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

OFFICE OF PREVENTION,
PESTICIDES, AND TOXIC SUBSTANCES

DATE: August 30, 2005

ACTION MEMORANDUM

SUBJECT: Inert Reassessment—n-Butanol, CAS# 71-36-3 and Isobutyl Alcohol, CAS# 78-83-1

FROM: Pauline Wagner, Chief Pauline Wagner 9/6/05
Inert Ingredient Assessment Branch
Registration Division (7505C)

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

I. FQPA REASSESSMENT ACTION

Action: Reassessment of two exemptions for one chemical and one exemption for another from the requirement of tolerance. The exemptions are being reassessed as-is.

Chemicals: n-Butanol and Isobutyl Alcohol

CFR: 40 CFR 180.910 and 40 CFR 180.930 (n-butanol); 40 CFR 180.920 (isobutyl alcohol)

CAS #: 71-36-3 (n-butanol) and 78-83-1(isobutyl alcohol)

Use Summary: The butyl alcohols are widely-used industrial solvents. Applications include solvents for paints, lacquers, varnishes, natural and synthetic resins, gums, vegetable oils, dyes, camphor, alkaloids, and pesticides. In terms of pesticides, n-butanol and isobutyl alcohol are used as inert ingredients in pesticide formulations only; there are no registered pesticide products containing n-butanol or isobutyl alcohol as an active ingredient. As inert ingredients, n-butanol and isobutyl alcohol are solvent and cosolvents in a number of pesticide products, including those used in agriculture, on animals, ornamental plants, and in and around the home.

List Reclassification Determination: The current List Classification for n-butanol is 4B; it will retain its current Classification. The current List Classification for isobutyl alcohol is 3. Because EPA has determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to isobutyl alcohol used as inert ingredients in pesticide formulations, the List Classification for isobutyl will change from List 3 to List 4B.

II. MANAGEMENT CONCURRENCE

I concur with the reassessment of the two exemptions from the requirement of a tolerance for the inert ingredient n-butanol (CAS# 71-36-3) and with the List reclassification determination, as described above. I also concur with the reassessment of the one exemption from the requirement of a tolerance for the inert ingredient isobutyl alcohol (CAS# 78-83-1) and with the List reclassification determination, as described above. I consider the two exemptions established in 40 CFR 180.910 and 40 CFR 180.930 (n-butanol) and the one exemption in 40 CFR 180.920 (isobutyl alcohol) 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 A. Rossi

Lois A. Rossi, Director
Registration Division

9/20/05
Date:

pc: Debbie Edwards, SRRD
Joe Nevola, SRRD

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

OFFICE OF PREVENTION,
PESTICIDES, AND TOXIC SUBSTANCES

August 29, 2005

MEMORANDUM

SUBJECT: Reassessment of the Two Exemptions from the Requirement of a Tolerance for n-Butanol and One Exemption from the Requirement of a Tolerances for Isobutyl Alcohol

FROM: Kathleen Martin, Chemist KA Mar. 8/31/05
Inert Ingredient Assessment Branch
Registration Division (7505C)

TO: Pauline Wagner, Chief Pauline Wagner 8/31/05
Inert Ingredient Assessment Branch
Registration Division (7505C)

BACKGROUND

Attached is the science assessment for n-butanol and isobutyl alcohol. The purpose of this document is to reassess the three existing exemptions from the requirement of tolerances for residues of n-butanol and isobutyl alcohol as required under the Food Quality Protection Act. This assessment summarizes available information on the use, physical/chemical properties, toxicological effects, exposure profile, and environmental fate and ecotoxicity of these two alcohols.

EXECUTIVE SUMMARY

This report evaluates n-butanol and isobutyl alcohol, pesticide inert ingredients for which a total of three exemptions from the requirement of tolerances exist for their residues when used in accordance with good agricultural practice as inert ingredients in pesticide formulations applied to: growing crops or to raw agricultural commodities after harvest (40 CFR 180.910, n-butanol); growing crops only (40 CFR 180.920, isobutyl alcohol); or to animals (40 CFR 180.930, n-butanol).

EPA expects that exposures to n-butanol and isobutyl alcohol are widespread, though not at high concentrations. First, both n-butanol and isobutyl alcohol occur in nature and are found in fusel oils obtained by carbohydrate fermentation (Elvers, et al

1989). Second, the butyl alcohols are widely-used industrial solvents. Applications include solvents for paints, lacquers, varnishes, natural and synthetic resins, gums, vegetable oils, dyes, camphor, alkaloids, and pesticides (Pohanish 2002). Finally, n-butanol and isobutyl alcohol are U.S. Food and Drug Administration Direct Food Additives (as flavoring substances).

When used as inert ingredients in pesticide formulations, EPA expects that exposure to n-butanol and isobutyl alcohol would primarily be through the oral route, via consumption of agricultural crops to which these inert ingredients have been applied as a solvent or cosolvent and, through drinking water. Additional exposure may occur through the dermal and inhalation routes via the use of residential pesticides containing n-butanol and/or isobutyl alcohol as inert ingredients. Such products include those for: home vegetable gardens; ornamental plants; and home indoor and outdoor surfaces such as crack and crevice treatment.

n-Butanol and isobutyl alcohol exhibit low acute toxicity for animals via the dermal, inhalation, and oral routes of exposure (Elvers 1989). Neither alcohol has been shown to be mutagenic or carcinogenic. Developmental and neurotoxic effects were noted; however, effects were only seen at high doses.

Overall exposure from to the inert use of n-butanol and isobutyl alcohol in pesticide formulations is expected to result in human exposure below any dose level that would produce any adverse effect. Exposure to n-butanol and isobutyl alcohol in food and drinking water is expected via the oral route. Both alcohols occur naturally as a product of fermentation of carbohydrates. JECFA, the Joint World Health Organization/Food And Agriculture Organization, reports that linear saturated aliphatic alcohols, which include n-butanol and isobutyl alcohol, are ubiquitous in nature; they have been detected in almost every known fruit and vegetable (IPCS 1998). In addition to their natural occurrence, n-butanol and isobutyl alcohol are deliberately added to foods. Finally, EPA does not expect to find n-butanol and isobutyl alcohol in drinking water at levels that would be of concern. Both alcohols degrade readily in aerobic and anaerobic conditions. And, based on the high volatility of most aliphatic alcohols and aeration sequences used in many drinking water utilities, it is unlikely that most of these compounds will be found in treated water at concentrations equivalent to those in the environment.

To gain some understanding of the magnitude of an individual's worst-case exposure in a residential setting, EPA modeled indoor inhalation exposure using E-FAST (U.S. EPA 2004d). Assuming a person would be using an aerosol paint in an enclosed room for 20 minutes, exposure is estimated at 0.07 ppm (0.2 mg/m^3); this estimate is the same for n-butanol and isobutyl alcohol. Considering the toxicity levels where no inhalation effects were reported (3,500 ppm for n-butanol and 820 ppm for isobutyl alcohol), the estimated level of exposure in a residential setting is far below the level where any toxic effects would be seen.

Taking into consideration all available toxicity and exposure information on n-butanol and isobutyl alcohol, EPA has determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to n-butanol and isobutyl alcohol used as inert ingredients in pesticide formulations when considering dietary exposure and all other nonoccupational sources of pesticide exposure for which there is reliable information. Therefore, it is recommended that the two exemptions from the requirement of a tolerance established for residues of n-butanol (40 CFR 180.910 and 40 CFR 180.930) and the one tolerance established for isobutyl alcohol (40 CFR 180.920) can be considered reassessed as safe under section 408(q) of the Federal Food, Drug, and Cosmetic Act.

I. Introduction

This report evaluates n-butanol and isobutyl alcohol, pesticide inert ingredients for which a total of three exemptions from the requirement of tolerances exist for their residues when used in pesticide formulations applied to: growing crops or to raw agricultural commodities (RACs) after harvest (40 CFR 180.910, n-butanol); growing crops only (40 CFR 180.920, isobutyl alcohol); or animals (40 CFR 180.930, n-butanol).

There are four structural isomers of the butanols: n-butanol; isobutanol (also known as isobutyl alcohol); sec-butanol; and tert-butanol. This report provides a qualitative evaluation of n-butanol and isobutyl alcohol, pesticide inert ingredients for which exemptions from the requirements of tolerances exist for its residues. Both n-butanol and isobutyl alcohol occur in nature, and are found in fusel oils[1] obtained by carbohydrate fermentation (Elvers, et al 1989). Commercially, the butanols are synthesized from petrochemicals, and are widely used as organic solvents and as intermediates in the manufacture of other organic chemicals. Apart from slight differences in the boiling point and water solubility, the physical properties of the isomers are similar. (IPCS 1987a)

[1]Fusel oils are volatile oily mixtures consisting largely of amyl alcohols.

II. Use Information

A. Pesticides

The exemptions from the requirement of a tolerance for the inert ingredients n-butanol and isobutyl alcohol are provided in Table 1 below.

Table 1. Exemptions from the Requirement of a Tolerance

Tolerance Exemption Expression	CAS Registration Number	40 CFR 180§	Use Pattern (Pesticidal)
n-Butanol	71-36-3	.910[a]	solvent, cosolvent
		.930[b]	solvent for blended emulsifiers
Isobutyl alcohol	78-83-1	.920[c]	solvent

[a]Residues listed in 40 CFR 180.910 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 or to RACs after harvest.

[b]Residues listed in 40 CFR 180.930 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 animals.

[c]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.

B. Other Uses

The butyl alcohols are used as solvents for paints, lacquers, varnishes, natural and synthetic resins, gums, vegetable oils, dyes, camphor, and alkaloids. They are also used as intermediates in the manufacture of pharmaceuticals and chemicals and in the manufacture of artificial leather, safety glass, rubber and plastic cements, shellac, raincoats, photographic films, perfumes, and in plastic fabrication. (Pohanish 2002)

In addition to their industrial uses, n-butanol and isobutyl alcohol are added to foods as a flavoring substance and adjuvant. n-Butanol is also permitted to be used as an additive in the preparation of sulfate butyl oleate and modified hop extract. Isobutyl alcohol is used in the preparation of sucrose fatty acid esters. Provided in Table 2 are the U.S. Food and Drug Administration (FDA) Direct Food Additive uses.

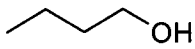
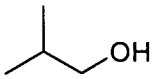
Table 2. FDA Direct Food Additive Uses

Name	21 CFR §	Use Pattern
172: Food Additives Permitted For Direct Addition To Food For Human Consumption—n-Butanol		
1-Butanol	172.270	Used in the preparation of sulfate butyl oleate as a food additive
Butyl alcohol; 1-butanol	172.515	Synthetic flavoring substances and adjuvants used in food in the minimum quantity required to produce their intended effect, and otherwise in accordance with all the principles of good manufacturing practice.
n-Butyl alcohol	172.560	In the preparation of modified hop extract.
172: Food Additives Permitted For Direct Addition To Food For Human Consumption—Isobutyl Alcohol		
Isobutyl alcohol	172.515	Synthetic flavoring substances and adjuvants used in food in the minimum quantity required to produce their intended effect, and otherwise in accordance with all the principles of good manufacturing practice.
Isobutyl alcohol	172.859	Used in the preparation of sucrose fatty acid esters.

III. Physical and Chemical Properties

Some of the physical and chemical characteristics of n-butanol and isobutyl alcohol, along with their structure and nomenclature, are found in Table 3.

Table 3. Physical and Chemical Properties of n-Butanol and Isobutyl Alcohol

Parameter	Value and Reference	
	n-Butanol	Isobutyl Alcohol
Structure		
Empirical Formula	$C_4H_{10}O$	$C_4H_{10}O$
CAS #	71-36-3	78-83-1
Common Names	1-Butyl alcohol; Propyl carbinol; Butanol; Butyl alcohol; Butyric alcohol; n-Butyl alcohol; n-Butanol (NIH 2004a)	1-Propanol, 2-methyl-; Isobutanol; 2-Methylpropan-1-ol (NIH 2004a)
Physical State	refractive liquid (U.S. EPA 1994)	refractive liquid (Merck 2005)
Molecular Weight	74.12 (U.S. EPA 1994)	74.12 (U.S. EPA 1994)
Melting Point	-90°C (U.S. EPA 1994)	-108°C (NIH 2004a)
Boiling Point	117-118 °C (U.S. EPA 1994)	108°C (NIH 2004a)
Water Solubility	9.1 mL/100 mL H_2O @ 25°C (U.S. EPA 1994)	8.50×10^4 mg/L (NIH 2004a)

Parameter	Value and Reference	
	n-Butanol	Isobutyl Alcohol
Vapor Pressure	7.00 mm Hg @ 25°C [930 Pa] (U.S. EPA 1994)	10.5 mm Hg @ 25°C [1400 Pa] (NIH 2004a)
log Kow	0.88 (U.S. EPA 1994)	0.76 (NIH 2004a)
Henry's Law Constant	8.81×10^{-6} atm-m^3/mole @ 25°C (U.S. EPA 1994)	9.78×10^{-6} atm-m^3/mole @ 25°C (NIH 2004a)
Relative Density (water=1)	0.8 (NIOSH 1995)	0.806 (Merck 2005)

IV. Hazard Assessment

To assess the hazard posed by the use of n-butanol and isobutyl alcohol as inert ingredients in pesticide formulations, EPA relied on a 1987 peer-reviewed International Programme on Chemical Safety (IPCS) Environmental Health Criteria (EHC) (IPCS 1987a)[2] document. Also considered were: EPA's Integrated Risk Information System (IRIS) Database for Risk Assessment (U.S. EPA 2004a and 2004b)[3]; the Organization for Economic Cooperation and Development's (OECD) HPV Screening Information Data Set (SIDS) Program[4]; and the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) report on n-butanol (ECETOC 2003).

Both n-butanol and isobutyl alcohol have been identified as chemicals meeting the criteria for EPA's High Production Volume (HPV) Challenge Program[5]. They are being handled under the auspices of the OECD HPV SIDS Program; the United States

[2]IPCS is a joint venture of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization. Their EHC monographs represent a thorough evaluation of a chemical's risks. In 1987, IPCS published EHC 65—Butanols: Four Isomers.

[3]IRIS is a database of human health effects that may result from exposure to various substances found in the environment. IRIS was initially developed for EPA staff in response to a growing demand for consistent information on chemical substances for use in risk assessments, decision-making and regulatory activities. Both n- and iso-butanol are listed in the IRIS database. For n-butanol, a chronic oral reference dose (RfD) was established in 1990 and the carcinogenicity was assessed in 1991. For isobutanol, a chronic RfD was established in 1991.

[4]The SIDS Program is a voluntary cooperative international testing program that began in 1989. It is focused on developing base level test information on approximately 600 poorly characterized international HPV chemicals. The SIDS data are used to "screen" the chemicals and set priorities for further testing or risk assessment/management activities. The priorities are set at the SIAM.

[5]HPV chemicals are those that are manufactured or imported into the United States in volumes greater than one million pounds per year. There are approximately 3,000 HPV chemicals that are produced or imported into the United States. The HPV Challenge Program is a voluntary partnership between industry, environmental groups, and EPA which invites chemical manufacturers and importers to provide basic hazard data on the HPV chemicals they produce/import. The goal of this program is to facilitate the public's right-to-know about the potential hazards of chemicals found in their environment, their homes, their workplace, and in consumer products.

is the sponsoring country. n-Butanol was reviewed at SIAM (SIDS Initial Assessment Meeting) 13, which was held in Switzerland on November 6 to 9, 2001. SIAM participants, which include representatives of the sponsor countries, recommended that the "data collected for SIDS elements were considered adequate for hazard identification. BA [n-butanol] is currently recommended for low priority for further work" (OECD SIDS 2001). Isobutanol was reviewed at SIAM 19, which was held in Germany October 19 to 22, 2004. The participants recommended that the "chemical is currently of low priority for further work" and that it "possesses properties indicating a hazard for human health (dermal and eye irritation). Although these hazards do not warrant further work (as they are related to reversible, transient effects that may become evident only at very high exposure levels), they should nevertheless be noted by chemical safety professionals and users" (OECD SIDS 2004).

A. Toxicological Data

Provided below is a summary of n-butanol and isobutyl alcohol's major toxicological effects, which indicate slight acute toxicity, developmental toxicity, and neurotoxicity. Note that due to limitations in the databases, reliable data are not available for all toxicity endpoints or exposure routes.

Acute

Elvers (1989) reports that according to animal studies, the butanols have low acute oral, dermal, and inhalation toxicity. For n-butanol, the lowest median lethal doses (LD_{50}) reported are 790 mg/kg (rat, oral) and 4,200 mg/kg (rabbit, dermal). For isobutyl alcohol, the LD_{50} values are 2,460 mg/kg (rat, oral) and 4,250 mg/kg (rabbit, dermal). The lowest median lethal concentration (LC_{50}) reported is 8,000 ppm or 24 mg/L (rats, four hours); the same result was observed for isobutyl alcohol. Application of drops of n-butanol into the rabbit eye produces severe corneal irritation. n-Butanol has a slight to moderate irritating effect on rabbit skin. Application of isobutyl alcohol to the rabbit eye causes moderate to severe irritation. A moderate irritation was observed after 24 hours of exposure of the rabbit skin. A summary of these acute toxicity data along with the 40 CFR 156.62 Acute Toxicity Categories is provided in Table 4.

Acute neurotoxicity data are available for isobutyl alcohol (U.S. EPA 2005). In an acute Functional Observational Battery (FOB) and a Motor Activity study, rats were dosed via the inhalation route at 0; 1,500; 3,000; or 6,000 ppm (0; 5; 9; or 18 mg/L) for six hours. In the FOB, isobutyl alcohol caused a rapidly reversible general depression of the central nervous system at concentration of 3,000 and 6,000 ppm (9 and 18 mg/L) during the exposure period. There were no treatment-related effects in rats at the 3,000 ppm (9 mg/L) concentration following exposure. Minimal effects (hypoactivity) were seen in rats at 1,500 ppm (5 mg/L) during, but not after exposure. No treatment-related findings were observed in any tissue or organ during gross necropsy. The LOEL (lowest observed effect level) was 1,500 ppm (5 mg/L). For Motor Activity, the transient

decrease in alertness in the female rats, transient decrease in motor activity in male and female rats, and transient, slight incoordinated gait observed in one male rat were considered residual anesthetic effects at 6,000 ppm (18 mg/L). The LOEL was 1,500 ppm (5 mg/L).

Table 4. Summary of Acute Toxicity Data for n-Butanol and Isobutyl Alcohol and the Corresponding Acute Toxicity Categories

Parameter	n-Butanol	Isobutyl Alcohol
Oral LD_{50}, rat (Elvers 1989)	790 mg/kg *Toxicity Category III*	2,460 mg/kg *Toxicity Category III*
Dermal LD_{50}, rabbit (Elvers 1989)	4,200 mg/kg *Toxicity Category III*	4,250 mg/kg *Toxicity Category III*
Inhalation LC_{50}, rat (Elvers 1989)	8,000 ppm (24 mg/L) *Toxicity Category IV*	8,000 ppm (24 mg/L) *Toxicity Category IV*
Eye Irritation, rabbit (Elvers 1989)	severe corneal irritation	moderate to severe
Skin Irritation, rabbit (Elvers 1989)	slight to moderate	moderate
Acute FOB[6] (U.S. EPA 2005)	--	LOEL=1,500 ppm (5 mg/L)
Acute Motor Activity[6] (U.S. EPA 2005)	--	LOEL=1,500 ppm (5 mg/L)

Subchronic, Oral

n-Butanol. EPA has established a reference dose (RfD) for n-butanol (U.S. EPA 2004a); it is listed in IRIS. The critical effect is hypoactivity and ataxia. In a 13-week rat oral study, which was sponsored by EPA, rats were gavaged with n-butanol at 0; 30; 125; or 500 mg/kg/day. Data generated from this study on body and organ weight changes, food consumption, moribundity, mortality, ophthalmological, gross, and histopathologic examinations did not show any dose-related differences between control and treated animals. Slight but significant reductions in some hematologic parameters were observed in the mid- and high-dosed females at the interim, but not at final sacrifice. This effect was considered to be transitory rather than adverse. Ataxia and hypoactivity were consistently observed in high-dosed (500 mg/kg/day) males and females during the final six weeks of the dosing period. Thus, the 125 mg/kg/day dose of n-butanol is considered a NOAEL (no observed adverse effect level) for central nervous system effects in rats. By application of an uncertainty factor of 1,000 an RfD of 0.1 mg/kg/day is derived.

[6]Pursuant to a Toxic Substances Control Act (TSCA) rule, acute neurotoxicity studies on isobutyl alcohol were submitted to the Agency (59 FR 60985).

Isobutyl Alcohol. EPA has established an RfD for isobutyl alcohol (U.S. EPA 2004b); it is listed in IRIS. The critical effect is hypoactivity and ataxia. In a 13-week rat oral study, which was sponsored by EPA, rats were given isobutyl alcohol at doses of 0; 100; 316; or 1,000 mg/kg/day. This study contained data on body weight changes, food consumption, ophthalmologic examinations, clinical and biochemical parameters, and gross and microscopic examinations. An evaluation of the data revealed no effect on body weight or clinical and histopathologic parameters at doses less than or equal to 316 mg/kg/day. Treatment at the high dose (1,000 mg/kg/day) resulted in a minor decrease in body weight gain during week 2 and decreased serum potassium levels and hypoactivity. Hypoactivity was the most frequently observed clinical sign. It occurred in every rat in the 1,000 mg/kg/day dose group during week 1; hypoactivity was markedly decreased by week 4 and occurred only sporadically thereafter. Ataxia was also seen at low incidence in the 1,000 mg/kg/day dose group throughout the study. The NOEL (no observed effect level) for this study is 316 mg/kg/day. By the application of an uncertainty factor of 1,000 an RfD of 0.3 mg/kg/day is derived.

In a subchronic oral toxicity study, isobutyl alcohol was administered to Wistar rats in drinking water at 0; 1,000; 4,000; or 16,000 ppm (0, 80; 340; or 1,450 mg/kg/day) for 90 days; no toxic effects were noted. The NOAEL is 16,000 ppm or 1,450 mg/kg/day. (Schilling et al 1997)

Chronic

n-Butanol. Effects of repeated inhalation exposure of n-butanol in animals include pathological changes in the lungs, degenerative lesions in the liver and kidneys, and narcosis. However, it is not possible to determine a NOAEL on the basis of the animal studies available. (IPCS 1987a)

Isobutyl Alcohol. No chronic toxicity data were identified for isobutyl alcohol.

Mutagenicity

In summary, based on the available data, n-butanol and isobutyl alcohol appear to be nonmutagenic.

n-Butanol. n-Butanol is not mutagenic to *Salmonella typhimurium* in an Ames test, with and without activation (Lington and Bevan 1991). In a study designed to determine the usefulness of a new tester strain (*Salmonella typhimurium* TA102) for screening purposes in mutagenicity testing, n-butanol was tested in three labs. All three concluded that n-butanol is not mutagenic. (Müller, et al 1993). In other testing, n-butanol did not induce sister chromatid exchanges or chromosomal breakage in the chick embryo cytogenetic test. There were no sister chromatid exchanges in Chinese hamster ovary cells

treated with n-butanol, and no micronuclei were formed in V79 Chinese hamster cells treated with n-butanol.

Isobutyl Alcohol. Negative results were observed with isobutyl alcohol in Ames tests with *Salmonella typhimurium* strains TA97,TA98, TA100, TA1535, and TA1537 at concentrations of 100 to 10,000 g/plate. Negative mutagenicity results were also observed in tests using *Salmonella typhimurium* TA98, TA100, TA1535, TA1537, and TA1538; and *E. coli* strain WP2 uvrA-. (IPCS 1998)

Carcinogenicity

EPA has classified n-butanol as a Group D carcinogen. For isobutyl alcohol, the available data are inadequate to assess the carcinogenic potential.

n-Butanol. Based on the lack of data, EPA has classified n-butanol under Group D, not classifiable as to human carcinogenicity; this determination was made in 1990. This group is generally used for agents with inadequate human and animal evidence of carcinogenicity or for which no data are available. In 2003, a screening-level literature review was conducted to ascertain the availability of more recent studies pertinent to the cancer assessment of n-butanol; no critical studies were identified. (U.S. EPA 2004a)

Isobutyl Alcohol. Data to evaluate the carcinogenic potential of isobutyl alcohol are inadequate (Lington and Bevan 1991). The Agency has not yet undergone a complete evaluation and determination under EPA's IRIS program for evidence of human carcinogenic potential (U.S. EPA 2004b).

Developmental Toxicity

n-Butanol may be developmentally toxic, but only at high doses. Isobutyl alcohol has not been shown to be developmentally toxic.

n-Butanol. Information on the developmental and reproductive toxicity of n-butanol is limited. Evidence from animal studies indicates that exposure to high levels of n-butanol may adversely affect the developing fetus and reproductive system (U.S. EPA 1994).

In an oral study, female rats were dosed at 300; 1,000; or 5,000 mg/kg/day for eight weeks before and during gestation. Developmental effects (skeletal and central nervous system anomalies such as delayed ossification, wavy rib, and hydrocephalus) were seen at 1,000 mg/kg/day. No effects were noted in the maternal animals. The study investigator suggests that the "high resistance of pregnant female rats to the toxic action of n-butanol is probably attributable to its very rapid metabolism." (Sitarek et al 1994)

In an inhalation study, rats were dosed at 0; 3,500; 6,000; or 8,000 ppm n-butanol (0; 11; 18; or 24 mg/L) for 7 hours/day on days 1 to 19 of gestation. At the highest dose tested (8,000 ppm or 24 mg/L), narcosis was seen in 50% of the maternal animals and about 10% died. Maternal weight gain and food consumption decreased, fetal body weights were decreased, and fetal skeletal malformations increased (rudimentary cervical ribs were observed). At the mid-dose (6,000 ppm or 18 mg/L) maternal food consumption decreased but maternal weights were unaffected. Also, fetal weights were decreased (there were no significant increases in malformations). No effects were noted at the low-dose (3,500 ppm or 11 mg/L). (Nelson et al 1989)

Isobutyl Alcohol. In an inhalation study, rats and rabbits were exposed to isobutyl alcohol at vapor concentrations of 0.5; 2.5; or 10 mg/L (164; 820; 3,300 or ppm) for six hours/day. The rats were dosed on days six to 15 postcoitum and the rabbits on days seven to 19 postinsemination. At sacrifice, the fetuses were removed from the uteruses and examined for compound-related effects. It was noted that at the high dose (10 mg/L or 3,300 ppm), maternal rabbits had a slight retardation of body weight gain; this effect was not observed in the rats. The fetuses of both species exhibited no signs of developmental effects. The maternal rabbit and rat NOAELs are 2.5 mg/L (820 ppm) and 10 mg/L (3,300 ppm), respectively. For both species, the developmental NOAEL is 10 mg/L. (Klimisch HJ and Hellwig J 1995)

Neurotoxicity

EPA has established RfDs for n-butanol and isobutyl alcohol based on neurotoxicity concerns.

n-Butanol. n-Butanol causes adverse central nervous system effects in animals by both the oral and inhalation routes of exposure (U.S. EPA 1994). Based on ataxia and hypoactivity, EPA has established an RfD for neurotoxic effects of n-butanol. As discussed in the "Subchronic" section above, a NOAEL of 125 mg/kg/day and a LOAEL (lowest observed adverse effect level) of 500 mg/kg/day were identified; the RfD is 0.1 mg/kg/day (U.S. EPA 2004a).

Isobutyl Alcohol. Based on ataxia and hypoactivity, EPA has established an RfD for neurotoxic effects of isobutyl alcohol. As discussed in the "Subchronic" section above, a NOEL of 316 mg/kg/day was identified; the RfD is 0.3mg/kg/day. (U.S. EPA 2004b)

Under the authority of TSCA, further neurotoxicity testing was required for isobutyl alcohol.[7] A review of these data is available in the literature (Li et al 1999); it is described below. Over three months, rats were exposed to isobutyl alcohol at 0; 250; 1,000; or 2,500 ppm (0; 1; 3; or 8 mg/L) via inhalation for six hours/day, five days/week. A comprehensive battery of neurotoxicity tests, histopathology, and blood chemistry evaluations was conducted. "There were no morphological or behavioral effects indicative of a specific, persistent or progressive effect of isobutanol on the nervous system at exposure concentrations up to 2,500 ppm. A slight decrease in response to external stimuli was observed during all exposures at all concentrations. These effects are likely transient effects of acute exposure to isobutanol." The NOAEL was 2,500 ppm for neurotoxicity and 1,000 ppm for repeated-dose toxicity (OECD SIDS 2004).

B. Metabolism and Pharmacokinetics

n-Butanol. Animal studies have shown that n-butanol is readily absorbed by the respiratory tract, the gastrointestinal tract, and the skin (U.S. EPA 1994a). n-Butanol appears to follow the same metabolic pathway as other alcohols: oxidation to the aldehyde (n-butylaldehyde), then to the acid (n-butryic acid), and ultimately to carbon dioxide and water. Once absorbed, n-butanol disappears rapidly from the blood. (U.S. EPA 1994; Lington and Bevan 1991)

Isobutyl Alcohol. In animals, isobutyl alcohol is absorbed through the skin, lungs, and gastrointestinal tract (IPCS 1987a). Isobutyl alcohol also follows the same metabolic pathways as the other alcohols: oxidation to the aldehyde (isobutylaldehyde), then to the acid (isobutryic acid), and ultimately carbon dioxide and water. Isobutyl alcohol is rapidly cleared from the blood following systemic absorption. (Lington and Bevan 1991)

[7] In a 1993 Final Rule (58 FR 40262), EPA required that isobutyl alcohol manufacturers and processors conduct neurotoxicity testing. Three studies were submitted in 1996 (61 FR 17700): (1) Three Month Neurotoxicity Study of Isobutanol Administered by Whole-Body Inhalation to CD Rats; (2) Three Month Scheduled Controlled Operant Behavior Study of Isobutanol Administered by Whole-Body Inhalation to CD Rats; and (3) Exposure Concentration Range-Finding Study for a Subchronic Inhalation Neurotoxicity Study of Isobutanol Administered by Whole-Body Inhalation to CD Rats. A review of the data is provided in Li et al 1999.

C. Summary of Subchronic, Developmental, and Neurotoxicity

Because of the complexity of addressing the toxicity of two similar chemicals in one document, provided in Table 5 is a summary of the subchronic, developmental, and neurotoxicity data reported for n-butanol and isobutyl alcohol.

Table 5. Summary of Subchronic, Developmental, and Neurotoxicity Studies for n-Butanol and Isobutyl Alcohol

Type of Test	Dose	Route, Species	Toxicity	Data Source
n-Butanol				
Subchronic	0; 30; 125; or 500 mg/kg/day	Oral, rat	NOAEL of 125 mg/kg/day based on hypoactivity and ataxia. An RfD of 0.1 mg/kg/day was derived.	U.S. EPA 2004a
Developmental and Reproductive	300; 1,000; or 5,000 mg/kg/day	Oral, rat	Developmental: at 1,000 mg/kg/day effects were seen Maternal: no effects were noted	Sitarek et al 1994
	0; 3,500; 6,000; or 8,000 ppm	Inhalation, rat	Developmental: at 3,500 ppm, no effects seen; at 6,000 ppm, effects were noted Maternal: at 3,500 ppm, no effects seen; at 6,000 ppm, effects were noted	Nelson et al 1989
Neurotoxicity	0; 30; 125; or 500 mg/kg/day	Oral, rat	NOAEL of 125 mg/kg/day based on central nervous effects. An RfD of 0.1 mg/kg/day was derived. Note: this is the same study listed under "Subchronic."	U.S. EPA 2004a
Isobutyl Alcohol				
Subchronic	0; 100; 316; or 1,000 mg/kg/day	Oral, rat	NOEL of 316 mg/kg/day based on hypoactivity and ataxia. An RfD of 0.3 mg/kg/day was derived.	U.S. EPA 2004b
	0, 80; 340; or 1,450 mg/kg/day	Oral, rat	NOAEL of 1,450 mg/kg/day	Schilling et al 1997
	0; 250; 1,000; or 2,500 ppm	Inhalation, rat	NOAEL of 1,000 ppm	61 FR 17700; Li et al 1999
Developmental and Reproductive	164; 820; 3,300 or ppm	Inhalation, rats and rabbits	Developmental: at 3,300 ppm no effects in either species Maternal: NOAEL, rat 3,300 ppm; NOAEL, rabbit 820 ppm	Klimisch HJ and Hellwig J 1995
Neurotoxicity	0; 100; 316; or 1,000 mg/kg/day	Oral, rat	NOEL of 316 mg/kg/day based on hypoactivity and ataxia. An RfD of 0.3 mg/kg/day was derived. Note: this is the same study listed under "Subchronic."	U.S. EPA 2004b
	0; 250; 1,000; or 2,500 ppm	Inhalation, rat	NOAEL of 2,500 ppm. Note: this is the same study listed under "Subchronic."	61 FR 17700; Li et al 1999

D. Special Considerations for Infants and Children

Based on the available information, n-butanol and isobutyl alcohol are of low toxicity for human health endpoints (including developmental and reproductive effects) at doses expected from their inert use in pesticide formulations. One developmental toxicity study (Sitarek et al 1994) conducted by the oral route of exposure (n-butanol in rats) did show developmental toxicity in the absence of maternal toxicity (1,000 mg/kg/day; no effects at 300 mg/kg/day). However, the low potential for exposure mitigates any concern for increased risk to infants and children. Also, three developmental toxicity studies conducted by the inhalation route showed no developmental effects. In a study where rats were dosed with n-butanol, Nelson et al (1989) observed no developmental effects at 3,500 ppm; Klimisch and Hellwig (1995) observed similar results for isobutyl alcohol—in a study where rats and another where rabbits were dosed with isobutyl alcohol, they noted that no developmental effects were seen at 3,300 ppm for both species.

Thus, based on the available information there is no concern, at this time, for increased sensitivity to infants and children to n-butanol and isobutyl alcohol when used as an inert ingredient in pesticide formulations. For the same reason, a safety factor analysis has not been used to assess risk and, therefore, the additional tenfold safety factor for the protection of infants and children is also unnecessary.

V. Environmental Fate Characterization and Drinking Water Considerations

The Office of Pesticide Programs Environmental Fate and Effects Division (EFED) has reviewed (U.S. EPA 2002) the fate and environmental effects of the aliphatic alcohols by reviewing the available data and considering Structure Activity Relationships (SAR). As a group, the C1 through C4 alcohols, which includes n-butanol and isobutyl alcohol, are very highly water soluble and very mobile in terrestrial and aquatic environments, moving mainly with the water phase to surface and groundwater. Volatility from soil (vapor pressure for n-butanol and isobutyl alcohol, respectively, are 7.0 and 10.5 mm Hg) and water (Henry's Law constant n-butanol and isobutyl alcohol, respectively, are 8.81×10^{-6} and 9.78×10^{-6} atm-m^3/mole @ 25°C) and microbially-mediated degradation are expected to limit transport to surface and ground water from applications or releases to land, with biodegradation being the major route of environmental degradation. (U.S. EPA 2002) IPCS (1987a) also points out that n-butanol and isobutyl alcohol are readily biodegradable and that these alcohols do not bioaccumulate.

Transformation and/or degradation via hydrolysis and direct soil and water photolysis is not an important pathway. Fugacity modeling predicts approximately 50% of releases will be associated with the water phase and 40% with soils. Predicted dissipation half-lives range from 2.5 to 3.5 days in rivers and 30 to 40 days in lakes. These data suggest that n-butanol and isobutyl alcohol are not persistent in the environment. (U.S. EPA 2002)

n-Butanol and isobutyl alcohol may contaminate shallow aquifer groundwater; however, biologically-mediated degradation in both aerobic and anaerobic conditions will limit loadings, thus concentrations. Based on the high volatility of most aliphatic alcohols and aeration sequences used in many drinking water utilities, it is unlikely that most of these compounds will be found in treated water at concentrations equivalent to those in the environment. Available ambient water monitoring data indicate that many short chain aliphatic alcohols are found in surface water in the low- to mid-ppb range. There are no ambient water quality criteria or drinking water maximum contaminant or health advisory levels for any of the aliphatic alcohols. (U.S. EPA, 2002)

VI. Exposure Assessment

EPA expects that exposure to n-butanol and isobutyl alcohol would primarily be through the oral route, via consumption of agricultural crops to which this inert ingredient has been applied as a solvent or cosolvent. Additional exposure may occur in the residential setting through the butanols' use in pesticide products used in and around the home. Residential exposure is expected primarily through the inhalation and dermal routes.

Food and Drinking Water

As an inert ingredient of pesticide products that are applied to growing crops, RACs after harvest, or to animals, potential human exposure would be via the oral route, through consumption of food to which an n-butanol or isobutyl alcohol containing pesticide product has been applied, or through drinking water. EPA expects that such exposure would be low—both n-butanol and isobutyl alcohol are readily biodegradable and do not bioaccumulate (IPCS 1987a).

n-Butanol and isobutyl alcohol occur naturally as a product of fermentation of carbohydrates. JECFA, the Joint World Health Organization (WHO)/Food And Agriculture Organization (FAO), reports that linear saturated aliphatic alcohols, which include n-butanol and isobutyl alcohol, are ubiquitous in nature; they have been detected in almost every known fruit and vegetable (IPCS 1998). As shown in Table 6, both alcohols have been detected in a wide-variety of foods. Concentrations of isobutyl alcohol in a number of common food items (e.g., nonalcoholic beverages, ice cream, beans) range from 0.04 to 34 mg/L (which is approximately equal to 0.04 to 34 mg/kg); EPA would expect to see similar results for n-butanol. For alcoholic beverages, concentrations of isobutyl alcohol are reported as high as 1,000 mg/L.

In addition to their natural occurrence, FDA permits n-butanol and isobutyl alcohol to be deliberately added to food "in the minimum quantity required to produce their intended effect." And, JECFA has evaluated the use of n-butanol and isobutyl alcohol as an extraction solvent and flavoring agent (IPCS 2001a and 2001b).

Table 6. n-Butanol and Isobutyl Alcohol Found in Foods

Food	Concentration in Food	Reference
n-Butanol		
Volatile emissions of roasted filberts	identified but not quantified	as reported in NIH 2005
Volatile emissions of raw beef	identified but not quantified	as reported in NIH 2005
Volatile emissions of hot dogs	identified but not quantified	as reported in NIH 2005
Volatile emissions of roasted almonds	identified but not quantified	as reported in NIH 2005
Beer	identified but not quantified	as reported in IPCS 1987a
Grape and apple brandies	identified but not quantified	as reported in IPCS 1987a
Wine	identified but not quantified	as reported in IPCS 1987a
Whisky	identified but not quantified	as reported in IPCS 1987a
Volatiles of hops	identified but not quantified	as reported in IPCS 1987a
Volatiles of jack fruit	identified but not quantified	as reported in IPCS 1987a
Volatiles of heat-treated milks	identified but not quantified	as reported in IPCS 1987a
Volatiles of muskmelon	identified but not quantified	as reported in IPCS 1987a
Volatiles of southern pea seed	identified but not quantified	as reported in IPCS 1987a
Volatiles of cooked rice	identified but not quantified	as reported in IPCS 1987a
Deep frying of corn and cottonseed oil	identified but not quantified	as reported in IPCS 1987a
Deep frying of trilinolein and triolein	identified but not quantified	as reported in IPCS 1987a
Isobutyl Alcohol		
Apples	identified but not quantified	as reported in NIH 2005
Prickly pear pads	identified but not quantified	as reported in NIH 2005
Dried bonito	identified but not quantified	as reported in NIH 2005
Coffee	identified but not quantified	as reported in IPCS 1987a
Cider	identified but not quantified	as reported in IPCS 1987a
Cheddar cheese	identified but not quantified	as reported in IPCS 1987a
Hop oil	identified but not quantified	as reported in IPCS 1987a
Volatiles of potatoes in storage	identified but not quantified	as reported in NIH 2005
Volatiles from ripening bananas	identified but not quantified	as reported in NIH 2005
Volatiles from raw and roasted almonds	identified but not quantified	as reported in NIH 2005
Wine	up to 1000 mg/L	as reported in NIH 2005
Distilled alcoholic beverages	up to 1000 mg/L	as reported in NIH 2005
Whiskeys	up to 1000 mg/L	as reported in NIH 2005
Nonalcoholic beverages	12 mg/L	as reported in NIH 2005
Ice cream	7.0 mg/L	as reported in NIH 2005
Candy	34 mg/L	as reported in NIH 2005
Baked goods	32 mg/L	as reported in NIH 2005
Cream	4.0 mg/L	as reported in NIH 2005
Beans	0.07 mg/L	as reported in NIH 2005
Split peas	0.14 mg/L	as reported in NIH 2005
Lentils,	0.10 mg/L	as reported in NIH 2005
Soybeans	1.1 to 26 mg/L	as reported in NIH 2005

Residential

Residential exposure is expected to occur through the dermal and inhalation routes. Consumer pesticide products where n-butanol and/or isobutyl alcohol is used as an inert ingredient include those for: home vegetable gardens; lawns (including golf courses); ornamental plants such as shrubs, flowers, and trees; home indoor and outdoor surfaces such as crack and crevice treatment, carpets, and garbage areas; antifouling paint; and home sanitizers. According to the U.S. National Institutes of Health (NIH) National Household Products Database (NIH 2004b), the highest concentration of n-butanol and isobutyl alcohol in a consumer product is 4%.

To estimate worst-case residential indoor inhalation exposure, EPA modeled a scenario where an aerosol paint product contained 10% of either alcohol and was sprayed for 20 minutes in an enclosed utility room. To estimate worst-case dermal exposure, EPA modeled a scenario where indoor-use of latex paint contained 10% of either alcohol. Using E-FAST[8] (U.S. EPA 2004d) and standard model assumptions (runs are provided in Appendix A), EPA determined that the Average Daily Concentration (which is an exposure metric for inhalation exposure) for either n-butanol or isobutyl alcohol would be 0.2 mg/m^3 (0.07 ppm); for dermal exposure, the Average Daily Dose (which is an exposure metric for dermal exposure) is 0.01 mg/kg/day. Provided in Table 7 is a summary of the E-Fast results.

Table 7. Representative Residential-Use Product Containing n-Butanol and Isobutyl Alcohol as an Inert Ingredient (NIH 2004b)

Exposure Route	E-FAST Scenario Used to Model Exposure	Percent n-Butanol or Isobutyl Alcohol	Exposure[a]
n-Butanol			
Inhalation	Indoor Aerosol Paint	10	0.2 mg/m^3 (0.07 ppm)
Dermal	Latex Paint[b]	10	0.01 mg/kg/day
Isobutyl Alcohol			
Inhalation	Indoor Aerosol Paint	10	0.2 mg/m^3 (0.07 ppm)
Dermal	Latex Paint[b]	10	0.01 mg/kg/day

[a]For inhalation exposure, Average Daily Concentration (mg/m^3 and ppm); for dermal exposure, Average Daily Dose (mg/kg/day).
[b]The "Latex Paint" model run also provides an estimate for inhalation exposure; however, this assessment relies on the inhalation estimate obtained from the "Indoor Aerosol Paint" scenario because it yields a higher, more conservative estimate.

[8]The E-FAST model, which stands for "Exposure and Fate Assessment Screening Tool" is used by EPA's Office of Pollution, Prevention and Toxics to conduct New Chemicals exposure assessment. It was developed to provide screening-level estimates of the concentrations of chemicals released from consumer products. Modeled estimates of concentrations and doses are designed to reasonably overestimate exposures, for use in screening level assessment.

This E-FAST estimate is considered worst-case for several reasons: (1) in the E-FAST run, a higher than expected concentration was assumed (10%) and it is unlikely that all indoor residential-use products containing n-butanol or isobutyl alcohol as an inert ingredient have such a concentration; (2) E-FAST is designed as a screening tool with modeled estimates of concentrations and doses designed to reasonably overestimate exposures; and (3) the E-FAST scenarios that would yield the greatest exposures were used. For outdoor-use products, EPA believes that exposure would be no greater than for indoor use and, in fact, is expected to be much less due to the dissipation of n-butanol and isobutyl alcohol into the air.

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 n-butanol and isobutyl alcohol, qualitative assessments for all pathways of human exposure (food, drinking water, and residential) are appropriate given the lack of human health concerns associated with exposure to n-butanol and isobutyl alcohol as inert ingredients in pesticide formulations.

VIII. Cumulative Exposure

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."

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 n-butanol and isobutyl alcohol and any other substances and, n-butanol and isobutyl alcohol do not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has assumed that n-butanol and isobutyl alcohol do 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 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 n-butanol and isobutyl alcohol, EPA has determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to n-butanol and isobutyl alcohol used as inert ingredients in pesticide formulations when considering dietary exposure and all other nonoccupational sources of pesticide exposure for which there is reliable information. Therefore, it is recommended that the two exemptions from the requirement of a tolerance established for residues of n-butanol and the one exemption for isobutyl alcohol be considered reassessed as safe under section 408(q) of FFDCA.

n-Butanol and isobutyl alcohol exhibit low acute toxicity for animals via the dermal, inhalation, and oral routes of exposure (Elvers 1989). Neither alcohol has been shown to be mutagenic or carcinogenic. Developmental and neurotoxic effects were noted; however, effects were only seen at high doses. In the developmental toxicity study where developmental effects were noted, rats were dosed with n-butanol by the oral route (Sitarek et al 1994). Effects were seen, in the absence of maternal toxicity, at 1,000 mg/kg/day (no effects at 300 mg/kg/day). Three developmental toxicity studies conducted by the inhalation route showed no developmental effects at the highest dose tested (Nelson et al 1989; Klimisch and Hellwig 1995). Nelson dosed rats with n-butanol up to 3,500 ppm and Klimisch and Hellwig dosed rats and rabbits with isobutyl alcohol up to 3,300 ppm. In EPA's subchronic oral n-butanol neurotoxicity study, no effects were seen at 125 mg/kg/day (U.S. EPA 2004a); in a similar study for isobutyl alcohol, no effects were seen at 316 mg/kg/day (U.S. EPA 2004b). A subchronic isobutyl alcohol neurotoxicity study conducted by the inhalation route showed no neurotoxic effects at 2,500 ppm (OECD SIDS 2004).

Overall exposure from to the inert use of n-butanol and isobutyl alcohol in pesticide formulations is expected to result in human exposure below any dose level that would produce any adverse effect. Exposure to n-butanol and isobutyl alcohol in food and drinking water is expected via the oral route. Both alcohols occur naturally as a product of fermentation of carbohydrates. JECFA reports that linear saturated aliphatic alcohols, which include n-butanol and isobutyl alcohol, are ubiquitous in nature; they have been detected in almost every known fruit and vegetable (IPCS 1998). In addition to their natural occurrence, n-butanol and isobutyl alcohol are deliberately added to foods. FDA permits both alcohols to be added to foods as a flavoring substance and adjuvant. Specific limits are not stipulated, though the regulation permitting this use (40 CFR 172.515) does say that synthetic flavoring substances and adjuvants "used in food in the minimum quantity required to produce their intended effect...." JECFA has evaluated the use of n-butanol and isobutyl alcohol as an extraction solvent and flavoring agent. They reported that there is no "safety concern at current levels of intake when used as a flavouring agent" (IPCS 2001a and 2001b). Finally, EPA does not expect to find n-butanol and isobutyl alcohol in drinking water at levels that would be of concern. Both alcohols degrade readily in aerobic and anaerobic conditions. And, based on the high volatility of most aliphatic alcohols and aeration

sequences used in many drinking water utilities, it is unlikely that most of these compounds will be found in treated water at concentrations equivalent to those in the environment.

To gain some understanding of the magnitude of an individual's worst-case exposure in a residential setting, EPA modeled indoor inhalation exposure using E-FAST (U.S. EPA 2004d). Assuming the person would be using an aerosol paint in an enclosed room for 20 minutes, exposure is estimated at 0.07 ppm (0.2 mg/m^3); this estimate is the same for n-butanol and isobutyl alcohol. Considering the toxicity levels where no effects were reported (3,500 ppm for n-butanol and 820 ppm for isobutyl alcohol), the estimated level of exposure in a residential setting is far below the level where any toxic effects would be seen.

Thus, based on n-butanol and isopropyl alcohol's low toxicity and low exposure, it is recommended that the two exemptions from the requirement of tolerances established for residues of n-butanol (40 CFR 180.910 and 40 CFR 180.930) and the one tolerance established for isobutyl alcohol (40 CFR 180.920) can be considered reassessed as safe under section 408(q) of FFDCA.

X. Ecotoxicity and Ecological Risk Characterization

EFED finds that, based on their ecotoxicity estimates, n-butanol and isobutyl alcohol are practically nontoxic on an acute basis, both to aquatic species and animals. For freshwater and marine/estuarine fish, *Daphnia magna*, mysid shrimp, and green algae estimated acute toxicity is greater than 100 mg/L. Terrestrial animal acute toxicity based on available rat data show that n-butanol and isobutyl alcohol are practically nontoxic. Chronic toxicity for fish is estimated to be from 70 mg/L to >100 mg/L. (U.S. EPA 2002)

REFERENCES

ECETOC. 2003. ECETOC JACC No. 41: n-Butanol. European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) Joint Assessment of Commodity Chemicals (JACC) programme. Brussels.

Elvers, B.; et al. 1989. Ullman's Encyclopedia of Industrial Chemistry, 5th edition.

IPCS. 1987a. Environmental Health Criteria 65—Butanols: Four Isomers. United Nations Environment Programme. International Programme on Chemical Safety. World Health Organization. http://www.inchem.org/documents/ehc/ehc/ehc65.htm

IPCS. 1987b. 1-Butanol Health And Safety Guide No. 3. United Nations Environment Programme. International Programme on Chemical Safety. World Health Organization. 1987. http://www.inchem.org/documents/hsg/hsg/hsg003.htm

IPCS. 1987c. Isobutanol Health And Safety Guide No. 9. United Nations Environment Programme. International Programme on Chemical Safety. World Health Organization. 1987. http://www.inchem.org/documents/hsg/hsg/hsg009.htm

IPCS. 1998. Safety Evaluation of Certain Food Additives and Contaminants. WHO Food Additives Series 40. Saturated Aliphatic Acyclic Linear Primary Alcohols, Aldehydes, and Acids. United Nations Environment Programme. International Programme on Chemical Safety. World Health Organization. Prepared by: The forty-ninth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). 1988. http://www.inchem.org/documents/jecfa/jecmono/v040je10.htm

IPCS. 2001a. Summary of Evaluations Performed by the Joint FAO/WHO Expert Committee on Food Additives: Butyl Alcohol. United Nations Environment Programme. International Programme on Chemical Safety. World Health Organization. November 12, 2001. http://www.inchem.org/documents/jecfa/jeceval/jec_223.htm

IPCS. 2001b. Summary of Evaluations Performed by the Joint FAO/WHO Expert Committee on Food Additives: Isobutyl Alcohol. United Nations Environment Programme. International Programme on Chemical Safety. World Health Organization. November 12, 2001. http://www.inchem.org/documents/jecfa/jeceval/jec_1009.htm

Klimisch HJ and Hellwig J. 1995. Studies on the Prenatal Toxicity of 3-Methyl-1-Butanol and 2-Methyl-1-Propanol in Rats and Rabbits Following Inhalation Exposure. Fundam Appl Toxicol. 1995 Aug;27(1):77-89.

Li AA; Thake DC; Kaempfe TA; Branch DK; O'Donnell P; Speck FL; Tyler TR; Faber WD; Jasti SL; Ouellette R; and Banton MI. 1999. Neurotoxicity Evaluation of Rats After Subchronic Inhalation Exposure to Isobutanol. Neurotoxicology. 1999 Dec;20(6):889-900

Lington AW and Bevan C. 1991. Alcohols, in Patty's Industrial Hygiene and Toxicology. Wiley.

Merck. 2005. The Merck Index Online^{SM}. 2005 Merck & Co., Inc.

Müller W; Engelhart G; Herbold B; Jackh R; and Jung R. 1993. Evaluation Of Mutagenicity Testing With Salmonella Typhimurium TA102 In Three Different Laboratories. Environ Health Perspect. 1993 Oct;101 Suppl 3:33-6.

Nelson BK; Brightwell WS; Khan A; Burg JR; and Goad PT. 1989. Lack of Selective Developmental Toxicity of Three Butanol Isomers Administered By Inhalation to Rats. Fundam Appl Toxicol. 1989 Apr;12(3):469-79.

NIH. 2004a. ChemID Plus. U.S. Department of Health and Human Services. National Institutes of Health, Department of Health & Human Services. U.S. National Library of Medicine. September 9, 2004. http://chem.sis.nlm.nih.gov/chemidplus/

NIH. 2004b. Household Products Database. U.S. Department of Health and Human Services. National Institutes of Health, Department of Health & Human Services. U.S. National Library of Medicine. Specialized Information Services last update: May 12, 2004. http://householdproducts.nlm.nih.gov/

NIH. 2005. Hazardous Substances Data Bank. U.S. Department of Health and Human Services. National Institutes of Health, Department of Health & Human Services. U.S. National Library of Medicine. last modified: January 13, 2005. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB

NIOSH. 1995. U.S. Department of Health and Human Services. Centers for Disease Control. National Institute for Occupational Health and Safety. "International Chemical Safety Cards." March 13, 1995. ICSC # 111 http://www.cdc.gov/niosh/ipcsneng/neng0111.html

OECD SIDS. 2001. SIDS Initial Assessment Report For SIAM 13: n-Butyl Alcohol. November 6-9, 2001. Bern, Switzerland. http://cs3-hq.oecd.org/scripts/hpv/

OECD SIDS. 2004. SIDS Initial Assessment Report For SIAM 19: Isobutanol. October 19-22, 2004. Berlin, Germany. http://cs3-hq.oecd.org/scripts/hpv/

Pohanish, RP, editor. 2002. Sittig's Handbook of Toxic and Hazardous Chemicals and Carcinogens, 4th edition. Volume 1. Noyes Publications. New York.

Schilling K; Kayser M; Deckardt K; Kuttler K; and Klimisch HJ. 1997. Subchronic Toxicity Studies of 3-Methyl-1-Butanol and 2-Methyl-1-Propanol in Rats. Hum Exp Toxicol. 1997 Dec;16(12):722-6.

Sitarek K; Berlinska B; and Baranski B. 1994. Assessment Of The Effect Of n-Butanol Given to Female Rats in Drinking Water on Fertility and Prenatal Development of Their Offspring. Int J Occup Med Environ Health. 1994;7(4):365-70.

U.S. EPA. 1989. Health and Environmental Effects Document for 1-Butanol. U.S. Environmental Protection Agency. Office of Health and Environmental Assessment. Cincinnati, OH. EPA 500/ECAO-CIN-G062.

U.S. EPA. 1994. Chemical Summary For 1-Butanol. Office of Pollution Prevention and Toxics. United States Environmental Protection Agency. August 1994. EPA 749-F-94-007a. http://www.epa.gov/chemfact/s_butano.txt

U.S. EPA. 2002. Memo from Sid Abel, Environmental Fate and Effects Division to Kathryn Boyle. "Tolerance Review of Compounds Known as Aliphatic Alcohols of the C1 to C18 Category as Inert Ingredients in Terrestrial and/or Aquatic Agricultural and Non-Agricultural Uses. May 3, 2002.

U.S. EPA. 2004a. n-Butanol (CASRN 71-36-3). IRIS Database for Risk Assessment. National Center for Environmental Assessment. Office of Research and Development. U.S. Environmental Protection Agency. Last website update: November 18, 2004. http://www.epa.gov/iris/subst/0140.htm

U.S. EPA. 2004b. Isobutyl Alcohol (CASRN 78-83-1). IRIS Database for Risk Assessment. National Center for Environmental Assessment. Office of Research and Development. U.S. Environmental Protection Agency. Last website update: November 18, 2004. http://www.epa.gov/iris/subst/0169.htm

U.S. EPA. 2004c. Glossary of IRIS Terms. Last website update: November 18, 2004. http://www.epa.gov/iris/gloss8.htm

U.S. EPA. 2004d. Exposure, Fate Assessment Screening Tool. Office of Pollution Prevention and Toxics. U.S. Environmental Protection Agency. Last website update: May 25, 2004. http://www.epa.gov/opptintr/exposure/docs/efast.htm

U.S. EPA. 2005. Complete Listing of Testing Results. Chemical Information Collection and Data Development (Testing). Office of Pollution Prevention & Toxics (OPPT). U.S. Environmental Protection Agency. last update: June 20, 2005. http://www.epa.gov/oppt/chemtest/

APPENDIX A: E-FAST Results for n-Butanol and Isobutyl Alcohol

Note: Only the results for n-butanol are presented; the estimates for isobutyl alcohol are the same as for n-butanol.

Latex Paint (dermal exposure): Inputs

CEM Inputs

ID Number: But Latex

Product: Unknown

Chemical Name: n-Butanol

Scenario: Latex Paint

Population: Adult

Molecular Weight (g/mole): 74.12

Vapor Pressure (torr): 7

Weight Fraction - Median (unitless): 0.1

Weight Fraction - 90% (unitless): 0.1

Inhalation Inputs

Frequency of Use (events/yr): 4

Years of Use: 11

Mass of Product Used per Event - Median (g): 3635

Mass of Product Used per Event -90% (g): 1.272e+04

Inhalation Rate During Use (m^3/hr): 0.55

Duration of Use - Median (hours/event): 3

Inhalation Rate After Use (m^3/hr): 0.55

Duration of Use - 90% (hours/event): 8

Zone 1 Volume (m^3): 40

Whole House Volume (m^3): 369

Air Exchange Rate (air exchanges/hr): 0.45

Body Weight (kg): 71.8

Activity Patterns

User: 111111123111111112744411

Start Time: 10

Non-User: 111111113244247742274441 1

Room of Use: 1. Bedroom

Hour: 0 6 12 18

Dermal Inputs

Frequency of Use - Body (events/yr): 4

SA/BW - Body (cm2/kg): 4.5

Amount Retained/Absorbed to Skin (g/cm^2-event): 0.00232

Average Time, $LADD_{pot}$, $LADC_{pot}$ (days): 2.74e+04

Average Time, ADD_{pot}, ADC_{pot} (days): 4.02e+03

Average Time, ADR_{pot}, Cp_{pot} (days): 1.00e+00

Latex Paint (dermal exposure): Outputs

CEM Dermal Exposure Estimates

ID Number: But Latex

Scenario: Latex Paint Population: Adult

Years of Use (years): 11

SA/BW Body (cm^2/kg): 4.5

Frequency of Use (events/year): 4

Exposure Units	Result	AT (days)
Chronic Cancer		
$LADD_{pot}$ (mg/kg-day)	1.68e-03	2.74e+04
Chronic Non-Cancer		
ADD_{pot} (mg/kg-day)	1.14e-02	4.02e+03
Acute		
ADR_{pot} (mg/kg-day)	1.04e+00	1.00e+00

LADD - Lifetime Average Daily Dose (mg/kg-day)

ADD - Average Daily Dose (mg/kg-day)

ADR - Acute Dose Rate (mg/kg-day)

Note: 75 years = 2.738e+04 days pot - potential dose

Note: The general Agency guidance for assessing short-term, infrequent events (for most chemicals, an exposure of less than 24 hours that occurs no more frequently than monthly) is to treat such events as independent, acute exposures rather than as chronic exposure. Thus, estimates of long-term average exposure like ADD or ADC may not be appropriate for use in assessing risks associated with this type of exposure pattern. (Methods for Exposure-Response Analysis for Acute Inhalation Exposure to Chemicals (External Review Draft). EPA/600/R-98/051. April 1998

Aerosol Paint (inhalation exposure): Inputs

CEM Inputs

ID Number: But Aero

Product: Unknown

Chemical Name: n-Butanol

Scenario: Aerosol Paint

Population: Adult

Molecular Weight (g/mole): 74.12

Vapor Pressure (torr): 7

Weight Fraction - Median (unitless): 0.1

Weight Fraction - 90% (unitless): 0.1

Inhalation Inputs

Frequency of Use (events/yr): 6

Years of Use: 11

Mass of Product Used per Event - Median (g): 227

Mass of Product Used per Event -90% (g): 738

Inhalation Rate During Use (m^3/hr): 0.55

Duration of Use - Median (hours/event): 0.333

Inhalation Rate After Use (m^3/hr): 0.55

Duration of Use - 90% (hours/event): 1

Zone 1 Volume (m^3): 20

Whole House Volume (m^3): 369

Air Exchange Rate (air exchanges/hr): 0.45

Body Weight (kg): 71.8

Portion of Aerosol in Air (unitless): 0.01

Activity Patterns

User: 1 1 1 1 1 1 1 2 3 5 5 4 2 4 6 7 4 2 2 7 4 4 4 1

Start Time: 9

Non-User: 1 1 1 1 1 1 1 1 3 2 4 4 2 4 7 7 4 2 2 7 4 4 4 1

Room of Use: 5. Utility Room

Hour: 0 6 12 18

Dermal Inputs

There are no Dermal inputs for this scenario.

Average Time, $LADD_{pot}$, $LADC_{pot}$ (days): 2.74e+04

Average Time, ADD_{pot}, ADC_{pot} (days): 4.02e+03

Average Time, ADR_{pot}, Cp_{pot} (days): 1.00e+00

Aerosol Paint (inhalation exposure): Outputs

CEM Inhalation Exposure Estimates

ID Number: But Aero

Scenario: Aerosol Paint	Population: Adult
Inhalation Rate (m^3/day): 0.55	Years of Use (years): 11
Body Weight (kg): 71.8	Frequency of Use (events/year): 6

Exposure Units	Result	AT (days)
Chronic Cancer		
$LADD_{pot}$ (mg/kg-day)	6.48e-03	2.74e+04
$LADC_{pot}$ (mg/m^3)	3.52e-02	2.74e+04
Chronic Non-Cancer		
ADD_{pot} (mg/kg-day)	4.42e-02	4.02e+03
ADC_{pot} (mg/m^3)	2.40e-01	4.02e+03
Acute		
ADR_{pot} (mg/kg-day)	8.66e+00	1.00e+00
Cp_{pot} (mg/m^3)	8.49e+02	1.00e+00

LADD - Lifetime Average Daily Dose (mg/kg-

LADC - Lifetime Average Daily Concentration

ADD - Average Daily Dose (mg/kg-day)

ADC - Average Daily Concentration (mg/m^3)

ADR - Acute Dose Rate (mg/kg-day)

Cp - Peak Concentration (mg/m^3)

Note: 75 years = 2.738e+04 days

pot - potential dose

Note: The general Agency guidance for assessing short-term, infrequent events (for most chemicals, an exposure of less than 24 hours that occurs no more frequently than monthly) is to treat such events as independent, acute exposures rather than as chronic exposure. Thus, estimates of long-term average exposure like ADD or ADC may not be appropriate for use in assessing risks associated with this type of exposure pattern. (Methods for Exposure-Response Analysis for Acute Inhalation Exposure to Chemicals (External Review Draft). EPA/600/R-98/051. April 1998