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: 2-Ethyl-1-hexanol; CAS#104-76-7. 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 March 30, 2006 Action Memorandum regarding "Inert Reassessment: 2-Ethyl-1-hexanol; CAS#104-76-7." The corrected paragraph is:

> **List Reclassification Determination:** The current List Classification for 2-ethyl-1-hexanol 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 2-ethyl-1-hexanol 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 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: March 30, 2006

ACTION MEMORANDUM

SUBJECT: Inert Reassessment: 2-Ethyl-1-hexanol; CAS#104-76-7

FROM: Pauline Wagner, Chief Pauline Wagner 3/30/06
Inert Ingredient Assessment Branch
Registration Division (7505C)

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

FQPA REASSESSMENT ACTION

Action: Reassessment of three inert exemptions from the requirement of a tolerance. The reassessment decision is to maintain each of the three inert tolerance exemptions "as-is."

Chemical: 2-Ethyl-1-hexanol

CFR: 40 CFR part 180.910, 40 CFR part 180.920, and 40 CFR part 180.930

CAS Registry Number and Name: 104-76-7; 1-hexanol, 2-ethyl (9CI)

Use Summary: Industrially, 2-ethyl-1-hexanol (2-EH) is mainly used in the manufacture of ester plasticizers which are used in producing soft polyvinyl chloride. The other major use of 2-EH is in the manufacture of a chemical used in the manufacture of coating materials, adhesives, printing inks, and impregnating agents. In addition to its industrial uses, 2-EH is added to foods and beverages as a flavor volatile; there are two indirect FDA Food Additive uses for 2-EH.

List Reclassification Determination: The current List Classification for 2-ethyl-1-hexanol is List 3; it will retain its current Classification.

II. MANAGEMENT CONCURRENCE

I concur with the reassessment of the three exemptions from the requirement of a tolerance for the inert ingredient 2-ethyl-1-hexanol (CAS#104-76-7) and with the List classification determinations, as described above. I consider the three exemptions established in 40 CFR part 180.910, 40 CFR part 180.920, and 40 CFR part 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 Rossi

Lois A. Rossi, Director
Registration Division

3/30/06

Date:

cc: Debbie Edwards, SRRD
Joe Nevola, SRRD

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

OFFICE OF PREVENTION,
PESTICIDES, AND TOXIC SUBSTANCES

March 30, 2006

MEMORANDUM

SUBJECT: Reassessment of the Three Exemptions from the Requirement of a Tolerance for 2-Ethyl-1-hexanol (CAS#104-76-7)

FROM: Kathleen Martin, Chemist Kathleen Martin 3/30/06.
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 2-ethyl-1-hexanol (2-EH). The purpose of this document is to reassess the three existing exemptions from the requirement of tolerance for residues of 2-EH 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 2-EH.

EXECUTIVE SUMMARY

2-EH is a branched, eight-carbon alcohol. After the lighter alcohols (those with one to four carbons such as methanol or butanol), 2-EH is the most important synthetic alcohol. Industrially, 2-EH is mainly used in the manufacture of ester plasticizers which are used in producing soft polyvinyl chloride. The other major use of 2-EH is in the manufacture of a chemical used in the manufacture of coating materials, adhesives, printing inks, and impregnating agents. EPA expects that exposure to 2-EH is widespread, though not at high concentrations. It occurs naturally in food and is used as a flavor volatile and is approved as an indirect U.S. Food and Drug Administration (FDA) Food Additive. In addition, 2-EH is used as a pesticide inert ingredient in pesticide formulations applied to growing crops, raw agricultural commodities (RACs), or animals. As such, it has three tolerance exemptions: 40 CFR 180.910; 40 CFR 180.920; and 40 CFR 180.930.

Individuals may be exposed to 2-EH through the oral, dermal, and inhalation routes of exposure. In terms of a pesticide inert ingredient, EPA expects that exposure to 2-EH would primarily be through the oral route, via consumption of agricultural crops to which this inert ingredient has been applied as a solvent, cosolvent, or defoamer and exposure through drinking water. Additional dermal and inhalation exposure may occur from residential use of pesticide products containing 2-EH on ornamental plants and lawns, as well as from the use in and around the home and on textiles. EPA expects that exposure to 2-EH will be low, both through food (which includes drinking water) and residential exposure.

Overall, 2-EH is of low acute toxicity by the oral and dermal routes; however, it is moderately irritating to the skin and severely irritating to the eye. In subchronic repeat dose studies, hepatic effects were noted, including increased liver weights and peroxisome proliferation in rats and mice. To explore this finding and EPA's concern that it could induce cancer, EPA required oncogenicity testing under the Toxic Substances Control Act. After reviewing the studies submitted under the test rule, the Agency concluded that 2-EH is not carcinogenic in the mouse or rat. No evidence of neurotoxicity was identified. The available data indicate that 2-EH is not mutagenic. Further, the available data show that 2-EH is not developmentally toxic. Because exposure to 2-EH is expected to be low and developmental toxicity is not expected, a safety factor analysis was not used to assess the risks resulting from the use of 2-EH.

Taking into consideration all available information on 2-EH, EPA has determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to 2-EH used as an inert ingredient in pesticide products 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 2-EH 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 2-EH can be considered reassessed as safe under section 408(q) of FFDCA.

I. Introduction

This report evaluates 2-ethyl-1-hexanol (2-EH), which has three exemptions from the requirement of a tolerance when used in accordance with good agricultural practice as an inert ingredient in pesticide formulations applied to: growing crops or raw agricultural commodities (RACs) after harvest (40 CFR 180.910); growing crops only (40 CFR 180.920); or animals (40 CFR 180.930). Two of the exemptions–40 CFR 180.910 and 40 CFR 180.930—have use limitations of not more than 2.5% of the pesticide formulation.

2-EH is a branched, eight-carbon alcohol. After the lighter alcohols (those with one to four carbons such as methanol or butanol), 2-EH is the most important synthetic alcohol (Elvers et al 1989). 2-EH occurs naturally in food, is used as a flavor volatile (JECFA 1993), and is approved as an Indirect Food Additive by the U.S. Food and Drug Administration (FDA). A flavor volatile is a compound naturally present in a food or added by the manufacturer. In a food product these compounds may be present in the air about a food and when eaten and can affect the sensory properties of the food as it is hydrated and diluted with saliva.

2-EH is not sponsored under EPA's High Production Volume (HPV) Challenge Program[1]. However, it is listed under the Organization for Economic Cooperation and Development's (OECD) Integrated HPV Database and, as such, is part of the SIDS (Screening Information Data Set) Program[2] with Sweden the sponsoring country (OECD 1995).

II. Use Information

A. Pesticides

In terms of pesticide use, 2-EH is used only as an inert ingredient. There are currently no registered pesticide products containing 2-EH as an active ingredient. 2-EH is used as a solvent, cosolvent, adjuvant of surfactants, or defoamer in pesticide products used on agricultural food crops, animals, ornamental plants, and in residential-use pesticides such as insect sprays. The exemptions from the requirement of a tolerance for 2-EH are provided in Table 1 below.

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[1]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. http://www.epa.gov/opptintr/chemrtk/hpvchmlt.htm

[2]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. http://cs3-hq.oecd.org/scripts/hpv/

Table 1. Exemptions from the Requirement of a Tolerance

Citation as it Appears in the CFR				CAS Registry Number and 9CI Name
40 CFR 180	Tolerance Exemption Expression	Limits	Uses	
.910[a]	2-Ethyl-1-hexanol	Not more than 2.5% of pesticide formulation	Solvent, adjuvant of surfactants	104-76-7 1-hexanol, 2-ethyl-
.920[b]	2-Ethylhexanol	--	Cosolvent, defoamer, solvent for all pesticides used before crop emerges from soil and in herbicides before or after crop emerges	
.930[c]	2-Ethyl-1-hexanol	Not more than 2.5% of pesticide formulation	Solvent, adjuvant of surfactants	

[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 180.920 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.

[c]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.

B. Other Uses

Industrially, 2-EH is mainly used in the manufacture of ester plasticizers which are used in producing soft polyvinyl chloride. The other major use of 2-EH is in the manufacture of a chemical used in the manufacture of coating materials, adhesives, printing inks, and impregnating agents. (Elvers et al 1989) In addition to its industrial uses, 2-EH is added to foods and beverages as a flavor volatile (JECFA 1993); there are two indirect FDA Food Additive uses for 2-EH (see Table 2).

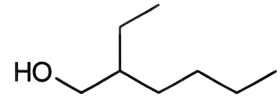
Table 2. FDA Food Additive Uses for 2-EH

Name	21 CFR	Use Pattern
2-Ethylhexanol	176.210	Indirect Food Additives: Paper And Paperboard Components. Defoaming agents used in the manufacture of paper and paperboard.
2-Ethylhexyl alcohol	177.1200	Indirect Food Additives: Polymers. Substances for Use as Basic Components of Single and Repeated Use Food Contact Surfaces

III. Physical and Chemical Properties

Some of the physical and chemical characteristics of 2-EH, along with its structure and nomenclature, are found in Table 3. Except for the log Kow, all values are measured as opposed to being estimated.

Table 3. Physical and Chemical Properties of 2-EH

Parameter	Value	Reference
Structure		--
CAS # and Name	104-76-7; 1-hexanol, 2-ethyl-	US EPA 2004a
Empirical Formula	$C_8H_{18}O$	US EPA 2004a
Molecular Weight	130.23	US EPA 2004a
Common Names	2-ethylhexanol; 2-ethylhexyl alcohol; 1-hexanol, 2-ethyl-; 2-Ethylhexan-1-ol;octyl alcohol	NIH 2004a
Physical State	Colorless liquid,with characteristic odor	NIOSH 1996
Melting Point	<-76°C	NIOSH 1996
Boiling Point	184-185°C	NIOSH 1996
Water Solubility	poor	NIOSH 1996
Relative Density (water=1)	0.83	NIOSH 1996
Relative Vapor Density (air = 1)	4.5	NIOSH 1996
Vapor Pressure	48 Pa at 20°C (0.36 mm Hg)	NIOSH 1996
log Kow	2.73 (estimated)	US EPA 2004b
Henry's Law Constant	2.3×10^{-5}	US EPA 2004b

[a]Note: Some sources refer to 2-ethyl-1-hexanol as octyl alcohol, the name by which 1-octanol or n-octanol (a straight chain eight-carbon alcohol) is also known. In this risk assessment, only information that clearly refers to 2-ethyl-1-hexanol was used.

IV. Hazard Assessment

A. Hazard Profile

To assess the hazard posed by the use of 2-EH as an inert ingredient in pesticide formulations, EPA considered a number of publicly-available sources including: published literature, peer-reviewed international documents (IUCLID[3] JECFA[4], OECD SIDS), and other standard available references.

[3]IUCLID, International Uniform Chemical Information Database, is a database of existing chemicals that is being compiled by the European Chemicals Bureau (ECB). IUCLID is the basic tool for data collection and evaluation within the EU-Risk Assessment Programme; it has been accepted by the OECD as the data exchange tool under the OECD Existing Chemicals Programme. http://ecb.jrc.it/

[4]JECFA is the Joint WHO/FAO Expert Committee on Food Additives. It conducts toxicological evaluations of food additives and contaminants in food. The resulting monographs are used by the Codex Alimentarius Commission and national governments to set international food standards and safe levels for protection of the consumer. In 1993 they published Food Additives Series 32. 2-Ethyl-1-Hexanol. http://www.inchem.org/documents/jecfa/jecmono/v32je04.htm

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. Except for eye and skin irritation, 2-EH is not acutely toxic.

Table 4. Summary of Acute Toxicity Data for 2-EH

Parameter		Toxicity Value *Toxicity Category*[a]	Reference
Oral LD_{50}	rat	2,000 to 3,700 mg/kg *Toxicity Category III*	JECFA 1993, citing Smyth et al 1969, Albro 1975; Scala 1973
	mouse	3,200 to 6,400 mg/kg *Toxicity Category III*	
Dermal LD_{50}	rabbit	2,000 to >2,600 mg/kg *Toxicity Category III*	JECFA 1993, citing Smyth et al 1969; Scala 1973
Inhalation, mice[b]		>227 ppm (1.21 mg/L) @ 6 hours; no deaths were seen	Scala 1973
Inhalation, rat[b]		>227 ppm (1.21 mg/L) @ 6 hours; no deaths were seen	Scala 1973
Eye Irritation, rabbit		severe[c]	Scala 1973
Skin Irritation, rabbit		moderate[c]	Scala 1973

[a]40 CFR 156.62

[b]Concentration of the 2-EH was "at atmospheres nearly saturated with the vapor..."

[c]Based on the researcher's scale of "slight-moderate-marked-severe;" the animals were observed for seven days.

Subchronic Toxicity

Patty's Handbook of Industrial Hygiene (Lington and Bevan 1991) and the JECFA report (1993) provided summaries of several subchronic toxicity studies, as follows. They are summarized in Table 5.

- Mice were fed 2-EH in their diet at a dose of approximately 1,500 mg/kg for four days. Increases in hepatic peroxisomes were observed (Lundgren et al 1988, as cited in Lington and Bevan 1991).

- Mice were gavaged with 0; 143; 351; 702; 1,053; or 1,755 mg/kg of 2-EH for 14 days. A significant increase in liver weight and number of hepatic peroxisomes were observed at the 702 mg/kg and higher doses (Keith et al 1992, as cited in Lington and Bevan 1991).

- Rats gavaged with 1,350 mg/kg of 2-EH for seven days showed increased liver weights and liver peroxisomes (Lake et al 1975, as cited in Lington and Bevan 1991).

- Rats fed 2.0% 2-EH (≈1,000 mg/kg) in their diet for 14 days showed no significant effects on peroxisome enzymes (Ganning et al 1982 cited in Lington and Bevan 1991).

- However, in another dietary study where rats were also fed 2.0% 2-EH in their diet (about 1,000 mg/kg) but for 21 days, a number of effects were noted including: decreased serum lipids, increased liver weights, and an increase in liver peroxisomes (Moody and Reddy 1978 and 1982, as cited in Lington and Bevan 1991).

- Rats were gavaged with 2-EH at a dose of 130 mg/kg/day for 14 days. No significant effects were seen on the testes, serum lipids, and various liver end points, including peroxisome induction (Rhodes et al 1984, as cited in Lington and Bevan 1991).

- Rats were gavaged with 100; 320; or 950 mg/kg for five days/week for 28 days. Liver weights and liver peroxisomes were significantly increased at 320 and 950 mg/kg (Hodgson 1987, as cited in Lington and Bevan 1991).

- Rats were gavaged with 0; 143; 351; 702; or 1,053 mg/kg of 2-EH for 14 days. A significant increase in liver weight and number of hepatic peroxisomes were observed at the 702 mg/kg and higher doses (Keith et al 1992, as cited in Lington and Bevan 1991).

Table 5. Summary of Subchronic Toxicity Data for 2-EH

Route, Species	Toxicity			Reference
	Dose	Exposure Duration (days)	Effect	
Oral, Mouse	1,500 mg/kg	4	↑ hepatic peroxisomes	Lundgren et al 1989, as cited in Lington and Bevan 1991
Oral, Rat	1,350 mg/kg	7	↑ in liver peroxisomes; ↑ liver weights	Lake et al 1975, as cited in Lington and Bevan 1991
Oral, Mouse	702 mg/kg	14	↑ in liver peroxisomes; ↑ liver weights	Keith et al 1992, as cited in Lington and Bevan 1991
Oral, Rat	702 mg/kg	14	↑ in liver peroxisomes; ↑ liver weights	Keith et al 1992, as cited in Lington and Bevan 1991
Oral, Rat	130 mg/kg/day	14	no significant effects were observed	Rhodes et al 1984, as cited in Lington and Bevan 1991
Oral, Rat	1,000 mg/kg	14	no significant effects on peroxisomes	Ganning et al 1982 cited in Lington and Bevan 1991
Oral, Rat	1,000 mg/kg	21	↑ in liver peroxisomes; ↑ liver weights; ↓ serum lipids	Moody and Reddy 1978 and 1982, as cited in Lington and Bevan 1991
Oral, Rat	320 mg/kg	28	↑ in liver peroxisomes; ↑ liver weights	Hodgson 1987, as cited in Lington and Bevan 1991

Neurotoxicity

No neurotoxicity data were identified for 2-EH.

Mutagenicity and Genotoxicity

Provided in Table 6 is a summary of available published genotoxicity data available on 2-EH. This table is adapted from the World Health Organization (WHO) Report (JECFA 1993, Table 2). All the reported results were negative except those of Seed (1982).

Table 6. Summary of Available Genotoxicity Data

Test	Test Subject	2-EH Concentration	Result	Reference
Ames Test[a]	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	0 to 1.0 µL/plate	negative	JECFA 1993, citing Kirby et al 1983
Ames Test[a]	*S. typhimurium* TA98, TA100, TA1535, TA1537	0 to 220 µg/plate	negative	JECFA 1993, citing Zeiger et al 1985
Ames Test[a]	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538, TA2637	0 to 2,000 µg/plate	negative[b]	JECFA 1993, citing Agarwal et al 1985
8-Azaguanine resistance assay[c]	*S. typhimurium* TA100	0 to 1.5 mM	positive[d]	JECFA 1993, citing Seed 1982
Mouse lymphoma assay[a]	L5178Y/TK+/- mouse lymphoma cells	0.01 to 0.24 µL/mL	negative	JECFA 1993, citing Kirby et al 1983
Rec assay	*Bacillus subtilis*	500 µg/disk	negative	JECFA 1993, citing Tomita et al 1982
CHO (Chinese hamster ovary) mutation assay	CHO cells	1.5 to 2.8 mM	negative	JECFA 1993, citing Phillips et al 1982
Unscheduled DNA synthesis assay	Primary rat hepatocytes	Not given	negative	JECFA 1993, citing Hodgson et al 1982
In vivo dominant lethal assay	ICR/SIM mice	250; 500; or 1,000 mg/kg bw/day for 5 days	negative	JECFA 1993, citing Rushbrook et al 1982
In vivo chromosomal aberration assay	F344 rat bone marrow cells	0.02; 0.07; or 0.21g/kg bw/day for 5 days	negative	JECFA 1993, citing Putnam et al 1983

[a]Both with and without metabolic activation.

[b]Moderate toxicity was reported in most cultures.

[c]Without metabolic activation.

[d]Small dose-related increase (maximum increase was approximately 3.5 times background) in mutation frequency accompanied by decreased survival (cytotoxicity).

In addition to what JECFA (1993) reported, a chromosome aberration study was reported by NTP[5] (1989) in which CHO cells were exposed *in vitro* to concentrations of 2-EH of 50, 108, or 233 μg/mL with and without activation. There was no increase in chromosome aberrations reported for any concentration of the test material either with or without activation.

Carcinogenicity

In the late 1980's EPA required (under TSCA, the Toxic Substance Control Act of 1976, section 4) that carcinogenicity data be submitted on 2-EH; in 1992 the results of two studies were submitted. In an 18-month oral study (see 57 FR 5454; February 14, 1992), male and female mice were gavaged with 2-EH at doses of 0; 50; 200; or 750 mg/kg/day. No substance-related changes were seen at 50 or 200 mg/kg/day. At 750 mg/kg/day, reduced body weight gain related to decreased food consumption and increased mortality was noted; also treatment-related hematological changes and slight, but not statistically-significant, increases were noted in focal hyperplasia of the epithelium of the forestomach. No statistically-significant increases were noted in tumor incidence.

In a 24-month oral study (see 57 FR 8454; March 10, 1992), male and female rats were gavaged five days/week for 24-weeks at 0; 50; 150; or 500 mg/kg/day. Dose-related reduced body weight gain was noted at 150 mg/kg/day and higher; clinical findings included poor general condition, labored breathing, and piloerection. Mortality occurred in females at 500 mg/kg/day. In summary, 2-EH was not shown to be carcinogenic in the mouse or rat. (US EPA 2006)

Developmental and Reproductive Toxicity

Oral

In an oral study, pregnant mice were gavaged with 2-EH at 1,525 mg/kg/day over gestation days (GD) 6 through 13. Severe maternal toxicity was observed as evidenced by lethality (34%, which is 17 dead out of 49 treated) and decreased body weight gain (3.9%). Neonatal death also was observed at this dosage (Hardin et al 1987; Lington and Bevan 1991).

In another oral study, pregnant rats were gavaged with 2-EH at ≈800 and 1,600 mg/kg bw (6.25 or 12.5 mmol/kg bw) on GD 12. On GD 20 the rats were killed; following cesarean section, implantation sites were determined *in situ* and the number of dead or resorbed fetuses was determined. Live fetuses were removed and examined; internal and external soft tissue and skeletal malformations were recorded. At the high-dose, statistically-significant effects were seen in the live fetuses; these

[5]NTP. 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.

include: hydronephrosis (8%), tail defects (5%), and limb defects (10%). The study investigator did not discuss maternal effects. (Ritter et al 1987; JECFA 1993)

In an oral study conducted by NTP (1991), microencapsulated 2-EH was provided to mice on GD 0 to 17 at 0%, 0.009%, 0.03%, or 0.09% in feed (these doses are equivalent to: 0; 13.5; 45.0; or 135 mg/kg/day) . At sacrifice (GD 17), the number of ovarian *corpora lutea* and uterine implantation sites, including resorptions, and dead or live fetuses, were recorded. Live fetuses were sexed and examined for external, visceral and skeletal malformations and variations. No dams died, delivered early or were removed from study. Pregnancy rate was high (93-96%) and equivalent across all groups. One control litter at 0% was fully resorbed; all other pregnant animals had live litters at scheduled necropsy. The numbers of live litters evaluated were 27 at 0.009% and 0.03% and 26 at 0) and 0.09% 2-EH. There was no treatment-related maternal toxicity observed in this study. Maternal body weights, weight gains (absolute or corrected for gravid uterine weight), gravid uterine weight and liver weight (absolute or relative to body weight) were unaffected. Food consumption (g/kg/day and g/day) was significantly increased for GD 0 to 3 at 0.09% and unaffected for all other time points evaluated. There were no effects of exposure to dietary 2-EH on any gestational parameters. The number of *corpora lutea*, uterine implantation sites (live, dead, resorbed), pre- and postimplantation loss, sex ratio (%, males) and live fetal body weight per litter (all fetuses or separately by sex) were all equivalent across all groups. There were also no treatment-related changes in the incidence of individual, external, visceral, skeletal or total malformations or variations. In conclusion, there were no maternal or developmental toxic effects of 2-EH dietary exposure throughout gestation at a concentration up to 135 mg/kg/day.

Dermal

2-EH is on the Office of Pollution Prevention and Toxics (OPPT) "Master Testing List"[6] for developmental toxicity data. In 1987 (see 52 FR 27452; July 21, 1987) the Chemical Manufacturers Association submitted two studies under TSCA section 4: "11 day dermal probe study in male and female B6C3F1 mice" and "11 day dermal probe study in male and female Fischer F344 rats." In the rat study, 25 mated females were dosed (via occluded dermal patch) for six hours/day over GD 6 through 15 at levels of: 0.3; 1.0; or 3.0 mL/kg/day (neat). Maternal toxicity (reduced weight gain) was noted at 3.0 mL/kg/day; exfoliation at the application site was seen at 1.0 mL/kg/day. No evidence of embryotoxicity, fetotoxicity, or teratogenicty were noted at any dose level. The NOAEL for maternal toxicity was 0.3 mL/kg/day, and for developmental toxicity, at least 3.0 mL/kg/day (US EPA 2006).

[6]The Master Testing List (MTL) provides a consolidated listing of OPPT's existing chemical testing priorities under TSCA and also includes the priority industrial chemical testing needs of OPPTS, other EPA Program Offices (e.g., Office of Water), other Federal agencies (e.g., U.S. Occupational Safety and Health Administration) and the TSCA Interagency Testing Committee.

In a dermal study, 2-EH was administered to pregnant rats by occluded dermal applications for six hour/day from GD 6 to 15 at doses of 0.0; 0.3; 1.0; or 3.0 mL/kg/day (equivalent to 0; 252; 840; and 2,520 mg/kg/day). Maternal effects included reduced body weight gain at the high dose and exfoliation and encrustation at the application site across all doses. There was no evidence of treatment-related developmental effects. The study authors report a NOAEL for maternal toxicity of 252 mg/kg/day based on skin irritation; the developmental NOEAL was at least 2,520 mg/kg/day with no teratogenicity (Tyl et al 1992; Lington and Bevan 1991).

Inhalation

To examine the validity of Richardson's Law[7], Nelson (Nelson et al 1990) reported a summary of his findings from a series of studies investigating the developmental toxicology of aliphatic alcohols administered by inhalation to rats. Pregnant rats were exposed to the maximally attainable vapor concentration of 2-EH which is 850 mg/m^3 (~190 ppm), for seven hours/day during GD 1 to 19. For developmental toxicology evaluations, dams were sacrificed on GD 20. Fetuses were removed, weighed, sexed, and examined for external malformations. No developmental toxicity was observed; the only maternal toxicity observed was a decrease in food consumption of 10-15%.

Dermal Absorption

The *in vitro* dermal flux for 2-EH was calculated to be 0.22 $mg/cm^2/hr$ in full thickness rat skin. (Lington and Bevan 1991; Barber 1992)

C. Metabolism and Pharmacokinetics

2-EH can be absorbed by the oral, dermal, and inhalation routes of exposure. The rate and extent of dermal uptake appears to be low. The metabolic fate of 2-EH has been studied in rats and rabbits. It is readily converted to 2-ethylhexanoic acid which can then be oxidized to a hydroxy acid and a diacid (Lington and Bevan 1991).

[7]In the late 1800's Richardson observed that, among the alcohols, toxicity to adult animals generally increased with chain length, up to about six carbons, after which the toxicity decreased.

D. Special Considerations for Infants and Children

2-EH is of low acute toxicity by the oral and dermal routes (Toxicity Category III). In an oral developmental toxicity study conducted by NTP (1991), no maternal or developmental toxic effects were noted up to a concentration 135 mg/kg/day. The Agency expects that any oral, dermal, or inhalation exposure to 2-EH resulting from its use as an inert ingredient in pesticide products will be low. For example, one researcher found 2-EH in fruit at 1 to 4 ppb (Gomez et al 1993) and worst-case inhalation exposure is estimated to be 0.11 mg/kg/day (US EPA 2004b). Thus, based on the available information, a safety factor analysis has not been used to assess the risks resulting from the use of 2-EH; therefore, an additional tenfold safety factor for the protection of infants and children is unnecessary.

V. Environmental Fate Characterization and Drinking Water Considerations

The Office of Pesticide Programs (OPP) Environmental Fate and Effects Division (EFED) has reviewed (US 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 C6 through C8 alcohols, which includes 2-EH, are water soluble and mobile in terrestrial and aquatic environments, moving mainly with the water phase to surface and ground water receptors. Volatility from soil (vapor pressure 0. 36 mm Hg), and water (Henry's law constant of 2.3×10^{-5}atm m^3/mole) 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 dissipation. Fugacity modeling predicts approximately 50% to 55% of releases will be associated with the water phase and 40% with soils. Predicted dissipation half-lives range from 1.0 to 1.5 days in rivers and 15 to 20 days in lakes. These data suggest that 2-EH is not very persistent in the environment.

2-EH 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. (US EPA 2002)

VI. Exposure Assessment

Individuals may be exposed to 2-EH through the oral, dermal, and inhalation routes of exposure. In terms of a pesticide inert ingredient, EPA expects that exposure to 2-EH would primarily be through the oral route, via consumption of agricultural crops to which this inert ingredient has been applied as a solvent, cosolvent, or defoamer and exposure through drinking water. Additional dermal and inhalation exposure may occur from residential use of pesticide products containing 2-EH on ornamental plants and lawns, as well as from the use in and around the home and on textiles. Expected food, drinking water, and residential exposures are discussed below.

Food and Drinking Water

As an inert ingredient of pesticide products applied to growing crops, RACs after harvest, or to animals, potential human exposure would be via the oral route, through consumption of food[8] to which a 2-EH containing pesticide product has been applied or through drinking water. Because of its environmental fate properties, EPA expects that drinking water exposures would be low as 2-EH readily biodegrades in soil and water.

2-EH is expected to be found in food, but not necessarily at significant levels. It has been identified as a plant volatile in a number of fruits including cassava, apricots, plums, apples, and nectarines. For example, Gomez et al (1993) noted that 2-EH is found as a volatile in apricots and plums at 1 to 4 ppb. Also, it is used as a flavoring agent (JECFA 1993) and an FDA indirect food additive.

Residential

Exposure to 2-EH's use as an inert ingredient may occur in residential settings through its use on ornamental grasses; ornamental plants; forest lands; termite control; general insect control around buildings; crack and crevice treatment; home vegetable gardens; insect repellent for pets; home bug spray; weed killer for patios, driveways, etc.; and fungi control in textiles.

Residential exposure may occur through the inhalation or dermal route. To estimate worst-case residential indoor inhalation exposure, EPA modeled a scenario where an aerosol paint product contained 95% 2-EH 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% 2-EH (i.e., "Latex Paint" scenario). Using E-FAST[9] (US EPA 2004b) and standard model

[8]Food crops include berries, grapes, citrus, nuts, pome fruits, stone fruits, hops, cucurbits, tomatoes, cole crops, leafy greens, tubers, corn, beans, grasses, grains, and cotton. Ornamental grasses and plants include sod farms, golf courses, lawns, parks, flowers, trees, miscellaneous plants such as privet, and Christmas trees.

[9]The E-FAST (Exposure and Fate Assessment Screening Tool) 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.

assumptions (model results are provided in Appendix A), EPA determined that the Average Daily Concentration (which is an exposure metric for inhalation exposure) for 2-EH would be 1.7 mg/m^3 (0.31 ppm); for dermal exposure, the Average Daily Dose (which is an exposure metric for dermal exposure) is 0.11 mg/kg/day. A summary of the E-FAST results is provided in Table 7. Note that for outdoor-use products, EPA believes that exposure would be no greater than for indoor use due to its vapor pressure and more ready dissipation outdoors.

Table 7. Modeled Exposure Estimates for Inhalation and Dermal Exposure to 2-EH

Exposure Route	E-FAST Scenario Used to Model Exposure	%2-EH Assumed to Be in Product	Exposure[a]
Inhalation	Indoor Aerosol Paint	95	1.7 mg/m^3 (0.31 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.

These estimates are considered worst-case for several reasons:

(1) In the E-FAST run, a high concentration of 2-EH was assumed (i.e., 95%); it is unlikely that all indoor residential-use products containing 2-EH as an inert ingredient contain it at such a high concentration. For example, a search on the National Institutes of Health (NIH) Household Products Database (NIH 2004b) yielded no home-use products with 2-EH has an ingredient. A cursory review of several Material Safety Data Sheets (MSDS) for residential-use pesticides containing 2-EH as an inert ingredient shows 2-EH concentrations less than 10%.

(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 scenarios that would yield the greatest exposures (indoor aerosol paint for inhalation and latex paint for dermal) were used.

Therefore, EPA does not expect actual exposure from residential use of 2-EH as an inert ingredient to exceed these modeling estimates and expects that outdoor exposure concentrations also would be lower.

Modeled estimates of concentrations and doses are designed to reasonably overestimate exposures, for use in screening level assessment.

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 2-EH, 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 2-EH as an inert ingredient in pesticide formulations.

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 2-EH and any other substances and, 2-EH 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 2-EH 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 2-EH, EPA has determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to 2-EH used as an inert ingredient in pesticide products 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 2-EH is expected to result in human exposure below any dose level that would produce any adverse effect. This is based on available animal toxicity studies, the use patterns of the 2-EH, and the fact that two of the tolerance exemptions have formulation limits of 2.5%. Therefore, it is recommended that the three exemptions from the requirement of a tolerance established for residues of 2-EH can be considered reassessed as safe under section 408(q) of FFDCA.

Overall, 2-EH is of low acute toxicity by the oral and dermal routes (Toxicity Category III); however, it is moderately irritating to the skin and severely irritating to the eye (JECFA 1993; Scala 1973). In subchronic repeat dose studies, hepatic effects, which included increased liver weights and peroxisome proliferation in rats and mice, were noted at doses of 320 mg/kg for an exposure duration of 28 days. Due to its concern that 2-EH's ability to cause peroxisome proliferation may induce cancer, EPA required oncogenicity testing under TSCA section 4 (proposed rule; 51 FR 45487, December 19, 1986) After reviewing the studies submitted under the rule, the Agency concluded that 2-EH is not carcinogenic in the mouse or rat (US EPA 2006).

No evidence of neurotoxicity was identified. The available data indicate that 2-EH is not mutagenic. Some of the developmental toxicity studies showed effects; however, EPA believes these are not of concern due to limitations in the studies. For example, Hardin et al (1987) reported teratogenic effects in the offspring but they occurred at a high dose (1,525 mg/kg/day) and in the presence of severe maternal toxicity; only a single dose level was used in the study. Ritter et al (1987) also reported developmental effects in offspring at a high dose (1,600 mg/kg bw) but they did not report whether or not there were maternal effects so it is difficult to determine the significance of their data. A key oral developmental toxicity study, that conducted by NTP (1991) in mice, concluded that 2-EH did not cause maternal or developmental toxic effects at doses as high as 135 mg/kg/day. A dermal toxicity study conducted in mice and rats showed no developmental toxicity at 3.0 mL/mg/day. An inhalation study performed using rats showed no developmental toxicity at 850 mg/m^3 (~190 ppm). In summary, EPA believes that the overall weight of evidence shows that 2-EH is not developmentally toxic.

Further, the Agency believes that any exposure to 2-EH used as an inert ingredient in pesticide formulations would occur at a level much lower than the levels where any effects were noted in animal studies. Individuals are exposed to 2-EH naturally—it has been found as a flavor volatile in a number of fruits. The WHO has approved its use as a flavoring agent (JECFA 1993) and FDA allows it as an indirect food additive, which means that 2-EH may come in contact with food through its use in paper products. Thus, any residues on food resulting from 2-EH's use as an inert ingredient in a pesticide formulation are expected to be low because 2-EH is biodegradable, and levels are not expected to be greater than what occurs naturally in foods consumed.

For residential uses, EPA does not expect exposure levels to be significant. Worst-case chronic dermal exposure, which assumes that the product is 95% 2-EH, is estimated to be 0.11 mg/kg/day. In a dermal developmental toxicity study (Tyl et al 1992), maternal effects such as reduced body weight gain and exfoliation were seen at the highest dose tested, which was 2,520 mg/kg/day. Worst-case chronic inhalation exposure, where again the product was assumed to be 95% 2-EH, is estimated to be 0.31 ppm or 1.7 mg/m^3. In a developmental study conducted by the inhalation route (Nelson et al 1990), only a slight maternal effect was observed (decreased food consumption) at the highest dose tested, which was 850 mg/m^3 (~190 ppm). Thus, the Agency believes that residential exposure resulting from the inert use of 2-EH will not be of concern.

X. Ecotoxicity and Ecological Risk Characterization

The Agency finds that, based on ecotoxicity estimates, 2-EH is practically nontoxic on an acute basis. For freshwater and marine/estuarine fish, the acute toxicity estimates range from 6.5 to 19.5 mg/L and for *Daphnia magna*, 22.4 mg/L. For mysid shrimp, acute toxicity is estimated to be 3.4 mg/L and for algae 14.6 mg/L. (U.S EPA 2002) On an acute basis, 2-EH is practically nontoxic for terrestrial animal toxicity; this is based on available rat toxicity data.

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APPENDIX A: E-FAST Results for 2-Ethyl Hexanol

Inhalation Exposure: Inputs

CEM Inputs		ID Number: 2-EH	
Product: Aerosol		Chemical Name: 2-Ethyl Hexanol	
Scenario: Aerosol Paint		Population: Adult	
Molecular Weight (g/mole):	130.2	Vapor Pressure (torr):	0.36
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		

Inhalation Exposure: Outputs

CEM Inhalation Exposure Estimates

ID Number: 2-EH

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)	4.45e-02	2.74e+04
	$LADC_{pot}$ (mg/m^3)	2.42e-01	2.74e+04
Chronic Non-Cancer			
	ADD_{pot} (mg/kg-day)	3.04e-01	4.02e+03
	ADC_{pot} (mg/m^3)	1.65e+00	4.02e+03
Acute			
	ADR_{pot} (mg/kg-day)	4.91e+01	1.00e+00
	Cp_{pot} (mg/m^3)	2.52e+03	1.00e+00

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

LADC - Lifetime Average Daily Concentration (mg/m^3)

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

Dermal Exposure: Inputs

CEM Inputs		ID Number: 2-EH	
Product: Dermal		Chemical Name: 2-Ethyl Hexanol	
Scenario: Latex Paint		Population: Adult	
Molecular Weight (g/mole):	130.2	Vapor Pressure (torr):	0.36
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 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:	111111123111111111112744411	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/cm2-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		

Dermal Exposure: Outputs

CEM Inhalation Exposure Estimates

ID Number: 2-EH

Scenario: Latex 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): 4

Exposure Units	Result	AT (days)
Chronic Cancer		
$LADD_{pot}$ (mg/kg-day)	1.47e-02	2.74e+04
$LADC_{pot}$ (mg/m^3)	8.00e-02	2.74e+04
Chronic Non-Cancer		
ADD_{pot} (mg/kg-day)	1.09e-01	4.02e+03
ADC_{pot} (mg/m^3)	5.45e-01	4.02e+03
Acute		
ADR_{pot} (mg/kg-day)	2.27e+01	1.00e+00
Cp_{pot} (mg/m^3)	3.35e+02	1.00e+00

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

LADC - Lifetime Average Daily Concentration (mg/m^3)

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

ADC - Average Daily Concentration (mug/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