

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



OFFICE OF PREVENTION,
PESTICIDES, AND TOXIC SUBSTANCES

DATE: August 15, 2006

ACTION MEMORANDUM—Errata

SUBJECT: Inert Reassessment—Three Exemptions from the Requirement of a Tolerance for Methyl Alcohol (CAS# 67-56-1). Correction to the List Classification Determination Paragraph.

FROM: Pauline Wagner, Chief *Pauline Wagner 8/16/06*
Inert Ingredient Assessment Branch
Registration Division (7505P)

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

This memorandum corrects the “List Reclassification Determination” paragraph under section I, FQPA Reassessment Action, of the April 12, 2006 Action Memorandum regarding “Inert Reassessment—Three Exemptions from the Requirement of a Tolerance for Methyl Alcohol (CAS# 67-56-1).” The corrected paragraph is:

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

MANAGEMENT CONCURRENCE:

I concur with the correction noted above.

Lois A. Rossi
Lois A. Rossi, Director
Registration Division

August 16, 2006
Date

cc: Debbie Edwards, SRRD
Joe Nevola, SRRD

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



OFFICE OF PREVENTION,
PESTICIDES, AND TOXIC SUBSTANCES

DATE: April 12, 2006

ACTION MEMORANDUM

SUBJECT: Inert Reassessment—Three Exemptions from the Requirement of a Tolerance for Methyl Alcohol (CAS# 67-56-1)

FROM: Pauline Wagner, Chief *Pauline Wagner 4/12/06*
Inert Ingredient Assessment Branch

I. FQPA REASSESSMENT ACTION

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

Chemical: Methyl Alcohol (methanol)

40 CFR parts 180.910; 180.920; and 180.930

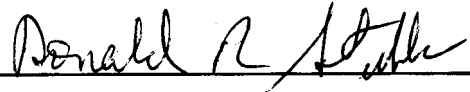
CAS #: 67-56-1

Use Summary: Methyl alcohol is used as an inert ingredient in agricultural and residential-use pesticides. It is also found in a wide-array of consumer products including paints, cleaning products, adhesives, and alternative fuels. Further, methyl alcohol is used as a feedstock in the production of other chemicals (e.g., acetic acid, formaldehyde, and methyl tertiary-butyl ether).

List Reclassification Determination: Methyl alcohol will remain on List 3 (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 methanol (CAS# 67-56-1) and with the List reclassification determinations, as described above. I consider the three exemptions established in 40 CFR parts 180.910, 180.920, and 180.930 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, Director
Registration Division

4/12/06
Date:

cc: Debbie Edwards, SRRD
Joe Nevola, SRRD



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

OFFICE OF PREVENTION,
PESTICIDES, AND TOXIC SUBSTANCES

April 12, 2006

MEMORANDUM

SUBJECT: Reassessment of the Three Exemptions from the Requirement of a Tolerance for Methanol (CAS 67-56-1)

FROM: Kathleen Martin, Chemist *Kathleen A. Martin*
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 methanol. The purpose of this document is to reassess the three existing exemptions from the requirement of a tolerance for residues of methanol 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 methanol.

EXECUTIVE SUMMARY

This report provides a qualitative risk assessment for methanol, a pesticide inert ingredient for which exemptions from the requirement of a tolerance exists for its residues when used in pesticide formulations under 40 CFR 180.910, 180.920, and 180.930. As such, methanol is used as a solvent, cosolvent, or synergist.

Individuals are widely exposed to methanol, though not at high concentrations. It is produced naturally in the human body and is found in expired air and body fluids. In the environment, methanol is emitted through volcanic gases, vegetation, microbes, and insects (IPCS 1997). Humans are also exposed to methanol through contact with anthropogenic sources. Methanol is a constituent in consumer products such as varnishes, paints, windshield washer fluids, adhesives, and is used as an alternative fuel. As a pesticide chemical, methanol is an inert ingredient in an array of products, both agricultural and

residential. Overall, food is the primary source of human methanol exposure—methanol occurs naturally in fresh fruits and vegetables and additional release is expected following ingestion due to breakdown of pectins in the gastrointestinal tract (NTP 2003).

Methanol is rapidly absorbed by all routes of exposure. In its review, NTP (2003) pointed out “that the metabolism and toxicity of methanol is independent of the route of exposure.” Methanol is acutely toxic. Based on what is known from human poisonings, high doses can cause blindness and death (Klaassen et al 1986). Animals studies show that methanol may cause developmental toxicity at doses greater than 1,000 ppm via the inhalation route. However, compared to the exposure from natural sources of methanol and various methanol-containing consumer products, the potential for exposure through the inert use of methanol is low. Because of the low potential for inert exposure, an additional tenfold safety factor for the protection of infants and children was not deemed necessary.

As an inert ingredient in pesticide products that are applied to growing crops, potential human exposure would be through consumption of food to which a methanol-containing pesticide product has been applied. Residues in food are not expected through pesticide application—methanol remaining after application would evaporate as methanol is quite volatile. Further, methanol residues resulting from pesticide application are expected at levels far below those from naturally-occurring methanol in food.

As an inert ingredient in residential-use pesticides, EPA expects that exposure would be through the inhalation and dermal routes. Because the potential for inhalation exposure is expected to be much greater than for dermal, EPA modeled (using E-FAST) a worst-case exposure estimate assuming that an aerosol indoor-use, methanol-containing residential pesticide product contained 90% methanol. The resulting screening-level inhalation exposure estimates were also low.

Methanol is readily degraded in the environment by photooxidation and biodegradation. Methanol is not likely to appreciably bioconcentrate in aquatic and terrestrial organisms. The Environmental Protection Agency (EPA or the Agency) believes that the inert ingredient use of methanol would not result in methanol being present in drinking water due to the ready biodegradation.

Taking into consideration all available information on methanol, EPA has determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to methanol used as an inert ingredient when considering dietary exposure and all other nonoccupational sources of pesticide exposure for which there is reliable information. Therefore, it is recommended that the exemptions from the requirement of a tolerance established for residues of methanol in/on raw agricultural commodities (RAC's) can be considered reassessed as safe under section 408(q) of the Federal Food, Drug, and Cosmetic Act (FFDCA).

I. Introduction

This report provides a qualitative assessment for methanol, a pesticide inert ingredient with three tolerance exemptions under: 40 CFR 180.910, 180.920, and 180.930. Methanol, which is also known as methyl alcohol, is a colorless, water-soluble simple alcohol containing one carbon atom. It occurs naturally in plants and animals. Commercially, it has been used for over 100 years. Today, methanol is among the world's most widely produced chemicals. In 1995, methanol production in the United States totaled over 11 billion pounds (C&E News 1996). About 70% of the volume produced is for use as a feedstock in chemical syntheses (e.g., formaldehyde, acetic acid, and methyl tertiary-butyl ether) (NTP 2003). Human exposure is derived both from the diet and metabolic processes (IPCS 1997). Also, methanol is a constituent in blood, urine, saliva, milk, and expired air.

II. Use Information

A. Pesticides

Methanol is used as an inert ingredient only; there are no registered pesticide products containing methanol as an active ingredient. As an inert ingredient, methanol is used as a solvent, cosolvent, or synergist in a wide variety of pesticide products, as discussed under the Exposure Assessment, below. The tolerance exemptions for the inert ingredient methanol are provided in Table 1.

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 <u>CFR</u> 180	Tolerance Exemption Expression	Limits	Uses	
.910 ^a	methyl alcohol	(none)	solvent	67-56-1 Methanol
.920 ^b	methyl alcohol	(none)	synergist	
.930 ^c	methyl alcohol	(none)	solvent, cosolvent	

^aResidues 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 (RAC's) after harvest.

^bResidues 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.

^cResidues 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.

B. Other Uses

In addition to its use as an inert ingredient, methanol is used in a wide-array of consumer products such as varnishes, paints, windshield washer fluids, adhesives, and as an alternative fuel. Also, methanol is used as a feedstock in the production of other chemicals (e.g., acetic acid, formaldehyde, and methyl tertiary-butyl ether).

III. Physical and Chemical Properties

Some of the physical and chemical characteristics of methanol, along with its structure and nomenclature, are found in Table 2.

Table 2. Physical and Chemical Properties of Methanol

Parameter	Value	Reference
Structure	$\text{H}_3\text{C}-\text{OH}$	
Common Names	methyl alcohol, carbinol, wood alcohol, wood spirits, wood naphtha, colonial spirit, hydroxymethane, methylol, methylhydroxide, monohydroxymethane, pyroxylic spirit	IPCS 1997
CAS #	67-56-1	U.S. EPA 1994
	colorless liquid	
	CH_4O	
	32.04	
	-97.8°C	
	64.7°C at 760 mm Hg	
	miscible	
	0.7915 g/mL at 20°C	
	1.11	
	9	
	-0.77	
	126 mm Hg at 25°C	
	$4.55 \times 10^{-6} \text{ atm m}^3/\text{mol}$	

IV. Hazard Assessment

A. Toxicological Data

Methanol has been recognized as a toxic agent since the end of the 19th century (IPCS 1997) and its toxicity has been well-studied. To assess the hazard posed by the use of methanol as an inert ingredient, EPA relied on: standard available references (e.g., Casarett and Doull's Toxicology), animal data from the published literature, and EPA's IRIS Database for Risk Assessment (U.S. EPA 2005)¹. In addition, the Agency considered information from its and High Production Volume (HPV) Challenge Program (AMI 2001a; AMI 2001b)².

B. Hazard Profile

Provided below is a summary of methanol's major toxicological effects, which are acute toxicity and developmental effects, and a description of methanol's metabolism in humans and mammals. An important distinction between acute and developmental toxicity is that acute toxicity is thought to occur through the formation of the metabolite formate (formic acid) rather than to exposure to methanol, per se; developmental toxicity is believed to occur through exposure to methanol per se. In its review, NTP (2003) determined "that the metabolism and toxicity of methanol is independent of the route of exposure."

Acute Toxicity

Animal data and human historical epidemiological information show that methanol may produce acute toxicity. Casarett and Doull's Toxicology (Klaassen et al 1986) points out that whenever access to ethanol had been restricted (e.g., during Prohibition in the 1920s), the incidence of methanol poisoning has increased. "The characteristic results of an epidemic are that a third of those exposed to methanol recover with no residues, a third have severe visual loss or blindness, and a third die. Thus in sufficiently high doses methanol has profound systemic effects."

¹IRIS 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. This database provided an oral subchronic reference dose (RfD).

²HPV 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. Methanol is currently being sponsored by the American Methanol Institute (AMI).

Typical findings include temporary mild central nervous system depression, metabolic acidosis, and ocular toxicity, including blindness. IPCS (1997) notes that the acute toxicity of methanol varies greatly among species, with toxicity being highest in species with a relatively poor ability to metabolize formate (e.g., humans). In humans fatal methanol poisoning occurs as a result of metabolic acidosis and neuronal toxicity (initial blood methanol levels in the range of 1,500-2,000 mg/L). In animals that can readily metabolize formate, consequences of central nervous system depression (coma, respiratory failure, etc.) are usually the cause of death. (IPCS 1997).

EPA's Office of Pesticide Programs' Label Review Manual (U.S. EPA 2003) provides guidance to reviewers in the Program who are responsible for performing pesticide label reviews. For pesticide products where the concentration of methanol is 4% or more, the manual *recommends* that the word "Poison" and the skull and crossbones symbol appear on the pesticide container (i.e., as the Signal Word), along with the statement "Methanol may cause blindness." The term "Poison" and the skull and crossbones are required (under 40 CFR 156.64) for products classified as Toxicity Category I for acute oral, acute dermal, or acute inhalation.

IPCS (1997) reports that the oral minimum lethal dose for humans in the absence of medical treatment is 300 to 1,000 mg/kg/day (Toxicity Category II to III). NTP (2003) reports that the oral minimum lethal dose for rats is 9,500 mg/kg/day (Toxicity Category IV). Looking at various acute effects in terms of blood levels of methanol, IPCS (1997) found that in humans CNS effects appear above blood methanol levels of 200 mg/L; ocular symptoms appear above 500 mg/L; and fatalities have occurred in untreated patients with initial methanol levels in the range of 1,500 to 2,000 mg/L.

Subchronic Toxicity

In 1986 EPA established a subchronic RfD using a rat oral 90-day study. Because of the lack of data at the time, EPA's Office of Solid Waste sponsored the 90-day subchronic testing of methanol in rats. The RfD (0.5 mg/kg/day) was based on increased serum alkaline phosphatase (SAP) and serum glutamic pyruvic transaminase (SGPT), and decreased brain weight; the NOAEL was 500 mg/kg/day and the LOAEL was 2500 mg/kg/day.

Chronic Toxicity

IPCS (1997) reported that there are little data on the chronic effects of methanol exposure. The limited epidemiological case reports suggest that "extended exposure to methanol may cause effects qualitatively similar to those observed from relatively high levels of acute exposure."

Two entities have estimated inhalation levels of methanol that are thought to cause no chronic adverse effects. California's Office of Environmental Health Hazard Assessment (OEHHA) established a chronic Reference Exposure Level (REL) and Starr and Festa (2003) a reference concentration (RfC), both of which were derived from an NTP-described developmental toxicity study (i.e., the Rogers, et al 1993 study which was conducted in mice).

California's OEHHA is responsible for conducting health risk assessments of chemical contaminants found in air. Assessments include development of cancer potency factors to assess the cancer risk from carcinogens, and development of reference exposure levels (REL) to assess noncancer health impacts. A chronic REL is an airborne level that would pose no significant health risk to individuals indefinitely exposed to that level (OEHHA, no date). Using Rogers' analysis of the study results (i.e., a Benchmark Dose calculation) and the use of several uncertainty factors, OEHHA (no date) derived an REL of 4 mg/m³ or 3 ppm.

A pair of investigators, Starr and Festa (2003), sought to develop an RfC for inhalation exposure to methanol. An RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime (U.S. EPA 2005). Using the concentration of methanol in circulating blood as the primary dose metric in Benchmark Dose modeling and then employing this result in a biologically-based pharmacokinetic model, Starr and Festa (2003) estimated that the maximum likelihood inhalation RfC was 298 mg/m³, with a 95% confidence bound of 135 mg/m³.

Developmental Toxicity

Animal data indicate that exposure to methanol may cause developmental toxicity. NTP reports the findings of several developmental toxicity studies in rodents and primates; three in which NTP has high or fairly high confidence are summarized in Table 3. Specific developmental effects observed include: cleft palate, exencephaly, and skeletal malformations.

Table 3. Summary of Developmental Toxicity

Study	Dose		Route of Exposure	Species	Toxicity	
	ppm	mg/L			Developmental Effects	Maternal Effects
Nelson et al 1985, as cited in NTP 2003	0 5,000; 10,000; or 20,000	(d); 1,000 to 2,170 ^b ; 1,840 to 2,240, 5,250 to 8,650	inhalation	Crl: Sprague- Dawley rats	NOAEL ^a : 5,000 ppm blood level ^c : 1,000 to 2,170 mg/L	NOAEL: 10,000 ppm (blood level: 1,840 to 2,240 mg/L)

Table 3. Summary of Developmental Toxicity

Study	Dose		Route of Exposure	Species	Toxicity	
	ppm	mg/L			Developmental Effects	Maternal Effects
Japanese New Energy Development Organization 1987, as cited in NTP 2003	0; 200; 1,000; or 5,000	not provided	inhalation	Cri:CD Sprague-Dawley rats	NOAEL: 1,000 ppm LOAEL ^b : 5,000 ppm (based on increased late resorptions, reduced numbers of live fetuses, decreased fetal weight, and increased numbers of litters containing fetuses with malformations, variations, and delayed ossification)	not provided
Rogers et al 1993, as cited in NTP 2003	control 1,000, 2,000, 5,000, 7,500, 10,000, or 15,000	1.6; 97; 537; 1,650; 3,178; 4,204; 7,330	inhalation	Cri:CD-1 mice	NOAEL: 1,000 ppm (blood level ^e : 97 mg/L) LOAEL: 2,000 ppm (based on increased cervical ribs) blood level ^e : 537 mg/L	

^aNOAEL=No observed adverse effect level.

^bLOAEL=Lowest observed adverse effect level.

^cThe blood levels are expressed as ranges because they were measured on three separate days of exposure (days 1, 10, an 19).

^dThe blood concentration equivalent to 0 ppm was not reported.

^eThe blood levels are averages for three gestational days.

NTP (2003) considers the investigation by Rogers et al to be the critical developmental toxicity study in animals. “This study is sufficient to conclude that prenatal exposure of mice to methanol vapor at concentrations of 2,000 ppm or greater for 7 hours/day on gd [gestation day] 6–15 can cause developmental toxicity as evidenced by cleft palate, exencephaly and skeletal malformations.” In addition to the inhalation route, Rogers et al also exposed animals by the oral route to determine comparability of effects between exposure routes. The study investigators chose dose levels that would produce blood methanol levels that were observed in the inhalation study at the higher doses. It was found that the gavaged mice “gave a pattern of response similar to that seen in the mouse group exposed to 10,000 ppm by inhalation.” Mean daily maternal blood methanol levels one hour following the second daily exposure (3,856 mg/L) were slightly lower than comparable blood levels in dams inhaling 10,000 ppm methanol in a previous experiment (4,204 mg/L).

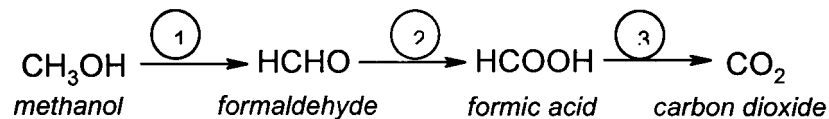
Other Effects

Methanol is not considered to be a reproductive toxicant. NTP (2003) was not able to establish that methanol would affect female or male reproductive function. IPCS (1997) finds no evidence from animal studies to suggest that methanol is a carcinogen, and its structure does not suggest that it would be genotoxic.

C. Metabolism and Pharmacokinetics

“Methanol is rapidly and well absorbed by inhalation, oral, and topical exposure routes” (Klaassen et al 1986); the absorption capabilities do not appear to differ substantially across mammalian species (NTP 2003). The general scheme for the biotransformation of alcohol in Figure 1 below:

Figure 1. Biotransformation of Methanol



In humans and rats, methanol is metabolized to formaldehyde, then formic acid, and finally carbon dioxide. In the rat, guinea pig, and rabbit the “major route of methanol oxidation is through a catalase-dependent pathway, whereas in the monkey and humans, an alcohol dehydrogenase system functions *in vivo*” (Klassen et al 1986). In all mammals, methanol to formic acid biotransformation is quite rapid. The formic acid “is further oxidized to carbon dioxide by an enzymatic pathway dependent on the presence of the cofactor, folic acid. The enzyme is active in both rodents and primates” (Klassen et al 1986).

Klassen et al (1986), in “Casarett and Doull’s Toxicology,” reports that the monkey appears to be an appropriate animal model for studying methanol poisoning as the effects seen closely resemble those seen in humans. Accordingly, researchers have determined that the biotransformation of formic acid to carbon dioxide occurs slowly and are such that large doses of formic acid accumulates in tissues, including the eye.

D. Special Considerations for Infants and Children

NTP (2003) finds “that there is concern for adverse developmental effects in fetuses if pregnant women are exposed to methanol at levels that result in high blood methanol concentrations. This conclusion is based on evidence that blood methanol levels in humans suffering acute methanol poisoning are similar to maternal blood methanol levels resulting in developmental toxicity in rodents. Further, evidence suggests that methanol, rather than one of its metabolites, results in developmental toxicity.” They also find “that there is minimal concern for adverse developmental effects when humans are exposed to methanol levels that result in low blood methanol concentrations” (i.e., <10 mg/L blood).” “These methanol concentrations have been associated with consumption of a common American diet and with work exposures that are below U.S. occupational exposure limits.”

EPA does not expect that the general population, including women, will be exposed to methanol levels that would result in high blood methanol concentrations. As discussed in the Exposure Assessment (below, section V), residues resulting from the inert use of methanol in agricultural and residential-use pesticides are expected to be low. Thus, even though methanol has been shown to be developmentally toxic at high doses, the low potential for exposure mitigates any concern for increased risk to infants and children. Therefore, an additional tenfold safety factor for the protection of infants and children was not deemed necessary.

V. Exposure Assessment

Individuals are exposed to methanol via the oral, dermal, and inhalation routes. Exposure occurs through a wide array of sources, though not at high concentrations. Methanol is produced naturally in the human body and is found in expired air and body fluids. In the environment, methanol is emitted through volcanic gases, vegetation, microbes, and insects (IPCS 1997). Humans are also exposed to methanol through contact with anthropogenic sources. Methanol is a constituent in consumer products such as varnishes, paints, windshield washer fluids, adhesives, and is used as an alternative fuel. As a pesticide chemical, methanol is an inert ingredient in numerous products, both agricultural and residential.

Food

As an inert ingredient in 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 a methanol-containing pesticide product has been applied. The Agency expects very little exposure to methanol through this manner. Given its vapor pressure (126 mm Hg at 25°C), EPA expects that methanol will evaporate soon after application.

Note that oral exposure can also occur through naturally-occurring or naturally-produced methanol in our diets. NTP (2003) believes that food is the primary source of human methanol exposure—methanol occurs naturally in fresh fruits and vegetables and additional amounts of methanol are expected to be released following breakdown of pectins in the gastrointestinal tract. People also are exposed to methanol through two direct food additives, the artificial sweetener aspartame (L-aspartyl-L-phenylalanine methyl ester) and dimethyl dicarbonate (DMDC). Aspartame is a dipeptide that is primarily comprised of phenylalanine and aspartic acid; when ingested, about 10% by weight of aspartame is hydrolyzed to free methanol. DMDC is a yeast inhibitor used in tea beverages, sports drinks, fruit or juice sparklers, wines, and wine substitutes; it is unstable in aqueous solutions (beverages) and primarily breaks down to methanol and carbon dioxide. (NTP 2003)

NTP (2003) reported that dietary “exposure is pervasive in the general population and has been characterized through survey studies. It is generally believed that dietary sources contribute to the observed background blood methanol concentrations (<5-10 mg/L).” IPCS (1997) reported that the concentration of naturally-occurring methanol in fruit juices (orange and grapefruit, primarily) averages 140 mg/L. They further noted that methanol has been identified as a volatile component of dried legumes, ranging from 1.5 to 7.9 mg/kg (which is ~1.5 to 7.9 mg/L) in beans to 4.4 mg/kg (~4.4 mg/L) in lentils. Regarding the amount of methanol exposure that occurs via the aspartame and DMDC routes, NTP reported that the general U.S. population ingests less than 1 mg/kg/day (~1 mg/L/day) from aspartame and approximately 1 mg/kg/day (~1 mg/L/day) from DMDC.

Residential

Limited residential exposure data are available for methanol. According to the Household Products Database (NIH 2004), methanol is used in an array of household products, from auto products such as deicers to home maintenance products such as paint strippers. Formulations include liquids, aerosols, pastes, and creams, with methanol concentrations of one to 100%. Exposure resulting from the use of methanol-containing residential pesticides is expected via the inhalation and dermal routes; however, the potential for inhalation exposure is expected to be much greater than for dermal.

To estimate worst-case exposure, EPA modeled a scenario where an aerosol indoor-use, methanol-containing residential pesticide product contained 90% methanol. Using E-FAST³ (U.S. EPA 2004) and standard model assumptions (run is provided in Appendix A), EPA determined that the indoor potential Average Daily Concentration (which is an exposure metric for inhalation exposure) of methanol exposure is 2.16 mg/m³ or 1.65 ppm. This estimate is considered worst-case for several reasons: (1) in the E-FAST run, a high weight fraction (90%) was assumed, it is unlikely that all indoor residential-use products containing methanol 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 (aerosol paint) was 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 methanol’s ability to quickly evaporate.

³The 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.

VI. Aggregate Exposures

In examining aggregate exposure, 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 the following reasons, a qualitative assessment for all exposure pathways is appropriate: the likelihood of methanol in drinking water is low; methanol occurs naturally in food; and exposure resulting from residential use is expected to be low.

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."

EPA does not have, at this time, available data to determine whether methanol has a common mechanism of toxicity with other substances. 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 methanol and any other substances and, methanol 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 methanol 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/>.

Environmental Fate Characterization and Drinking Water Considerations

For environmental fate data, EPA relied on the 1997 EHC monograph (IPCS 1997). Accordingly, methanol is readily degraded in the environment by photooxidation and biodegradation. Predicted biodegradation half-lives indicate days for primary degradation and days to weeks for ultimate degradation (mineralization to CO₂ and water). Base/acid-catalyzed hydrolysis is not expected to occur. Methanol will not appreciably bioconcentrate in aquatic and terrestrial organisms. Half-lives of seven to 18 days have been reported for the atmospheric reaction of methanol with hydroxyl radicals. For a model river (1 meter deep) and an environmental pond, volatilization half-lives of 5.3 and 2.6 days have been estimated for methanol, respectively. Methanol has a fairly low absorptive capacity on soils.

EPA believes that the inert ingredient use of methanol would not result in methanol being present in drinking water due to the ready biodegradation.

IX. Human Health Risk Characterization

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

In considering the risk posed by the inert use of methanol, EPA considered NTP's conclusion that "blood methanol concentration is a useful biomarker of exposure" (NTP 2003). Based on survey results, NTP expects that blood methanol levels will not exceed 10 mg/L from normal dietary or occupational exposures.

Both NTP and IPCS looked at sources of methanol in the diet; their analyses did not include the contribution from the use of methanol as an inert ingredient. They pointed out that consumption of methanol occurs in the normal diet—methanol is found naturally in fruits and vegetables and is a breakdown product of two food additives (aspartame and DMDC). NTP (2003) believes that food is the primary source of human methanol exposure. They reported that dietary exposure to methanol is pervasive in the general population and that dietary sources contribute to background blood methanol concentrations of <5 to 10 mg/L. EPA believes that residues from the inert use of methanol are not likely to exceed levels of naturally-occurring methanol in commonly eaten foods. Methanol is used as a solvent, cosolvent, or synergist in pesticide products applied to growing crops, crops after harvest, or animals. Given its vapor pressure (126 mm Hg at 25°C), EPA expects that methanol will evaporate soon after application, thus little is expected to be available in food. In addition, methanol residues remaining on growing crops are likely to be washed off in the field or during processing as methanol is miscible with water. In drinking water, residues are not expected due to methanol's ready biodegradation.

For inert ingredient risk assessments, EPA does not assess occupational exposure; however, because of the requirements of FQPA, residential exposure is considered. Limited residential exposure data are available for methanol. To gain some understanding of the magnitude of exposure incurred when using a methanol-containing residential pesticide product indoors, EPA generated a worst-case inhalation exposure estimate using E-FAST, which is 2.16 mg/m³ or 1.65 ppm (see Appendix A for details).

To put this worst-case inhalation estimate in context of human health risk resulting from indoor residential exposure, EPA considered two estimated chronic inhalation methanol levels that are thought to cause no adverse effects: (1) California's Office of Environmental Health Hazard Assessment inhalation reference exposure level (REL), which is 4 mg/m³ or 3 ppm (OEHHA, no date); and (2) Starr and Festa's (2003) maximum likelihood inhalation RfC of 298 mg/m³. Both these levels are above EPA's worst-case estimate of exposure.

X. Ecotoxicity and Ecological Risk Characterization (IPCS 1997; U.S. EPA 2000)

For ecological effects data, EPA relied on a 1997 report by the World Health Organization (IPCS 1997). Bioconcentration in most organisms is low and methanol is of low toxicity to aquatic and terrestrial organisms. IPCS (1997) reported metrics for a number of aquatic organisms. LC₅₀ values range from 1,300 to 15,900 mg/L for invertebrates (48-hour and 96-hour exposures), and 13,000 to 29,000 mg/L for fish (96-hour exposure).

Predicted toxicity values (ECOSAR, see U.S. EPA 2000) were generated to fill gaps in the available measured data. Certain aquatic organisms (e.g., marine/estuarine fish) may be more sensitive to methanol than freshwater fish. In addition, predicted chronic effects may occur at substantially lower concentrations (e.g., freshwater fish at approximately 600 ppm and *Daphnia magna* at approximately 100 ppm). Terrestrial organisms do not exhibit high acute toxicity; however, chronic data are lacking to determine potential for effects at environmental exposures.

REFERENCES:

AMI. 2001a. Test Plan for Methanol. The American Methanol Institute Testing Group. July 6, 2001. AR201-13104A. <http://www.epa.gov/chemrtk/methanol/c13104tc.htm>

AMI. 2001b. Robust Summary of Toxicity of Methanol. The American Methanol Institute. March 23, 2001. <http://www.epa.gov/chemrtk/methanol/c13104rs.pdf>

C&E News. 1996. Production by the U.S. Chemical Industry. *Chemical and Engineering News*. American Chemistry Society. June 24, 1996. <http://pubs.acs.org/hotartcl/cenear/960624/prod.html>

Klaasen, C.D. et al, editors. 1986. "Casarett and Doull's Toxicology," 3rd edition. Macmillan Publishing Company, New York.

IPCS. 1997. Environmental Health Criteria 196: Methanol. United Nations Environment Programme. International Programme on Chemical Safety. World Health Organization. <http://www.inchem.org/documents/ehc/ehc/ehc196.htm>

NIH. 2004. 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. "Household Products Database." May 12, 2004. <http://householdproducts.nlm.nih.gov/>

NTP. 2003. NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Methanol. National Toxicology Program. U.S. Department of Health and Human Services. Center for the Evaluation of Risks to Human Reproduction. September 2003. NIH Publication No. 03-4478. http://cerhr.niehs.nih.gov/news/methanol/Methanol_Monograph.pdf

OEHHA. no date. Chronic Toxicity Summary: Methanol. California's Office of Environmental Health Hazard Assessment. http://www.oehha.ca.gov/air/chronic_rels/AllChrels.html

Starr, TB and Festa, JL. 2003. A Proposed Inhalation Reference Concentration For Methanol. *Regulatory Toxicology and Pharmacology*. 38 (2003) 224-231.

U.S. EPA. 1994. Chemical Summary for Methanol. United States Environmental Protection Agency. Office of Prevention, Pesticides & Toxic Substances. Office of Pollution Prevention and Toxics. August 1994. EPA 749-F-94-013a. http://www.epa.gov/chemfact/s_methan.txt

U.S. EPA. 2000. ECOSAR, v. 0.99g. United States Environmental Protection Agency. Office of Prevention, Pesticides & Toxic Substances. Office of Pollution Prevention and Toxics. New Chemicals Program. January, 2000. <http://www.epa.gov/opptintr/newchems/21ecosar.htm>

U.S. EPA. 2003. Label Review Manual, 3rd Edition. United States Environmental Protection Agency. Office of Prevention, Pesticides & Toxic Substances. Office of Pollution Prevention and Toxics. August 2003. EPA 735-B-03-001. <http://www.epa.gov/oppfead1/labeling/lrm/labelreviewmanual.pdf>

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

U.S. EPA. 2005. IRIS Database for Risk Assessment. Last website update: March 10, 2005. <http://www.epa.gov/iris/index.html>

APPENDIX A—E-FAST Run

CEM Inputs		ID Number: MeOH A 0.9	
Product: Unknown		Chemical Name: None	
Scenario: Aerosol Paint		Population: Adult	
Molecular Weight (g/mole):	32.04	Vapor Pressure (torr):	126
Weight Fraction - Median (unitless):	0.9	Weight Fraction - 90% (unitless):	0.9
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, ADR _{pot} , C _{ppot} (days):		1.00e+00	
Avg. Time, ADD _{pot} , ADC _{pot} (days):		4.02e+03	

CEM Inhalation Exposure Estimates

ID Number: MeOHA 0.

Scenario: Aerosol Paint

Population: Adult

Inhalation Rate (m³/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)	5.84e-02	2.74e+04
LADC _{pot} (mg/m ³)	3.17e-01	2.74e+04
Chronic Non-Cancer		
ADD _{pot} (mg/kg-day)	3.98e-01	4.02e+03
ADC _{pot} (mg/m ³)	2.16e+00	4.02e+03
Acute		
ADR _{pot} (mg/kg-day)	7.84e+01	1.00e+00
C _{pot} (mg/m ³)	7.94e+03	1.00e+00

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

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

ADR - Acute Dose Rate (mg/kg-day) Cp - Peak Concentration (mg/

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