in humans isobornyl acetate is expected to readily hydrolyze to isobornyl alcohol in the first step of its biochemical pathway (JEFCA 2006), physical and chemical properties have been provided for this compound as well.

Table 3. Physical and Chemical Properties of Isobornyl Acetate and Isobornyl Alcohol

Parameter	Isobornyl Acetate	Isobornyl Alcohol
CAS Reg. No and Structure	125-12-2 	124-76-5 
9CI Name	Bicyclo[2.2.1]heptan-2-ol, 1,7,7-trimethyl-, acetate, (1R,2R,4R)-rel-	Bicyclo[2.2.1]heptan-2-ol, 1,7,7-trimethyl-, (1R,2R,4R)-rel-
Empirical Formula	$C_{12}H_{20}O_2$	$C_{10}H_{18}O$
Molecular Weight	196.29	154.25
Common Names	acetic acid, exo-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl, ester; Pichtosin; Pichtosine; isoborneol acetate Gangolli 2005	isoborneol; isobornyl alcohol US EPA 2006a
Physical State	colorless liquid when fresh, yellows upon storage; has a camphoraceous, piney, balsamic odor NAS 2003	white crystalline solid; piney, camphoraceous odor NAS 2003
Melting Point	>-50°C Gangolli 2005	26.56 °C (estimated) US EPA 2006b

Parameter	Isobornyl Acetate	Isobornyl Alcohol
Boiling Point	227°C NAS 2003	214°C NAS 2003
Water Solubility	Insoluble NAS 2003	---
Other Solubility	soluble in alcohol; slightly soluble in propylene glycol; insoluble in glycerin NAS 2003	slightly soluble in propylene glycol; insoluble in vegetable oil NAS 2003
Specific Gravity	0.979 to 0.984 @ 25°C NAS 2003	---
Vapor Pressure	0.23 mm Hg @ 25°C (estimated) US EPA 2006b	0.000429 mm Hg @ 25°C (estimated) US EPA 2006b
Log K_{ow}	3.86 (estimated) US EPA 2006b	3.24 (estimated) US EPA 2006b
Henry's Law Constant	4.37×10^{-4} atm m^3/mole (estimated) US EPA 2006b	6.7×10^{-6} atm m^3/mole (estimated) US EPA 2006b
Atmospheric Photo-oxidation Half-Life	1.4 days (estimated) US EPA 2006b	1 day (estimated) US EPA 2006b

IV. HAZARD ASSESSMENT

A. Hazard Profile

To assess the hazard posed by the use of isobornyl acetate as an inert ingredient in pesticide formulations, EPA considered a number of publicly-available sources including: published literature, peer-reviewed international documents (IUCLID, JEFCA[2]), and other standard available references. JEFCA, the Joint WHO (World Health Organization)/FAO (Food and Agriculture Organization) Expert Committee on Food Additives, was an important source of information. In conjunction with the 63rd meeting of JEFCA, which was held in June 2004, a comprehensive review of the monocyclic and bicyclic secondary alcohols, ketones, and related esters were considered as a group; isobornyl acetate (and isobornyl alcohol) are part of this group.

Because isobornyl acetate is expected to readily hydrolyze to isobornyl alcohol in the first step of its biochemical pathway (JEFCA 2006), where appropriate, data on this alcohol are reported in this assessment.

[2]JECFA is the Joint WHO/FAO Expert Committee on Food Additives. It conducts toxicological evaluations of food additives and contaminants in food. The resulting monographs are used by the Codex Alimentarius Commission and national governments to set international food standards and safe levels for protection of the consumer.

B. Toxicological Data

Acute Toxicity

A summary of the other acute toxicity parameters, along with their corresponding 40 CFR 156.62 Acute Toxicity Categories, is provided in Table 4.

Table 4. Summary of Acute Toxicity Data for Isobornyl Acetate and Isobornyl Alcohol

Parameter	Toxicity Value *Toxicity Category*[a]	Reference
Isobornyl Acetate		
Oral LD_{50} rat	>10 g/kg *Toxicity Category IV*	Opdyke 1979, citing Fogleman 1970
Dermal LD_{50} rabbit	>20 g/kg *Toxicity Category IV*	Opdyke 1979, citing Fogleman 1970
Isoborneol		
Oral LD_{50} rat	5.2 g/kg	JEFCA 2006, citing Moreno 1977a

[a]40 CFR 156.62

Subchronic Toxicity

Oral. Male and female rats were gavaged with isobornyl acetate at 0; 15; 90; or 270 mg/kg bw/day for 13 weeks. No deaths occurred during the study. No differences between treated and control animals were observed in body-weight gain, food intake, or results of hematological investigations. "The principal untoward effect of [isobornyl acetate] was on the kidney, especially in male animals." In the high-dose male rats (270 mg/kg), there was a decrease in renal concentrating ability, an increase in water intake, exfoliation of renal tubular cells, increased kidney weight, and vacuolation of the renal tubular cells. Signs of nephrotoxicity were also seen with daily doses of 90 mg/kg (male rats only). Vacuolation of the epithelium of the intrahepatic bile duct and an increase in liver weights were found at 270 mg/kg in male rats; the ceca (first part of the large intestines) were also enlarged at this dose level. The study investigators determined that the no effect level for this study is 15 mg/kg/day. (Gaunt et al 1971)

Mutagenicity

Because mutagenicity data were not available for isobornyl acetate, information on the bornyl alcohol, which is an isomer of isobornyl isomer, are reported. Provided in Table 5 is a summary of the mutagenicity data.

Table 5. Summary of Mutagenicity Data

Chemical	Test	Species	Dose or Concentration	Result	Reference
Bornyl Alcohol[b]	Reverse mutation	*S. typhimurium* TA98, TA100, TA97	1 mg/mL	negative[a]	JEFCA 2006, citing Azizan & Blevins 1995
Bornyl Alcohol	Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	≤5 mg/plate	negative[a]	JEFCA 2006 citing, Simmon et al 1977
Bornyl Alcohol	DNA repair	*B. subtilis* $M45^-$ and $H17^+$	≤ 10mg/disc	positive	JEFCA 2006, citing Yoo 1986
Bornyl Alcohol	Mutation test	*E. coli* WP2 uvrA (trp-)	0.4 to 3.2 mg/plate	negative	JEFCA 2006, citing Yoo 1986

[a]with and without metabolic activation [b]Bornyl alcohol is a stereoisomer of isobornyl alcohol

Chronic Toxicity and Carcinogenicity

"No information on long-term studies of toxicity and carcinogenicity was available" (JEFCA 2006).

Developmental and Reproductive Toxicity

No developmental or reproductive toxicity studies were identified for isobornyl acetate. However, data are available for camphor, which is a close analog to isobornyl acetate. They are provided below.

Rats, Oral. Pregnant rats were gavaged with camphor at 0; 216; 464; or 1,000 mg/kg bw/day during gestation day (GD) six through 17. On GD 20 the dams were sacrificed and examined macroscopically. Fetuses were examined for external, skeletal, and visceral anomalies. No adverse effects were seen in the dams of the 216 mg/kg bw/day dose group; however, at the two higher doses—464 and 1,000 mg/kg bw/day—salivation and reduced feed intake were reported. In addition, clonic convulsion, piloerection, reduced motility, and reduced body-weight gain were observed in the 1,000 mg/kg bw/day dose group. Necropsy revealed ulcers in the cardiac region of the stomach among the mid- and high-dose groups. In the fetuses, no effect on prenatal development was reported and no variations, retardations, or malformations were reported at any dose, even those causing maternal toxicity. (JEFCA 2006, citing Leuschner 1997).

Rats, Oral. Pregnant rats were gavaged with camphor at 0; 100; 400; or 800 mg/kg bw/day during GD six through 15. The dams were observed for clinical signs of toxicity and body weights; feed and water consumption were recorded. On GD 20, the dams were sacrificed. Body, liver, and intact uterus weights were recorded, and corpora lutea were counted. Numbers of implantation sites, resorptions, dead fetuses, and live fetuses were determined. Live fetuses were weighed, and examined for external, visceral, and skeletal abnormalities. No maternal deaths were reported. Initially, food consumption was significantly decreased at the two higher doses (400 and 800 mg/kg bw/day), but was reported to recover by the end of the study. Water intake was

increased in all treated groups, reaching statistical significance at the two higher doses at various timepoints during the study. In the low-dose group (100 mg/kg bw/day), water intake was significantly increased only on GDs six through nine. During the treatment period, a dose-dependent reduction in weight gain was reported, which reached levels of statistical significance in dams at the highest dose (800 mg/kg bw/day). Additionally, slight (≤10%) but significant and dose-dependent increases in absolute and relative weights of the liver were reported at the intermediate and highest doses. Exposure to d-camphor produced no effect on fetal growth, viability, or morphological development, even at doses causing maternal toxicity. (JEFCA 2006, citing National Toxicology Program 1992b)

Rabbits, Oral. Pregnant rabbits were gavaged with camphor at 0; 147; 316; or 681 mg/kg bw/day during GD six through 18. Does were observed for toxicity, and body weight and feed intake recorded daily. On GD 29, does were sacrificed and examined macroscopically. Fetuses were examined for external and skeletal anomalies. No effects were reported in does at the lowest (147 mg/kg bw/day) and intermediate (316 mg/kg bw/day) doses, while reduced body-weight gain and food intake were reported in does at the highest dose (681 mg/kg bw/day). At necropsy, no pathological findings were reported at any dose. In the fetuses, no effect on prenatal development was reported and no variations, retardations, or malformations were reported at any dose, even those causing maternal toxicity. (JEFCA 2006, citing Leuschner 1997)

C. Metabolism and Pharmacokinetics

Isobornyl acetate readily hydrolyzes (within hours) to isobornyl alcohol during the first step of it biochemical pathway. The alcohol will become conjugated with glucuronic acid and be excreted in the urine (expected within hours to days). (JEFCA 2006) Overall, JEFCA (2005a) expects that isobornyl acetate will be metabolized to innocuous products.

D. Special Considerations for Infants and Children

Isobornyl acetate has low acute toxicity. Oral and dermal LD_{50} values are in Toxicity Category IV. Developmental toxicity data are not available for isobornyl acetate, *per se*. However, the developmental toxicity data for camphor—a closely related chemical—show no effects in the offspring, even at doses where effects were seen in the maternal animals (i.e., no increased sensitivity). According to JEFCA (2006), ingested isobornyl acetate is expected to be readily metabolized to innocuous products that will be excreted in the urine within hours to days.

Based on this information, there is no concern, at this time, for increased sensitivity to infants and children to isobornyl acetate when used as an inert ingredient in pesticide formulations. For the same reason, a safety factor analysis has not been used to assess the risks resulting from the use of isobornyl

acetate; therefore, an additional tenfold safety factor for the protection of infants and children is unnecessary.

V. ENVIRONMENTAL FATE CHARACTERIZATION AND DRINKING WATER CONSIDERATIONS

A search of the open literature provided limited information on the fate and effects of isobornyl acetate and isobornyl alcohol; therefore, structure activity relationships (SAR) were heavily relied on to summarize the potential properties and environmental fate and transport. The ester and neutral organic classes were used to estimate properties, environmental behavior, and toxicity. Table 6 provides a summary of the estimated environmental behavior of isobornyl alcohol and isobornyl acetate relying on abiotic and biotic transformation processes and sorption characteristics. In summary, all these compounds were considered not readily biodegradable in terrestrial and aquatic environments. However, in a summary of the ready biodegradability of fragrance compounds using the OECD Ready Biodegradability test criteria, isobornyl acetate was classified as "ready biodegradable" (SIB 2006). Because of the structural similarity of these compounds, the alcohol is likely to behave similarly in the OECD Ready Biodegradability test; therefore, there is a high probability that the alcohol form will be readily biodegradable. Based on SAR results, both compounds will undergo primary degradation in days to weeks followed by mineralization to essentially carbon dioxide and water in aerobic systems in weeks to months. Under anaerobic conditions in both terrestrial and aquatic environments, degradation will likely occur at a slower rate for both compounds. Abiotically, isobornyl acetate will undergo base-catalyzed hydrolysis to form its corresponding alcohol, isobornyl alcohol, especially above pH 8; as pH increases so does the rate of hydrolysis to the corresponding carboxylic acid. Isobornyl alcohol will not undergo base-/acid-catalyzed hydrolysis. Occurrence in air via spray drift and volatilization (a minor route of dissipation) will undergo rapid hydroxyl radical reaction. Photolysis is not expected to be a major transformation route. Partitioning to air from water is not expected to contribute much to the dissipation of the isobornyl acetate despite its relatively high Henry's Law Constant. Isobornyl alcohol is not likely to partition to air once in water. Based on the log K_{ow}, isobornyl acetate and isobornyl alcohol are not expected to bioconcentrate. Movement in the environment in the dissolved or sorbed phase is expected to be significant based on their solubility and low estimated adsorption coefficients.

Table 6. Environmental Fate Properties of Isobornyl Acetate and Isobornyl Alcohol

Parameter	Isobornyl Acetate[a]	Isobornyl Alcohol[a]
Aerobic Ready Biodegradability	No (US EPA 2006b); Yes (SIB 2006)	No (US EPA 2006b)
Biodegradation Results	Primary in days to weeks; ultimate in weeks to months	Primary in days to weeks; ultimate in weeks to months
Atmospheric Oxidation ($T_{1/2}$)	Hydroxyl radical: ~1.3 days	Hydroxyl radical: ~1.0 day
Hydrolysis	Base-catalyzed hydrolysis important at $\geq$ pH 8	Not Applicable

Parameter	Isobornyl Acetate[a]	Isobornyl Alcohol[a]
Soil Adsorption (K_{oc})	~500	~57
Log BCF (bioconcentration factor)	2.27	1.37
Level III Fugacity	Air: <1% Water: ~13% Soil: ~83% Sediment: ~2.3%	Air: <1% Water: ~21% Soil: ~77% Sediment: <1%

[a]US EPA 2006b, unless otherwise noted.

Movement of the isobornyl compounds into surface water will be dependent on the proximity of environmental releases (applications to land and spray drift) and occurrence of runoff producing rainfall relatively shortly after applications, and microbial health of the environment. A delay in transport to surface water may substantially limit concentrations in ambient water. Once in surface water, further degradation of isobornyl acetate will occur as they move through the aquatic system to drinking water intakes. Once at drinking water intakes, removal of isobornyl acetate during treatment will be controlled mainly by the pH of the various steps and the efficiency of coagulation, flocculation and sedimentation operations. Because most publicly owned drinking water utilities maintain a pH of approximately 8 to reduce copper pipe corrosion, base-catalyzed hydrolysis is expected to impact final concentrations at consumer taps.

Isobornyl acetate and isobornyl alcohol may contaminate shallow aquifer groundwater; however, biologically-mediated degradation in aerobic conditions will limit loadings, thus concentrations. There are no ambient water quality criteria or drinking water maximum contaminant levels (MCLs) or health advisories (HAs) for isobornyl acetate and isobornyl alcohol.

VI. EXPOSURE ASSESSMENT

Isobornyl acetate is an inert ingredient in products used on agricultural food crops (field and tree). EPA expects that exposure would primarily be through the oral route, via consumption of agricultural crops to which this inert ingredient has been applied as a solvent, and exposure through drinking water. Additional exposure may occur through the dermal and inhalation routes via residential use of pesticide products containing isobornyl acetate. Expected food, drinking water, and residential exposures are discussed below.

Food and Drinking Water

EPA does not expect residues of concern on food from the application of pesticide products containing isobornyl acetate. Isobornyl acetate has been reported to occur naturally in foods such as butter, beef, beer, cheese, wine, fruit, herbs, mint, and cocoa (JEFCA 2006, citing Nijssen et al 2003). JEFCA (2006) estimates that in the United States (U.S.) daily per capita intake for isobornyl acetate is 236 µg, which

translates to 4 µg/kg bw/day. This figure takes into account the amount of isobornyl acetate produced in the U.S. annually, the population of the U.S., and body weight.

Upon application to growing crops, residues of isobornyl acetate would be expected to evaporate or break down rapidly; the atmospheric photooxidation half-life is estimated to be 1.4 days (US EPA 2006b). Because of its environmental fate properties, EPA does not anticipate exposures of concern from drinking water from the use of isobornyl acetate in pesticide products.

Residential

In addition, exposures through the dermal and inhalation routes are possible from residential use of pesticide products containing isobornyl acetate. However, EPA does not expect significant exposure through these routes. The acute oral and dermal LD_{50}'s are quite high (both are greater than 10 g/kg, Toxicity Category IV), which indicates that there is little to no absorption, and thus no exposure.

VII. AGGREGATE EXPOSURES

In examining aggregate exposure, the Federal Food, Drug, And Cosmetic Act (FFDCA) section 408 directs EPA to consider available information concerning exposures from the pesticide residue in food and all other nonoccupational exposures, including drinking water from ground water or surface water and exposure through pesticide use in gardens, lawns, or buildings (residential and other indoor uses). For isobornyl acetate, a qualitative assessment for all pathways of human exposure (food, drinking water, and residential) is appropriate given the lack of human health concerns associated with exposure to isobornyl acetate as inert ingredients in pesticide formulations.

VIII. CUMULATIVE EXPOSURE

Section 408(b)(2)(D)(v) of the 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."

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to isobornyl acetate and any other substances and, isobornyl acetate does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that isobornyl acetate has 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 the

policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

IX. HUMAN HEALTH RISK CHARACTERIZATION

Taking into consideration all available information on isobornyl acetate, EPA has determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to isobornyl acetate when used as an inert ingredient in pesticide products when considering dietary (i.e., food and water) exposure and all other nonoccupational sources of pesticide exposure for which there is reliable information. Overall exposure due to the use of isobornyl acetate as an inert ingredient in pesticide products is expected to result in human exposure below any dose level that would produce any adverse effect. This is based on available animal toxicity studies and the use pattern of isobornyl acetate. Therefore, it is recommended that the exemption from the requirement of tolerance established for residues of isobornyl acetate can be considered reassessed as safe under section 408(q) of FFDCA.

Isobornyl acetate has low oral and dermal acute toxicity (Toxicity Category IV). In a subchronic oral study, the "principal untoward effect of [isobornyl acetate] was on the kidney, especially in male animals;" nephrotoxicity was seen as low as 90 mg/kg/day (Gaunt et al 1971). The kidney effects were only seen in the male rats; the study investigator points out that over the course of the study the treated females gave results similar to the female controls (i.e., effects were generally not seen in female rats). A possible explanation for the nephrotoxic effects in males but not females is the accumulation of alpha-2u-globulin, a low molecular weight protein in the male rat kidney that appears to lead to renal tubule tumor formation (US EPA 1991). Female rats and other laboratory mammals administered the same chemicals do not accumulate it in the kidney and they do not develop renal tubule tumors (US EPA 1991). The no effect level reported from this subchronic study—15 mg/kg/day—is a dose much greater than would be expected from any potential food or drinking water exposure. Developmental toxicity data are not available for isobornyl acetate, *per se*. However, the developmental toxicity data for camphor—a closely related chemical—show no effects in the offspring, even at doses where effects were seen in the maternal animals (i.e., no increased sensitivity).

JEFCA (2006) estimates that daily exposure from isobornyl acetate as a food additive is 4 µg/kg bw/day. And, there is some everyday background exposure as this compound occurs naturally in certain foods such as butter, fruit, and cocoa (JEFCA 2006). JEFCA (2006) reports that any consumed isobornyl acetate is expected to readily metabolize to innocuous products. In 2004 JEFCA (2005b) determined that there is no "safety concern at current levels of intake when [isobornyl acetate is] used as a flavouring agent." Considering the low toxicity, physical-chemical properties, and rapid biodegradation in the environment, exposures of concern are not anticipated from

the use of isobornyl acetate as an inert ingredient in pesticide products applied to growing crops. Because of its environmental fate properties, EPA does not anticipate exposures of concern from drinking water from the use of isobornyl acetate in pesticide products.

X. ECOTOXICITY AND ECOLOGICAL RISK CHARACTERIZATION

EPA (US EPA 2006d) finds that based on SAR ecotoxicity estimates, isobornyl acetate and isobornyl alcohol span a narrow range of aquatic toxicity regardless of taxa. Isobornyl acetate would be considered moderately toxic to aquatic organisms based on SAR results, while isobornyl alcohol would be classified as slightly toxic. Table 7 provides estimated toxicity for isobornyl acetate and isobornyl alcohol based on ester and neutral organic compound classes. There were no effects data available on the Agency's ECOTOX Database (US EPA 2006c).

Using the rat as a surrogate for wild mammals, isobornyl acetate and isobornyl alcohol may be classified as practically nontoxic when given orally—the LD_{50} is >10 g/kg (Opdyke 1979, citing Fogleman 1970). On a chronic basis, exposures did not result in effects until doses reached >100 mg/kg day; however, the effects seen were generally not associated with the potential for continued survival or reproduction.

Table 7. Ecological Effects of Isobornyl Acetate and Isobornyl Alcohol

Taxa	Isobornyl Acetate[a]	Isobornyl Alcohol
Fish	96-hour LC_{50}: ~3.0 ppm (esters) 14-day LC_{50}: ~6.0 ppm (neutral organics, baseline) Chronic: ~0.3 ppm (esters)	96-hour LC_{50}: ~18.0 ppm (neutral organics) 14-day LC_{50}: ~38.0 ppm (neutral organics) Chronic: ~2.7 ppm (neutral organics)
Invertebrates	48-hour LC_{50}: ~3.0 ppm (esters)	48-hour LC_{50}: ~21.0 ppm (neutral organics
Green Algae	96-hour EC_{50}: ~0.3 ppm (esters)	96-hour EC_{50}: ~14 ppm (neutral organics)
Saltwater Fish	NA	96-hour LC_{50}: ~6.0 ppm (neutral organics)
Mysid Shrimp	NA	96-hour LC_{50}: ~3.0 ppm neutral organics)
Earthworm	NA	14-day LC_{50}: ~519 ppm

[a]All reported values are based on ECOSAR (US EPA 2000) and are rounded estimates.

Based on estimated environmental fate, transport and toxicity information, application to terrestrial systems of isobornyl acetate would need to exceed 3 pounds/A to exceed the Agency's endangered species level of concern (LOC) for the most sensitive species, fish and invertebrates, using results for isobornyl acetate.

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