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

OFFICE OF PREVENTION,
PESTICIDES, AND TOXIC SUBSTANCES

DATE: April 27, 2006

ACTION MEMORANDUM

SUBJECT: Inert Reassessment—Three Exemptions from the Requirement of a Tolerance for Ethyl Alcohol (CAS #64-17-5)

FROM: Pauline Wagner, Chief Pauline Wagner 4/27/06
Inert Ingredient Assessment Branch

TO: Lois A. Rossi, Director
Registration Division

I. FQPA REASSESSMENT ACTION

Action: Reassessment of three inert exemptions from the requirement of a tolerance. The tolerance exemptions are to be maintained.

Chemical: Ethyl alcohol (ethanol)

CFR: 40 CFR parts 180.910 (ethyl alcohol); 180.930 (ethyl alcohol); and 180.940 (ethanol)

CAS #: 64-17-5

Use Summary: The main use of ethyl alcohol is in the consumption of alcoholic beverages. Other uses are as a solvent in the laboratory and industry, and in the manufacture of denatured alcohol, pharmaceuticals, perfumes, and organic synthesis. Household products that contain ethyl alcohol as a solvent include: car waxes; home cleaning products such as detergents and fresheners; home maintenance items such as adhesives, sealers, and shellacs; and personal care products such as insect repellants, body sprays, perfumes, deodorant, makeup, mouthwash, wipes, and hair products; and pet care products. As a inert ingredient in pesticide formulations, ethyl alcohol is used as a solvent or cosolvent; and in food-contact surface sanitizing solutions.

List Reclassification Determination: Ethyl alcohol will remain on List 4B (i.e., it is not being reclassified).

II. MANAGEMENT CONCURRENCE

I concur with the reassessment of the three exemptions from the requirement of a tolerance for the inert ingredient ethyl alcohol or ethanol (CAS# 64-17-5) and with the List reclassification determinations, as described above. I consider the three exemptions established in 40 CFR parts 180.910, 180.930, and 180.940 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

5/3/06

Date:

cc: Debbie Edwards, SRRD
Joe Nevola, SRRD

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MEMORANDUM

SUBJECT: Reassessment of the Three Exemptions from the Requirement of a Tolerance for Ethyl Alcohol (CAS Reg. No. 64-17-5)

FROM: Kathleen Martin, Chemist Kathleen C. Martin 4/27/06.
Inert Ingredient Assessment Branch
Registration Division (7505C)

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

BACKGROUND

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

EXECUTIVE SUMMARY

This report provides a qualitative risk assessment for ethyl alcohol, a pesticide inert ingredient for which three tolerances exist for its residues when used in pesticide formulations applied to: growing crops or raw agricultural commodities after harvest (40 CFR 180.910); animals (40 CFR 180.930); or antimicrobial pesticide formulations (40 CFR 180.940). As such, ethyl alcohol is used as a solvent or cosolvent; or a food-contact surface sanitizing product. While EPA is aware that ethyl alcohol is a commonly-consumed alcoholic beverage, only ethyl alcohol's use as an inert ingredient is addressed in this risk assessment.

Ethyl alcohol is produced by the fermentation of organic material in the presence of microorganisms. According to Casarett and Doull (1986), there "is probably greater exposure to ethanol than to any other solvent with the exception of water." Exposure to

ethyl alcohol is ubiquitous. It occurs naturally in the human body at low levels (<0.1 mg/dL), most likely due to the action of microflora upon food in the intestine (Irvine 2003, citing the work of Sprung et al 1991). Ethyl alcohol also occurs naturally in certain fruits. Dudley (2002) reports that certain fruits manifest ethyl alcohol concentrations up to 12%. The U.S. Food and Drug Administration allows ethyl alcohol to be used as a direct food additive. Industrially, ethyl alcohol is used as a solvent and as a material in the manufacture of pharmaceuticals, perfumes, and organic chemicals. Household products that contain ethyl alcohol as a solvent include: car waxes; home cleaning products such as detergents and fresheners; home maintenance items such as adhesives, sealers, and shellacs; personal care products such as insect repellants, body sprays, perfumes, deodorant, makeup, mouthwash, wipes, and hair products; and pet care products (NIH 2004b). In addition, ethyl alcohol is used in gasoline as an octane booster (Merck 2005). But, the single greatest use of ethyl alcohol is as an alcoholic beverage.

Ethyl alcohol is readily absorbed by the oral and inhalation routes, but is minimally-absorbed through the skin. The principal organ responsible for the metabolism of ethyl alcohol is the liver. Ethyl alcohol is of low acute toxicity by all routes of exposure (Toxicity Category IV). At exposure levels expected for the use of ethyl alcohol as an inert ingredient in pesticide products, developmental and reproductive toxicity is not expected and the young are not expected to be more sensitive to its effects than adults. Thus, an additional tenfold safety factor for the protection of infants and children was not deemed necessary.

Allowable pesticidal uses of the inert ingredient include agricultural and antimicrobial products which provide exposures via the oral, dermal, or inhalation routes. Exposure via the oral route; however, is expected to be low, especially since ethyl alcohol is volatile and biodegradable therefore residues on food would be minimal. Dermal and inhalation exposure is also expected to be low based on worst-case modeled exposure estimates. Measurable concentrations in drinking water are not expected based on the rather rapid aerobic degradation on soils and in surface and ground water. In addition, concentrations entering a treatment plant will likely be reduced by various oxidation processes such as chlorination, ozonation, and ultraviolet (UV) radiation disinfection.

Taking into consideration all available information on ethyl alcohol, EPA has determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to ethyl alcohol when used as an inert ingredient 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 inert use of ethyl alcohol is expected to result in human exposure below any dose level that would produce any adverse effect. Therefore, it is recommended that the three exemptions from the requirement of a tolerance established for residues of ethyl alcohol in can be considered reassessed as safe under section 408(q) of Federal Food, Drug, and Cosmetic Act (FFDCA).

I. Introduction

This report evaluates ethyl alcohol, a pesticide inert ingredient for which three exemptions from the requirement of a tolerance exist for its residues when used in pesticide formulations applied to: growing crops or raw agricultural commodities after harvest (40 CFR 180.910); animals (40 CFR 180.930); or antimicrobial pesticide formulations (40 CFR 180.940).

Ethyl alcohol is produced by the fermentation of organic material in the presence of microorganisms. For example, alcoholic beverages are made by fermenting fruit juices in the presence of *Saccharomyces cerevisiae* and fuel is manufactured by fermenting agricultural wastes (Tortora 2001). According to Casarett and Doull (1986), there "is probably greater exposure to ethanol than to any other solvent with the exception of water. Exposure to ethyl alcohol is ubiquitous. It occurs naturally in the human body at low levels (<0.1 mg/dL), most likely due to the action of microflora upon food in the intestine (Irvine 2003, citing the work of Sprung et al 1991). Ethyl also occurs naturally in certain fruits. Dudley (2002) reports that agricultural fruits and fruit residues in domesticated plants manifest ethyl alcohol concentrations up to 12%. The U.S. Food and Drug Administration (FDA) allows ethyl alcohol to be used as a direct food additive. Industrially, ethyl alcohol is used as a solvent and as a material in the manufacture of pharmaceuticals, perfumes, and organic chemicals. But, the single greatest use of ethyl alcohol is as an alcoholic beverage.

The following risk assessment focuses only on the use of ethyl alcohol as an inert ingredient in pesticide formulations. EPA is aware that this chemical is a commonly-consumed beverage. However, only ethyl alcohol's use as an inert ingredient is addressed in this risk assessment.

II. Use Information

A. Pesticides

As an inert ingredient, ethyl alcohol is used as a solvent or cosolvent in pesticide products used in agricultural or in antimicrobial formulations used in food-contact surface sanitizing solutions. The specific tolerance exemptions for the inert ingredient ethyl alcohol are provided in Table 1 below.

Table 1. Exemptions from the Requirement of a Tolerance Being Reassessed in this Document

Citation as it Appears in the CFR				CAS Registry Number and 9CI Name
40 CFR 180	Tolerance Exemption Expression	Limits	Uses	
.910[a]	Ethyl alcohol	(none)	Solvent, cosolvent	64-17-5 Ethanol
.930[b]	Ethyl alcohol	(none)	Solvent, cosolvent	
.940[c]	Ethanol	None	Food-contact surface sanitizing solutions	

[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 raw agricultural commodities 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 180.940 are exempted from the requirement of a tolerance when used in accordance with good manufacturing practice as ingredients in an antimicrobial pesticide formulation, provided that the substance is applied on a semi-permanent or permanent food-contact surface (other than being applied on food packaging) with adequate draining before contact with food.

B. Other Uses

Human societies have consumed alcoholic beverages since the beginning of recorded time (Room et al 2005). In fact, this is the greatest use of ethyl alcohol. Industrially, ethyl alcohol is used as a solvent in the laboratory and in manufacturing. It is also used as a material is the production of pharmaceuticals, perfumes, and organic chemicals. In addition, ethyl alcohol is used in gasoline as an octane booster (Merck 2005).

Household products that contain ethyl alcohol as a solvent include: car waxes; home cleaning products such as detergents and fresheners; home maintenance items such as adhesives, sealers, and shellacs; personal care products such as insect repellants, body sprays, perfumes, deodorant, makeup, mouthwash, wipes, and hair products; and pet care products (NIH 2004b).

Ethyl alcohol has a number of uses relating to the manufacture and processing of food. The FDA Direct Food Additives related to ethyl alcohol are provided in Table 2.

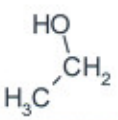
Table 2. FDA Direct Food Additives

Name	21 CFR	Use Pattern
172: Food Additives Permitted For Direct Addition To Food For Human Consumption		
Ethanol	172.340	In the preparation of fish protein isolate.
Ethyl alcohol	172.372	As a processing solvent in the preparation of the food additive N-acetyl-L-methionine.
Ethyl alcohol	172.560	In the preparation of modified hop extract.
173: Secondary Direct Food Additives Permitted In Food For Human Consumption		
Ethanol	173.25	Ion-exchange resins used in the treatment of food.
184: Direct Food Substances Affirmed As Generally Recognized As Safe		
Ethyl alcohol	184.1293	As an antimicrobial agent on pizza crusts prior to final baking at levels not to exceed 2.0 percent by product weight.
Ethyl alcohol	184.1848	In the preparation of butter starter distillate.

III. Physical and Chemical Properties

Some of the physical and chemical characteristics of ethyl alcohol, along with its structure and nomenclature, are found in Table 3.

Table 3. Physical and Chemical Properties of Ethyl Alcohol

Parameter	Value	Reference
Structure		
Common Names	Alcohol, ethyl; Denatured alcohol; Distilled spirits; Ethyl alcohol, undenatured; Ethanol; Ethyl alcohol; Methylcarbinol	http://hpd.nlm.nih.gov/cgi-bin/household/search
CAS #	64-17-5	
Empirical Formula	C_2H_6O	
Molecular Weight	46.1	
Physical State	colorless liquid, with characteristic odor	NIOSH 2000
Melting Point	-117°C	NIOSH 2000
Boiling Point	79°C	NIOSH 2000
Water Solubility	miscible	NIOSH 2000
Relative Density (water=1)	0.8	NIOSH 2000
Relative Vapor Density (air=1)	1.6	NIOSH 2000
Log P_{ow}	-0.32	NIOSH 2000
Vapor Pressure at 25°C	59.3 mm Hg	NIH 2004
Henry's Law Constant at 25°C	5.0×10^{-6} atm-m^3/mole	NIH 2004

IV. Hazard Assessment

A. Hazard Profile

To assess the hazard posed by the use of ethyl alcohol as an inert ingredient EPA relied heavily on the OECD SIDS for Ethanol[1], which was published in conjunction with the United Nations Environment Programme (UNEP 2005). The OECD SIDS document is important to this hazard assessment because first, it is a recently-published assessment but more importantly, it approaches ethyl alcohol from the perspective of an industrial solvent as opposed to a commonly consumed food item (i.e., an alcoholic beverage). The Agency also used its 1995 Reregistration Eligibility Decision (RED) for the Aliphatic Alcohols (EPA 1995)[2] and considered information from EPA's High Production Volume (HPV) Challenge Program (Ethanol HPV 2001b)[3].

B. Toxicological Data

Acute Toxicity

A summary of the acute toxicity data, along with the corresponding 40 CFR 156.62 Acute Toxicity Categories, is provided in Table 4. The main symptoms of acute exposure are those typical of substances which cause central nervous system depression (e.g., inebriation, gait disturbance and dose-related decrease in response to painful stimuli, respiratory depression and coma) (UNEP 2005). Overall, ethyl alcohol is not considered to be acutely toxic.

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[1]OECD, or the Organization for Economic Cooperation and Development, houses the Screening Information Data Set (SIDS) Program which 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 high production volume chemicals. The SIDS data are used to "screen" the chemicals and set priorities for further testing or risk assessment/management activities; priorities are set at the SIDS Meeting (SIAM). Some chemicals are published in conjunction with UNEP Chemicals. The United Nations Environment Programme (UNEP) Chemicals "is the center for all chemicals-related activities of the United Nations Environment Programme."

[2]In 1995 EPA issued a RED for the aliphatic alcohols, which includes ethyl alcohol. The RED was published before the promulgation of the Food Quality Protection Act.

[3]HPV chemicals are those that are manufactured or imported into the United States in volumes greater than one million pounds per year. The goal of the HPV program is to collect and make publicly-available a complete set of baseline health and environmental effects data on such chemicals. Industry sponsors volunteer to evaluate the adequacy of existing data and to conduct tests where needed to fill the gaps in the data, and EPA (and the public) has an opportunity to review and comment on the sponsors' robust summary report. Ethyl alcohol is currently being sponsored by the Ethanol HPV Challenge Consortium; in 2001 they submitted a Test Plan and Robust Summary (Ethanol HPV 2001b). The Consortium points out that because of ethyl alcohol's long history as an element of the human diet, there's a wealth of toxicological information available for this chemical.

Table 4. Summary of Acute Toxicity Data for Ethyl Alcohol

Parameter		Toxicity Value *Toxicity Category*[a]	Toxicity Category	Reference
Oral LD_{50}	rat	>7,000 mg/kg bw	*Toxicity Category IV*	US EPA 1995
	rat	15,000 mg/kg		UNEP 2005, citing Youssef et al 1992
	mouse	>7,000 mg/kg bw		US EPA 1995
	mouse	8,300 mg/kg		UNEP 2005, citing Bartsch et al 1976
LC_{50} Inhalation, mice		an LC_{50} value was not achieved at exposures up to 60,000 ppm ~ 113 mg/L) for 60 minutes	*Toxicity Category IV*	UNEP 2005, citing Moser 1985
		39 mg/L		US EPA 1995
Inhalation, rat		38 mg/L	*Toxicity Category IV*	US EPA 1995
Eye Irritation, rabbit		mild iritis and chemosis	*Toxicity Category IV*	US EPA 1995
Primary Dermal Irritation Study		nonirritating	*Toxicity Category IV*	US EPA 1995

[a]40 CFR 156.62

Subchronic Toxicity

Oral. Rats consuming an average of 10.2 g of ethyl alcohol/kg/day over a 12-week study period showed decreased mean body weights. Also, a high degree of fatty degeneration in the livers was noted. Other than the fatty changes in the liver, no other gross or histopathological changes were observed. (US EPA 1995, citing Kager et al 1974)

Studies (90-day) were conducted in rats and mice to assess whether 5% ethyl alcohol in drinking water would be an appropriate vehicle for a long-term toxicity and carcinogenicity study of urethane. Based on the water consumption data in the study and average body weights over the exposure period, this equated to doses of at least 4,000 mg/kg in rats and 7,500 mg/kg in mice. Data from this study yielded NOAEL values of >5% for male rats and female mice (dose equivalent >4,000 mg/kg) and <5% for male mice and female rats (dose equivalent <5,000 mg/kg). Male rats showed minor changes to organ weights and hematology/biochemistry; female rats showed minor biochemistry changes and increased length of estrus cycle along with liver nodules; male mice showed increased organ weights and some fatty changes to the liver and a decrease in sperm concentration. (UNEP 2005, citing NTP 1996)

Inhalation. In a 90-day aerosol inhalation study, several species of animals (rats, guinea pigs, rabbits, monkeys and dogs) were exposed continuously to ethyl alcohol vapors at 86 mg/m^3 (equivalent to 46 ppm). No deaths or clinical signs of toxicity were observed during the study; all hematology results were within normal limits. Histopathology findings were negative also. (US EPA 1995 citing Coon et al 1970)

Chronic Toxicity

In the two-year study in mice that followed the above 90-day National Toxicology Program[4] (NTP) study, ethyl alcohol caused a marginal exposure-related increase in survival in males but had no effect on the survival of females. There was evidence of an ethyl alcohol-induced reduction in water consumption that was more marked in males than in females. (UNEP 2005, citing NTP 2002)

Mutagenicity

There are numerous studies in the published literature on the mutatgenicity of ethyl alcohol, both *in vivo* and *in vitro*. Provided in the OECD SIDS for Ethanol (UNEP 2005) is a summation of the available data arrayed by the following titles: Bacterial Mutation Assays, Chromosome Aberration Tests, Cell Mutation Assays, Micronucleus Assays, Chromosome Aberration Tests, and Dominant Lethal Assays; they are not listed in this report.

Based on the results of these studies, UNEP (2005) finds that there is very little evidence to suggest that ethyl alcohol is genotoxic in somatic cells. It may have a very limited capacity to induce genetic changes *in vivo* but only under very specific circumstances and at very high doses, doses which would be achieved in humans only by deliberate oral ingestion (UNEP 2005, citing Phillips 2001).

Carcinogenicity

In animals, ethyl alcohol is not expected to be carcinogenic. In an experiment where rats were provided a liquid diet containing 1% or 3% ethyl alcohol for a period of 104 weeks study investigators concluded that there was no evidence of "carcinogenic activity of ethyl alcohol among Sprague-Daley [sic] rats." (Holmberg and Ekström 1995)

This finding of ethyl alcohol not being carcinogenic in rats is consistent with the findings of IARC (1998). In their monograph on Alcohol Drinking (IARC 1988), they concluded that there is inadequate evidence for the carcinogenicity of ethyl alcohol in experimental animals.[5] However, they did conclude that Alcoholic "beverages are carcinogenic to humans."

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[4]The U.S. Department of Health and Human Services National Toxicology Program (NTP) is an interagency program whose mission is to evaluate agents of public health concern by developing and applying the tools of modern toxicology and molecular biology.

[5]Regarding carcinogenicity in experimental animals, IARC (1998) defines the statement "inadequate evidence of carcinogenicity" to mean "The studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations, or no data on cancer in experimental animals are available."

Developmental and Reproductive Effects

In regard to developmental and reproductive toxicity, the OECD SIDS for Ethanol (UNEP 2005) points out that:

> many of the published studies in laboratory animals have investigated the effects of high-dose oral ethyl alcohol intake. High-dose studies are possible because of the low acute toxicity of ethyl alcohol; however, the use of high doses can cause difficulties when interpreting ethyl alcohol reprotoxicity data within the regulatory hazard assessment framework, because doses are often in excess of the maximum (1g/kg/day) recommended in current chemical testing guidelines (e.g., OECD 414, 416). Many rodent experimental studies are conducted using a 5% ethyl alcohol liquid diet, which provides 35-36% ethyl alcohol-derived calories. The achieved ethyl alcohol intake for a pregnant rat with this diet is approximately 10-12 g/kg/day (i.e., >10 times the limit dose of a standard OECD 414 developmental toxicity study). A reduction in nutrient intake during a critical period of gestation would reduce fetal/pup weights and cause other postnatal effects.

They conclude that the "collective weight of evidence is that the NOAEL for developmental effects in animals is high, typically ≥6,400 mg/kg bw, compared to maternally toxic effects at 3,600 mg/kg bw. The potential for reproductive and developmental toxicity exists in humans from deliberate over-consumption of ethanol." Provided below is a summary of available published reproductive and developmental toxicity data.

Oral. In a mouse reproductive study ethyl alcohol was administered to male mice at concentrations of approximately 8.5; 16.0; or 20 g/kg/day; only modest reproductive effects (reduced sperm motility) were seen at only 16.0 g/kg/day (NTP 1985). In another study (Abel 1993, as cited in UNEP 2005) male rats were gavaged with 2 or 3 g ethyl alcohol/kg/day over nine weeks; no effects were seen on fertility. However, the study did reveal higher incidences of runted pups at the 3 g kg/day dose. In a later study by the same investigator (Abel 1995, as cited in UNEP 2005), still no effect on fertility was seen even when male rats were dosed at 5 g/kg/day.

In an oral study, mice were fed a liquid diet from the fifth through the tenth day of gestation in which 17, 25, or 30% of the calories were derived from ethyl alcohol. The incidence of fetal resorptions and congenital malformations increased in a dose-related manner over the range of doses tested. Anomalies included skeletal, neurological, urogenital, and cardiovascular systems. (UNEP 2005, citing Randall 1979 and article abstract from PubMed[6]).

[6]PubMed: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?DB=pubmed

One investigator (Weir 1987, cited in UNEP 2005) used a "teratology probe" (i.e., examination of the uterine contents) and a 'limited' postnatal study in which offspring were examined and weighed through to weaning on postnatal day (PND) 22 to examine the teratogenicity of orally administered ethyl alcohol. Mice were gavaged with ethyl alcohol at 2.2; 3.6; 5.0; 6.4; and 7.8 g/kg/day on gestation days eight through 14. Post-implantation losses were seen at 5 g/kg/day and higher; in the postnatal component of the study, there were no significant effects on pup growth or survival at maternally toxic dose levels.

Inhalation. Nelson (UNEP 2005, citing Nelson 1985 and 1988) exposed rats to ethyl alcohol vapors at concentrations of 10,000 ppm; 16,000 ppm; or 20,000 ppm (which are equivalent to 19,000; 31,000; or 38,000 mg/m^3 respectively) for seven hours/day over six weeks in a developmental toxicity study. Severe maternal effects (narcosis, decreased food consumption) were noted at the high-dose. A small number of fetal effects among males (slight reduced body weights) were observed at the mid- and high-dose levels.

C. Metabolism and Pharmacokinetics

Ethyl alcohol is readily absorbed by the oral and inhalation routes, but is minimally-absorbed through the skin (CCOHS 2004). The metabolism of ethyl alcohol has been well described in the literature. The first step, oxidation to acetaldehyde, may involve various enzymes that act as mediators during alcohol metabolism. Acetaldehyde is further metabolized to acetate. The principal organ responsible for the metabolism of ethyl alcohol is the liver (IPCS 1970). Most ethyl alcohol is metabolized to carbon dioxide and water before it is eliminated (CCOHS 2004; IPCS 1970).

D. Special Considerations for Infants and Children

Ethyl alcohol is of low acute toxicity by all routes of exposure (Toxicity Category IV[7]). At exposure levels expected for the use of ethyl alcohol as an inert ingredient in pesticide products, developmental and reproductive toxicity is not expected and the young are not expected to be more sensitive to its effects than adults. UNEP (2005) points out that the "collective weight of evidence is that the NOAEL for developmental effects in animals is high, typically ≥6,400 mg/kg bw, compared to maternally toxic effects at 3,600 mg/kg bw." Based on this information, there is no concern, at this time, for increased sensitivity to infants and children to ethyl alcohol when used as an inert ingredient in pesticide formulations. For the same reasons, safety factor analysis has not been used to assess the risks resulting from the use of ethyl alcohol; therefore, an additional tenfold safety factor for the protection of infants and children is unnecessary.

[7]40 CFR 156. 156.62 Acute Toxicity Categories

V. Environmental Fate Characterization and Drinking Water Considerations (NIH, no date)

Ethyl alcohol will enter the environment as emissions from its manufacture, use as a solvent and chemical intermediate, and release in fermentation and alcoholic beverage preparation. When applied to land it is likely to volatilize, biodegrade, and leach into the ground water in sandy soils. When released into water it will only slightly volatilize, with biodegradation the dominant dissipation pathway with a half-life of days for primary degradation and days to weeks for mineralization under aerobic and anaerobic conditions. Once released to air, degradation will occur via hydroxyl radical reaction with a half-life of approximately three days. It would not be expected to adsorb to sediment or bioconcentrate in fish.

Measurable concentrations in drinking water are not expected based on the rather rapid aerobic degradation on soils and in surface and ground water. In addition, concentrations entering a treatment plant will likely be reduced by various oxidation processes such as chlorination, ozonation, and ultraviolet (UV) radiation disinfection.

VI. Exposure Assessment

Exposure to ethyl alcohol is ubiquitous. It occurs naturally in the human body at low levels and in certain fruits. The U.S. Food and Drug Administration allows it to be used as a direct food additive. Industrially, ethyl alcohol is used as a solvent and as a material in the manufacture of pharmaceuticals, perfumes, household products, and organic chemicals. In addition, ethyl alcohol is used in gasoline as an octane booster (Merck 2005). But, the single greatest use of ethyl alcohol is as an alcoholic beverage.

Allowable pesticidal uses of the inert ingredient include agricultural and antimicrobial products which provide exposures via the oral, dermal, or inhalation routes. Further details are provided in the inert assessments described below under "Food" and "Residential."

Food

EPA expects that ethyl alcohol would be a naturally-occurring component in certain foods, particularly fruit that is high in its sugar content. Sugars fermented in the presence of yeast produce ethyl alcohol as a by-product. Dudley (2002) reports that agricultural fruits and fruit residues in domesticated plants manifest ethyl alcohol concentrations up to 12%. Two factors affecting the alcohol content are climate (warmer and wetter climates are more conducive to fermentative yeast metabolism) and the degree of ripeness (riper fruit has higher sugar and thus higher ethyl alcohol content).

The National Library of Medicine's Hazardous Substances Data Bank (NIH 2005) reports that several investigators have quantified ethyl alcohol in beans and peas. For example, it has been found in lima, common, mung, and soy beans at an average concentration of 4.2 ppm (4.2 mg/L); split peas 3.6 ppm (3.6 mg/L); and lentils 4.4 ppm (4.4 mg/L).

In addition to its natural occurrence, FDA permits ethyl alcohol to be added to food through its use in food manufacturing and processing. And, JECFA, the Joint World Health Organization (WHO)/Food And Agriculture Organization (FAO) Expert Committee on Food Additives, has evaluated the use of ethyl alcohol as an extraction solvent, carrier solvent, and flavoring agent (IPCS 2001).

In terms of pesticide inert ingredients, ethyl alcohol is used as a solvent in agricultural pesticides and some antimicrobial food-contact surface products. Regarding agricultural pesticides, exposure is expected via the oral route through consumption of food to which an ethyl alcohol-containing pesticide product has been applied. Exposure is expected to be low, especially since ethyl alcohol is volatile and biodegradable, making food residues minimal. And, such residues would not contribute significantly to naturally-occurring levels nor would they be expected to be found in drinking water. Regarding antimicrobial pesticides, exposure is expected via the oral, dermal, and inhalation routes (dermal and inhalation are addressed in the next section). Similar to agricultural pesticides, ethyl alcohol would be expected to quickly evaporate from the surface it has been applied to, leaving little residue.

In summary, EPA expects that exposure resulting from the use of ethyl alcohol as an inert ingredient will be low and insignificant compared to the exposure resulting from intentional human exposure through consumption of alcoholic beverages.

Residential

Household products that contain ethyl alcohol as a solvent include: car waxes; home cleaning products such as detergents and fresheners; home maintenance items such as adhesives, sealers, and shellacs; personal care products such as insect repellants, body sprays, perfumes, deodorant, makeup, mouthwash, wipes, and hair products; and pet care products (NIH 2004b).

Exposure to ethyl alcohol as an inert ingredient in residential-use pesticides is expected via the dermal and inhalation routes, either indoors or outdoors. EPA believes that two types of products represent the range of residential-use products containing ethyl alcohol as an inert ingredient; they are provided in Table 5:

Table 5. Representative Residential-Use Products Containing Ethyl Alcohol as an Inert Ingredient (NIH 2004b)

Product	Percent Ethyl Alcohol	Type of Exposure	Location of Exposure
Insect Repellant	95	dermal, inhalation	outdoor
Disinfectant Spray Cleaner	79	dermal, inhalation	indoor

To estimate worst-case residential indoor inhalation exposure, EPA modeled a scenario where an aerosol paint product contained 95% ethyl alcohol and was sprayed for 20 minutes in an enclosed utility room (i.e., "Indoor Aerosol Paint"). To estimate worst-case dermal exposure, EPA modeled a scenario where indoor-use of latex paint contained 95% ethyl alcohol (i.e., "Latex Paint" scenario). Using E-FAST,[8] which stands for "Exposure and Fate Assessment Screening Tool," (U.S. EPA, 2004d) and standard model assumptions (model results are provided in Appendix A), EPA determined that the Average Daily Concentration (which is an exposure metric for inhalation exposure) for ethyl alcohol would be 2.3 mg/m^3 (1.2 ppm); for dermal exposure, the Average Daily Dose (which is an exposure metric for dermal exposure) is 0.11 mg/kg/day. Provided in Table 6 is a summary of these E-Fast results. Note that 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 ethyl alcohol's ability to quickly evaporate. In a six-week developmental toxicity study via the inhalation route (UNEP 2005, citing Nelson 1985 and 1988), no effects were seen at 19,000 mg/m^3, which is well above the modeled exposure estimate. EPA did not identify a subchronic or chronic dermal toxicity study. However, ethyl alcohol is nonirritating and it is not expected to be readily absorbed via the dermal route due to its volatility. Thus, the estimated dermal exposure is not expected to be of concern.

As mentioned above, ethyl alcohol is used as an inert ingredient in antimicrobial food-contact surface products. Because these are often sprayed, exposure can occur via the inhalation and dermal routes. The worst-case inhalation and dermal exposure estimates in Table 6 also apply to this scenario.

Table 6. Modeled Exposure Estimates for Inhalation and Dermal Exposure to Ethyl Alcohol

Exposure Route	E-FAST Scenario Used to Model Exposure	Percent Ethyl Alcohol	Exposure[a]
Inhalation	Indoor Aerosol Paint	95	2.3 mg/m^3 (1.2 ppm);
Dermal	Latex Paint[b]	95	0.11 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 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 estimate is considered worst-case for several reasons: (1) in the E-FAST run, a high weight fraction (95%) was assumed, it is unlikely that all indoor residential-use products containing ethyl alcohol as an inert ingredient have such a high weight fraction; (2) E-FAST is designed as a screening tool, modeled estimates of concentrations and doses are designed to reasonably overestimate exposures; and (3) the E-FAST scenario that would yield the greatest exposure since the high-end assumptions (i.e., those for aerosol paint) were used.

VI. 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 ethyl alcohol, 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 ethyl alcohol as an ingredient in pesticide formulations.

VII. 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 ethyl alcohol and any other substances and, ethyl alcohol 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 ethyl alcohol 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 ethyl alcohol, EPA has determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to ethyl alcohol when used as an inert ingredient 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 inert use of ethyl alcohol is expected to result in human exposure below any dose level that would produce any adverse effect. Therefore, it is recommended that the three exemptions from the requirement of a tolerance established for residues of ethyl alcohol in can be considered reassessed as safe under section 408(q) of FFDCA.

Ethyl alcohol does cause systemic effects (fatty degeneration of the liver), developmental effects, and is a possible human carcinogen at high doses and established durations. However, the effects seen are attributable to exposure levels that would be well above those expected from the inert use of ethyl alcohol. As Irvine (2003) points out, the data clearly show that the developmental and reproductive effects observed "can only be achieved by the deliberate oral consumption of alcoholic beverages." Finally, the increased risk of cancer seen in IARC's (1988) evaluation of epidemiological data is among people who consume alcoholic beverages on a routine and long-time basis. A number of the subjects had issues with alcohol consumption. Even though IARC (1998) concluded that alcoholic "beverages are carcinogenic to humans," they also found that there is inadequate evidence for the carcinogenicity of ethyl alcohol in experimental animals.

X. Ecotoxicity and Ecological Risk Characterization (U.S. EPA 1995)

In its 1995 risk assessment, EPA reported that ethyl alcohol is practically acutely non-toxic to terrestrial animals, as demonstrated by the high rat LD_{50} value (7,060 mg/kg). For aquatic animals, tests showed that ethyl alcohol is practically non-toxic to the rainbow trout (LC_{50}=13,000 ppm), fathead minnow (LC_{50}=14,200 ppm), *Daphnia* (LC_{50} >100 ppm), and *Palaemonetes kadiakensis* or glass shrimp (LC_{50}>250 ppm).

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APPENDIX A: E-FAST Results for Ethyl Alcohol

Exhibit 1. Inhalation Exposure Model Inputs

CEM Inputs		ID Number: EtOH 95	
Product: Aerosol		Chemical Name: Ethyl Alcohol	
Scenario: Aerosol Paint		Population: Adult	
Molecular Weight (g/mole):	46.1	Vapor Pressure (torr):	59.3
Weight Fraction - Median (unitless):	0.95	Weight Fraction - 90% (unitless):	0.95
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.			
Avg. Time, $LADD_{pot}$, $LADC_{pot}$ (days): 2.74e+04		Avg. Time, ADD_{pot}, ADC_{pot} (days): 4.02e+03	
Avg. Time, ADR_{pot}, Cp_{pot} (days): 1.00e+00			

Exhibit 2. Inhalation Exposure Model Estimates

CEM Inhalation Exposure Estimates

ID Number: EtOH 95

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)	6.16e-02	2.74e+04
$LADC_{pot}$ (mg/m^3)	3.35e-01	2.74e+04
Chronic Non-Cancer		
ADD_{pot} (mg/kg-day)	4.20e-01	4.02e+03
ADC_{pot} (mg/m^3)	2.29e+00	4.02e+03
Acute		
ADR_{pot} (mg/kg-day)	8.27e+01	1.00e+00
Cp_{pot} (mg/m^3)	8.37e+03	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

Exhibit 3. Dermal Exposure Model Inputs

CEM Inputs		ID Number: EtOH 95	
Product: Paint		Chemical Name: Ethyl Alcohol	
Scenario: Latex Paint		Population: Adult	
Molecular Weight (g/mole):	46.1	Vapor Pressure (torr):	59.3
Weight Fraction - Median (unitless):	0.95	Weight Fraction - 90% (unitless):	0.95

Inhalation Inputs			
Frequency of Use (events/yr):	4	Years of Use:	11
Mass of Product Used per vent - 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:	111111113244247742744411				Room of Use: 1. Bedroom	
Hour:	0	6	12	18		

Dermal Inputs			
Frequency of Use - Body (events/yr):	4	SA/BW - Body (cm^2/kg):	4.5
Amount Retained / Absorbed to Skin (g/cm^2-event):	0.00232		
Avg. Time, $LADD_{pot}$, $LADC_{pot}$ (days):	2.74e+04	Avg. Time, ADD_{pot}, ADC_{pot} (days):	4.02e+03
Avg. Time, ADR_{pot}, Cp_{pot} (days):	1.00e+00		

Exhibit 4. Dermal Exposure Model Estimates

CEM Dermal Exposure Estimates

ID Number: EtOH 95

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)	1.59e-02	2.74e+04
Chronic Non-Cancer		
ADD_{pot} (mg/kg-day)	1.09e-01	4.02e+03
Acute		
ADR_{pot} (mg/kg-day)	9.92e+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