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

OFFICE OF PREVENTION,
PESTICIDES, AND TOXIC SUBSTANCES

DATE: July 31, 2006

ACTION MEMORANDUM

SUBJECT: Inert Reassessment—Ethyl Acetate (CAS Reg. No. 141-78-6) and Amyl Acetate (CAS Reg. No. 628-63-7)

FROM: Pauline Wagner, Chief Pauline Wagner 8/1/06
Inert Ingredient Assessment Branch
Registration Division (7505P)

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

I. FQPA REASSESSMENT ACTION

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

Chemicals: Ethyl Acetate and Amyl Acetate

CFR: 40 CFR 180.910 (ethyl acetate); 40 CFR 180.910 (amyl acetate)

CAS #: 141-78-6 (ethyl acetate) and 628-63-7 (amyl acetate)

Use Summary: Both acetates have a number of industrial uses such as solvents for lacquers, paints, and inks. Pharmaceutically, ethyl acetate is a flavoring aid and amyl acetate is used in extraction of penicillin. As inert ingredients in pesticide formulations, ethyl acetate is used as a solvent or cosolvent; amyl acetate is used as a solvent, cosolvent, or attractant. Both are used on agricultural crops.

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

II. MANAGEMENT CONCURRENCE

I concur with the reassessment of the one exemption from the requirement of a tolerance for the inert ingredient ethyl acetate (CAS Reg. No. 141-78-6) and with the List reclassification determination, as described above. I also concur with the reassessment of the one exemption from the requirement of a tolerance for the inert ingredient amyl acetate (CAS Reg. No. 628-63-7) and with the List reclassification determination, as described above. I consider the two exemptions established in 40 CFR 180.910 to be reassessed for purposes of FFDCA's section 408(q) as of the date of my signature, below. A *Federal Register* Notice regarding this tolerance exemption reassessment decision will be published in the near future.

Lois A. Rossi

Lois A. Rossi, Director
Registration Division

August 1, 2006

Date:

cc: Debbie Edwards, SRRD
Joe Nevola, SRRD

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OFFICE OF PREVENTION,
PESTICIDES, AND TOXIC SUBSTANCES

July 31, 2006

MEMORANDUM

SUBJECT: Reassessment of One Exemption from the Requirement of a Tolerance for Ethyl Acetate (CAS Reg. No. 141-78-6) and One Exemption from the Requirement of a Tolerance for Amyl Acetate (CAS Reg. No. 628-63-7)

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

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

BACKGROUND

Attached is the science assessment for ethyl and amyl acetate. The purpose of this document is to reassess the existing exemptions from the requirement of a tolerance for residues of ethyl acetate and amyl acetate as required under the Food Quality Protection Act (FQPA). These two chemicals are being assessed in one document due to similar use patterns and toxicity profiles. This reassessment summarizes available information on the use, physical/chemical properties, toxicological effects, exposure profile, environmental fate, and ecotoxicity of ethyl and amyl acetate.

EXECUTIVE SUMMARY

Ethyl and amyl acetate are solvents. They are important industrially in lacquers, paints, and inks. Pharmaceutically, ethyl acetate is a flavoring aid and amyl acetate is used in extraction of penicillin. Both acetates are naturally-occurring constituents found in plants, including a wide-range of commonly consumed fruits such as apples, bananas, and nectarines. Its exemption from the requirement of a tolerance is under 40 CFR 180.910—ingredients in pesticide formulations applied to growing crops or to raw agricultural commodities after harvest.

The overall acute toxicity of ethyl and amyl acetate is low. Oral LD_{50} values for the rat and rabbit are at least in Toxicity Category III, and eye and skin irritation appears to be slight. At exposure levels expected for the use of ethyl and amyl acetate as inert ingredients in pesticide products, developmental toxicity is not expected and the young are not expected to be more sensitive to its effects than adults. Overall, ethyl acetate does not appear to be mutatgenic.

Any exposure to ethyl and amyl acetate is expected to occur at levels much lower than the levels where any effects were seen in animal studies. Individuals are exposed to ethyl and amyl acetate naturally—the acetates have been detected in various biological materials. The World Health Organization (WHO) has approved ethyl acetate as a flavoring agent (IPCS 2002) and FDA has classified it as GRAS (generally regarded as safe). Finally, because of the environmental fate properties of ethyl and amyl alcohol, EPA does not expect concentrations of concern to occur in drinking water and for the same reason, any residential exposure is expected to be low.

Taking into consideration all available information on ethyl and amyl acetate, EPA has determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to ethyl and amyl acetate when used as inert ingredients in pesticide products when considering dietary (i.e., food and drinking water) exposure and all other nonoccupational sources of pesticide exposure for which there is reliable information. Therefore, it is recommended that the two exemptions from the requirement of a tolerance established for residues of ethyl and amyl (one tolerance for each acetate) can be considered reassessed as safe under section 408(q) of FFDCA.

I. INTRODUCTION

This report provides a qualitative assessment for ethyl and amyl acetate, inert ingredients in pesticide formulations that are exempted from the requirement of a tolerance when applied to growing crops or raw agricultural commodities (RACs) after harvest (40 CFR 180.910). Because of their similar use patterns and toxicity, ethyl and amyl acetate are being assessed together, in this single document.

Ethyl acetate is an acetate molecule (CH_3COO^-) with a two carbon chain attached. Amyl acetate, on the other hand, is an acetate molecule with a five carbon straight-chain attached. Both acetates have a number of industrial uses such as solvents for lacquers, paints, and inks. Pharmaceutically, ethyl acetate is a flavoring aid and amyl acetate is used in extraction of penicillin. Both acetates are naturally-occurring constituents found in plants, including a wide-range of commonly consumed fruits such as apples, bananas, and nectarines.

Ethyl and amyl acetate have been identified as chemicals meeting the criteria of EPA's High Production Volume (HPV) Challenge Program[1]. They are being sponsored under the purview of the Organization for Economic Cooperation and Development's (OECD) SIDS (Screening Information Data Set) Program;[2] the United States is the sponsoring country. In 2002, participants at the SIDS Initial Assessment Meeting (SIAM) for ethyl acetate concluded that this "chemical is of low priority for further work because of low toxicity to humans and the environment and low potential for exposure" (OECD 2002). The SIARs (SIDS Initial Assessment Report) for ethyl acetate and for amyl acetate are currently under preparation.

II. USE INFORMATION

A. PESTICIDE USES

Ethyl and amyl acetate are currently used as inert ingredients only. There are currently no registered pesticide products containing ethyl or amyl acetate as active ingredients. As inert ingredients, ethyl acetate is used as a solvent or cosolvent; amyl acetate is used as a solvent, cosolvent, or attractant.

[1]HPV chemicals are those that are manufactured or imported into the United States in volumes greater than one million pounds /year. The HPV Challenge Program is a voluntary partnership among 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. 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. The priorities are set at the SIAM. http://cs3-hq.oecd.org/scripts/hpv/

The exemptions from the requirement of tolerance for ethyl and amyl acetate are provided in Table 1 below.

Table 1. Tolerance Exemptions Being Reassessed in this Document

CFR Citation				CAS Registry Number and 9CI Name
40 CFR 180	Inert Ingredient	Limits	Uses	
Ethyl Acetate				
.910[a]	Ethyl acetate	(none)	solvent, cosolvent	141-78-6 Acetic acid ethyl ester
Amyl Acetate				
.910[a]	Amyl acetate	(none)	solvent, cosolvent, attractant	628-63-7 Acetic acid, pentyl ester

[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 RAC's after harvest.

B. OTHER USES

Ethyl acetate is used as a solvent for lacquers, enamel coatings, inks, plastics, and in chemical synthesis. Amyl acetate is primarily used as a solvent for nitrocellulose lacquers and paints. Other important uses of these acetates are as extraction solvents in penicillin manufacture and electrostatic spray coatings for automobiles. Miscellaneous uses include solvents in photographic film, leather polishes, and dry cleaning preparations. (63 FR 1464; 62 FR 42123)

In addition to their industrial and pharmaceutical uses, ethyl acetate is used as a flavoring agent (note: amyl acetate is not used as a flavoring agent or additive). Ethyl acetate has been evaluated by JEFCA[3], the Joint WHO (World Health Organization)/FAO (Food and Agriculture Organization) Expert Committee on Food Additives (JECFA; IPCS 2002). Its U.S. Food and Drug Administration (FDA)-approved direct food additive uses are listed in Table 2 below.

Table 2. FDA Food Additive Uses for Ethyl Acetate[a]

Name	21 CFR	Use Pattern
Ethyl Acetate	173.228	Secondary Direct Food Additives Permitted In Food For Human Consumption—Solvents, Lubricants, Release Agents and Related Substances
Ethyl Acetate	182.60	Substances Generally Recognized As Safe—Synthetic flavoring substances and adjuvants

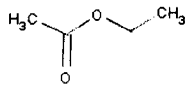
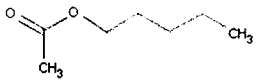
[a]**Note**: Amyl acetate is not an FDA food additive.

[3]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.

III. PHYSICAL AND CHEMICAL PROPERTIES

Some of the physical and chemical characteristics of ethyl and amyl acetate, along with their structure and nomenclature, are found in Table 3.

Table 3. Physical and Chemical Properties of Ethyl Acetate and Amyl Acetate

Parameter	Ethyl Acetate	Amyl Acetate
Structure		
CAS Reg. No. and 9CI Name	141-78-6 Acetic acid ethyl ester	628-63-7 Acetic acid, pentyl ester
Empirical Formula	$C_4H_8O_2$	$C_7H_{14}O_2$
Molecular Weight	88.11	130.19
Common Names	acetic ether, acetidin, acetoxyethane, ethyl ester, ethyl ethanoate, vinegar naphtha NIH 2004	1-pentanol acetate, 1-pentyl acetate, amyl acetic ester, banana oil, chlordantoin, pear oil, pentyl acetate, primary amyl acetate, n-amyl acetate, n-pentyl acetate, n-pentyl ethanoate NIH 2004
Physical State	Clear, volatile, flammable liquid; characteristic fruity odor; pleasant taste when diluted Merck 2005	Volatile solvent with a pear-like odor Grant and Schuman 1993
Melting Point	-83°C Merck 2005	-70.8°C Weast 1980
Boiling Point	77°C Bisesi 2001	149.25°C Weast 1980
Water Solubility	10% at 25°C Merck 2005	1,000 mg/L US EPA 2006a
Other Solubility	miscible with alcohol, acetone, chloroform, ether Merck 2005	miscible with alcohol, ether Weast 1980
Relative Density (water=1)	0.902 at 20°C Merck 2005	0.8756 at 20°C Weast 1980
Relative Vapor Density (air=1)	3.04 Merck 2005	4.5 Bisesi 2001
Vapor Pressure	74.4 mm Hg at 20°C AIHA 1964	4 mm Hg OSHA 1978
Log P_{ow}	0.73 US EPA 2006a, citing Hansch et al 1975	2.30 US EPA 2006a, citing Abraham et al 1994
Henry's Law Constant	1.34×10^{-4} atm m^3/mole US EPA 2006a, citing Butler et al 1935	3.88×10^{-4} atm m^3/mole US EPA 2006a, citing et al 1985

IV. HAZARD ASSESSMENT

A. Hazard PROFILE

To assess the hazard posed by the use of ethyl and amyl acetate as an inert ingredient in pesticide formulations, EPA considered a number of publicly-available sources including: published literature, peer-reviewed international documents (IUCLID[4], JEFCA), and other standard available references. Additionally, EPA-reviewed data were available for neurotoxicity and subchronic systemic toxicity.

In the early 1990's EPA issued a final rule (58 FR 40262) under the authority of the Toxic Substance Control Act (TSCA)[5] requiring manufacturers and/or processors to conduct testing for neurotoxicity on ethyl and n-amyl acetate. In 1995 (60 FR 28409) and 1997 (62 FR 42123) the Chemical Manufacturers Association submitted acute and subchronic neurotoxicity data on ethyl acetate. In 1997 (62 FR 11183) and 1998 (63 FR 1464) Regnet Environmental Services, on behalf of Union Carbide Corporation, submitted acute and subchronic neurotoxicity data on n-amyl acetate. Provided below under "Toxicological Data" are the data summaries posted on EPA's Prevention, Pesticides & Toxic Substances website (2006e).

Regarding the subchronic toxicity study, EPA's Office of Office of Solid Waste sponsored a 90-day oral study in 1986 because of a lack of information in the literature on the toxicity of ethyl acetate. Its summary from the Integrated Risk Information System (IRIS) database (US EPA 1988) is provided below.

B. TOXICOLOGICAL DATA

Acute Toxicity

A summary of the other acute toxicity parameters, along with their corresponding 40 CFR 156.62 Acute Toxicity Categories, is provided in Table 4. In addition to the information provided in Table 4, data are also provided in discussion format on the acute neurotoxicity of ethyl and amyl acetate.

[4]IUCLID, the International Uniform Chemical Information Database, is a database of existing chemicals that is being compiled by the European Chemicals Bureau (ECB).

[5]Section 4 of TSCA contains authority for EPA to require development of data relevant to assessing the risk to health and the environment posed by exposure to particular chemical substances or mixtures.

Table 4. Summary of Acute Toxicity Data for Ethyl and Amyl Acetate

Parameter		Toxicity Value *Toxicity Category*[a]	Reference
Ethyl Acetate			
Oral LD_{50}	rat	5.6 g/kg *Toxicity Category IV*	Patty 1981, citing Opdyke 1974
	rabbit	4.94 g/kg *Toxicity Category III*	Patty 1981, citing Munch 1972
Inhalation LC_{50}	rat (6-hour)	16,000 ppm (58 mg/L) *Toxicity Category IV*	NIOSH 1996, citing Clayton and Clayton 1981
	mouse (2-hour)	12,295 ppm (44 mg/L) *Toxicity Category IV*	NIOSH 1996, citing Izmerov et al 1982
	rat (unknown exposure period)	200.0 mg/L (55,000 ppm) *Toxicity Category IV*	Bisesi 2001, citing Snapper et al 1941
Dermal LD_{50} rabbit (24-hour covered contact)		>18 g/kg bw *Toxicity Category III*	CCOHS 1995, citing Smyth et al 1962
Eye Irritation, rabbit		Minimal[b] "slightly injurious"[b,c]	Bos et al 1991 Grant and Schuman 1993, citing Smyth 1962, 1969
Amyl Acetate			
Oral LD_{50}	rat	>1,600 mg/kg[d] *Toxicity Category III*	Eastman Kodak 1994
	rat	6,500 mg/kg *Toxicity Category IV*	Lewis 2000
	rabbit	7,400 mg/kg *Toxicity Category IV*	Lewis 2000
Inhalation LC_{Lo}, rat (8-hour exposure)		5,200 ppm (28 mg/L) *Toxicity Category IV*	Lewis 2000
Dermal LD_{50} rabbit		9.5 mL/kg	Ballantyne et al 1986
Skin Irritation, guinea pig		slight	Ballantyne et al 1986
Skin Sensitization, guinea pig[e]		Slight potential to induce immune-mediated hypersensitivity	Ballantyne et al 1986
Eye Irritation, rabbit		"slightly injurious"[b,c]	Grant and Schuman 1993, citing Smyth 1962, 1969

[a]40 CFR 156.62; [b]The Draize Test; [c]On a scale of 1 to 10, the investigators graded the irritation as 2 which the author reported as "slightly injurious;" [d]Submission under TSCA section 8(d); [e]Magnusson and Kligman procedure.

Acute Neurotoxicity

Ethyl Acetate. In acute testing (conducted according to Guideline EPA 540/09-01-123) male and female rats (14/sex/dose) were exposed via the inhalation route for six hours to concentrations of: 0; 600; 3,000; or 6,000 ppm. No mortality was observed during the study and no overt clinical signs were noted during the exposure or observation period. Body weight loss was noted for both sexes at all concentrations on the day following exposure. Decreased absolute body weight was noted for both sexes from the 6,000 ppm group following exposure. Body weight gains were observed for all exposure groups on subsequent days. There were no gross lesions in any animal at necropsy. Functional observational battery (FOB) findings were observed solely at the initial postexposure measurement period in animals from the 3,000 and 6,000 ppm

groups. They included drooping or closing eyelids, gait alterations, labored or audible breathing, decreased mean body temperature, hunched posture, decreased pupil size, piloerection, decreased mean forelimb grip strength, and sleeping during cageside observations. The NOEL for neurotoxicity was 600 ppm. (60 FR 28409; US EPA 2006e)

Amyl Acetate. In an acute whole-body inhalation test (conducted according to Guideline EPA 540/09-01-123) male and female rats (10/sex/dose) were exposed for six hours to concentrations of: 0; 500; 1,500; or 3,000 ppm. No overt clinical signs of toxicity or changes in body weight, automated motor activity measurements, or FOB evaluations were found under the conditions of this study. The NOEL in the study was 3,000 ppm. (62 FR 11183; US EPA 2006e)

Ethyl and Amyl Acetate. Bowen and Balster (1997) conducted experiments to compare the acute neurobehavioral effects of inhaled ethyl and amyl acetate after 20-minute inhalation exposures in mice using locomotor activity and a FOB. Ethyl acetate was tested at concentrations of 0; 250; 500; 1,000; or 2,000 ppm. Amyl acetate was tested at 0; 500; 1,000; 2,000; or 4,000 ppm. Ethyl acetate produced significant decreases in locomotor activity at the highest concentrations examined (2,000 ppm) while no effects were seen with amyl acetate. Recovery from the acute effects of ethyl acetate was rapid and began within minutes of removal from the exposure chamber.

Subchronic Toxicity

Ethyl Acetate, Oral. Groups of male and female rats were gavaged daily with 0; 300; 900; or 3,600 mg/kg/day of ethyl acetate for up to 93 days. An interim sacrifice was made on days 44 and 45, while the remaining rats were taken on days 91, 92, and 93. The rats were examined for mortality, morbidity, overt clinical signs, body weight gain, and food consumption. Hematology, clinical chemistry, and urinalysis parameters were monitored and ophthalmological examinations were performed before the interim and final sacrifices.

Survival was high—there were no deaths in the controls on 300 mg/kg/day groups. In the 900 mg/kg/day group, 93% of the animals survived to study completion and in the 3,600 mg/kg/day group, 77% of the animals survived. Males in the high-dose group (3,600 mg/kg/day) showed significant toxic effects, which manifested as depressed body and organ weights, and depressed food consumption. The next lower dose (900 mg/kg/day) did not produce any adverse effects in either male or female rats and is, therefore, considered a NOEL. (U.S. EPA. 1986; US EPA 1988)

Ethyl Acetate, Inhalation. In subchronic whole-body testing (conducted according to Guideline EPA 540/09-01-123) male and female rats were exposed to ethyl acetate vapor for 6 hours/day, 5 days/week, for 99 to 100 days to concentrations of: 0; 350; 750; or 1,500 ppm. Observations during exposure confirmed the presence of acute effects on nervous system function (diminished behavioral response to an alerting stimulus) at the 750 and 1,500 ppm level. The subchronic FOB did not identify compound-related sensory or motor anomalies of toxicological relevance. A statistically-significant reduction in motor activity (23% reduction in total duration of movements) for 1,500 ppm females was observed during test week 13. Reduction in motor activity was judged to be a nonspecific manifestation of systemic toxicity. Neuropathological evaluation did not reveal any compound-related abnormalities. The LOEL for male rats was 350 ppm and a NOEL was not demonstrated. The LOEL for female rats was 750 ppm and the NOEL was 350 ppm. (62 FR 42123; US EPA 2006e)

In a subchronic whole-body operant behavior study (conducted according to Guideline EPA 540/09-01-123), male rats were exposed to ethyl acetate vapor for 6 hours/day, 5 days/week, for 13 weeks to concentrations of: 0; 350; 750; or 1,500 ppm. There were treatment-related effects of 750 ppm and 1,500 ppm of ethyl acetate on clinical observations during exposures that consisted of a diminished alerting response to delivery of a punctate auditory stimulus. These sedative effects during exposure were acute rather than cumulative consequences of subchronic exposure. There were no treatment-related effects on clinical observations or performance of operant tasks. The NOEL was determined to be 350 ppm. Analysis of operant behavior did not reveal any cumulative or enduring effects on performance of complex behavioral tasks up to 1,500 ppm. (62 FR 42123; US EPA 2006e)

Amyl Acetate, Inhalation. In a subchronic whole-body inhalation test (conducted according to Guideline EPA 540/09-01-123) rats were exposed for 6 hours/day, 5 days/week, for 13 weeks to concentrations of: 0; 300; 600; or 1,200 ppm. Regarding FOB: during the first two weeks there was a reduction in activity during exposure to 600 and 1,200 ppm. This effect did not persist after the end of exposure. No concentration-related changes were found in FOB evaluations under the conditions of this study. For the acute sedative effects the LOEL was 600 ppm and the NOEL was 300 ppm. Looking at motor activity: no changes in automated motor activity measurements were found under the conditions of this study. The NOEL for motor activity was 1,200 ppm (the highest concentration tested). For neuropathology: microscopic evaluation of the brain and spinal cord from the high concentration rats revealed no morphological differences from the control rats; thus there were no compound-related changes. The NOEL for neuropathology was 1,200 ppm for the study (highest concentration tested). (63 FR 1464; US EPA 2006e)

Chronic Toxicity and Carcinogenicity

No information on chronic toxicity or carcinogenicity was identified for ethyl and amyl acetate.

Mutagenicity and Genotoxicity

Ethyl Acetate. Chinese hamsters were exposed to a single dose of 10 mL/kg (473 mg/kg) of ethyl acetate (a known inducer of aneuploidy in the yeast *Saccharomyces cerevisiae*) administered intraperitoneally. Results in the micronucleus test were negative. The study investigator repeated the experiment at a higher dose (2,500 mg/kg) using the oral route. Results were again negative. (Basler 1986)

Ishidate et al (1984) conducted a reverse mutation assay (Ames test) and *in vitro* chromosomal aberration test on ethyl acetate. In the reverse mutation assay, *Salmonella typhimurium* strains TA92, TA1535, TA100, TA1537, TA94, and TA98 were used without S9 activation. At the maximum dose, which was 5 mg of ethyl acetate/plate, no significant increases in the number of revertant colonies were detected (i.e., the test was negative for reverse mutation). In the chromosomal aberration test, Chinese hamster cells showed chromosome aberrations (i.e., the test was positive) at the maximum dose of 9.0 mg/mL.

Loveday et al (1990) reported the findings of research conducted by the Health and Human Services National Toxicology Program (NTP 1986b) where ethyl acetate was studied for its ability to induce sister chromatid exchanges (SCEs) and chromosomal aberrations in cultured Chinese hamster ovary (CHO) cells. Without S9 activation (and a dose of 1.51 mg/mL), ethyl acetate was negative for SCE and with activation (4.02 mg/mL), it was positive. In the chromosomal aberration tests without and with S9 activation (the doses were 5.02 and 5.01 mg/mL respectively), the results were negative.

NTP (1986a) conducted the Ames Test (or Salmonella Mutagenicity Test) on several strains of bacteria, with and without S9 activation, using the rat and hamster. The results were negative.

Provided in Table 5 is a summary of the mutatgenicity data found in the published literature. Overall, ethyl acetate does not appear to be mutagenic.

Table 5. Summary of Mutagenicity Data for Ethyl and Amyl Acetate

Test	Species	Dose	Result	Reference
Ethyl Acetate				
Micronucleus	Hamster	10 mL/kg (473 mg/kg)	negative	Basler 1986
		2500 mg/kg	negative	
Ames	*Salmonella typhimurium*	5 mg/plate (maximum dose)	negative	Ishidate et al 1984

Test	Species	Dose	Result	Reference
Chromosomal Aberration	Chinese hamster cells	9.0 mg/mL (maximum dose)	positive	Ishidate et al 1984
SCE's	CHO cells	1.51 mg/mL without activation 4.02 mg/mL with activation	negative positive	Loveday et al 1990; NTP 1986b
Chromosomal Aberration	CHO cells	5.01 mg/mL without activation 5.02 mg/mL with activation	negative negative	Loveday et al 1990; NTP 1986b
Amyl Acetate				
In vitro acute cytotoxicity	Ehrlich-Landschütz diploid (ELD) ascites tumor cells	50 ppm amyl acetate	2.5% injured cells after 5 hours	Holmberg and Malmfors 1974
		100 ppm amyl acetate	3.5% injured cells after 5 hours	

Developmental Toxicity

Ethyl Acetate. Verrett et al (1980) conducted a teratogenicity screen by administering ethyl acetate to developing chicken embryos under four test conditions: (1) injection via the air cell at preincubation, or zero hours; (2) injection via the air cell at 96 hours; (3) injection via the yolk at zero hours; and (4) injection via the yolk at 96 hours. For each condition, five doses (note: journal article does not specify the doses) up to 25 mg/egg were tested. All embryos and hatched chicks were examined grossly for any abnormalities in development, both structural and functional. The study investigators found that ethyl acetate posed no teratogenic effects under the conditions of the study.

When administered orally, the acetates hydrolyze rapidly into acetic acid and their corresponding alcohol (Bisesi 2001). In the case of ethyl acetate, acetic acid and ethanol are rapidly formed after oral administration. Because no reliable developmental or reproductive toxicity data conducted via the oral route of exposure were identified for ethyl acetate, EPA is citing the following oral route summaries from its review on ethanol (US EPA 2006b):

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

In summary, UNEP (2005) points out that regarding ethanol, the "collective weight of evidence is that the NOAEL for developmental effects

in animals is high, typically ≥6,400 mg/kg bw, compared to maternally toxic effects at 3,600 mg/kg bw."

Amyl Acetate. Under TSCA section 8(e) Union Carbide (1991, 1994a) submitted developmental toxicity data conducted on rats via the inhalation route. Groups of pregnant rats were exposed to a mixture of 65% n-amyl acetate and 35% 2-methyl butyl acetate at air concentrations of either: 0; 500; 1,000; or 1,500 ppm for six hours/day on gestation days (GDs) 6 through 16. The dams were sacrificed on GD 21 and were evaluated for liver, kidney, and gravid uterine weights. *Corpora lutea* were counted and the status of implantation sites were identified and recorded.

Maternal toxicity was observed in the 1,500 ppm group as was evidenced by decreases in: gestational body weight gains, corrected body weight, and corrected body weight gain. Food consumptions were decreased in all exposure groups from GD 17 to 21 (i.e., the postexposure period). Corrected body weight gains were slightly decreased in the 500 and 1,000 ppm groups.

In fetuses, there were no statistically-significant differences in individual external, visceral, or skeletal malformations by category or of total malformations among all groups. There were no exposure-related increases in the incidences of variations by category (e.g., external, visceral, skeletal) or of total variations. There were no statistically-significant decreases in fetal body weight for combined sexes or for male fetuses.

However, there were statistically-significant decreases in the female fetal body weights from the 1,000 and 1,500 ppm groups (3.5% and 4.2%, respectively). The incidence of ecchymosis in the head region and fetal atelectasis (condition in which the lungs of a fetus remain unexpanded at birth) were statistically-significant in the 1,500 ppm female group. Atelectasis was increased in the 1,000 ppm female group as well. Statistically-significant incidences of skeletal effects were seen among female fetuses of the 1,500 ppm group. Effects include: poorly ossified anterior arch of the atlas, thoracic centrum number 9 bilobed (having two lobes), and majority of the proximal phalanges of the hindlimb unossified. Skeletal effects were increased in the 1,000 ppm group and slightly increased in the 500 ppm group. The study investigator points out that the findings in the "500 ppm group were not observed in conjunction with reduced fetal body weights and were not considered to be of biological consequence."

In summary, the maternal LOAEL is ≤ 500 ppm, based on decreased body weight and food consumption; the NOAEL was not established. The developmental LOAEL is ≤ 500 ppm, based on increased incidence of skeletal variations at 500 ppm with increased incidence of skeletal variations also at 1,000 and 1,500 ppm; the developmental NOAEL was not established.

Amyl Acetate. Under TSCA section 8(e) Union Carbide (1994b) submitted developmental toxicity data conducted on rabbits via the inhalation route. Groups of pregnant rabbits were exposed to primary amyl acetate (which is a mixture of two isomers, n-amyl acetate and 2-methyl butyl acetate) vapor for six hours/day on GDs 6 through 18 at concentrations of: 0; 500; 1,000; and 1,500 ppm. Does were sacrificed on GD 29 and were evaluated for body weight, liver and kidney weights, and gravid uterine weights. *Corpora lutea* were counted and status of implantation sites were identified and recorded. No mortality occurred during the study. Maternal toxicity was observed in the 1,500 ppm group and included body weight losses during the first six days of the exposure period accompanied by reduced food consumption during the entire exposure period.

Fetal examination indicated no evidence of fetotoxicity or developmental toxicity in any of the exposure groups. External, visceral, and skeletal examinations of the fetuses revealed no exposure-related differences in the incidences of variations or malformations. According to the study investigator, the NOEL for maternal toxicity was 1,000 ppm and the NOEL for developmental toxicity was at least 1,500 ppm.

C. Metabolism and Pharmacokinetics

When administered orally, the acetates hydrolyze rapidly into acetic acid and their corresponding alcohol (Bisesi 2001). Ethyl acetate is hydrolyzed to ethanol and acetic acid, and the ethanol is eliminated via a combination of exhaled air, urination, and biotransformation (Bisesi 2001, citing von Oettingen 1960). The liver is likely the main ethyl acetate metabolizing organ (Riihimäki 1990). It has been shown that very little unchanged ethyl acetate will be excreted (Riihimäki 1990).

D. Special Considerations for Infants and Children

Ethyl and amyl acetate generally have low acute toxicity. Oral LD_{50} values for rat and rabbit are at least in Toxicity Category III, and eye and skin irritation appears to be slight. At exposure levels and exposure routes expected for the use of ethyl and amyl acetate as inert ingredient in pesticide products, developmental toxicity is not expected and the young are not expected to be more sensitive to its effects than adults. Upon ingestion, which is the expected route of exposure, ethyl acetate rapidly hydrolyzes to ethanol. UNEP (2005) points out that regarding ethanol, the "collective weight of evidence is that the NOAEL for developmental effects in animals is high, typically ≥6,400 mg/kg bw, compared to maternally toxic effects at 3,600 mg/kg bw."

The only available developmental toxicity studies for amyl acetate are via the inhalation route. Studies were conducted on two mammalian species—rats and rabbits. In the rat study, developmental toxicity was observed only at doses

causing maternal toxicity (Union Carbide 1994). Also, the doses where effects are occurring are much higher than EPA would expect from the use of DEA as an inert ingredient. Amyl acetate is naturally-occurring and because of its environmental fate properties EPA does not expect concentrations of concern to occur in drinking water and any residential exposure is expected to be low. In the rabbit developmental toxicity study for amyl acetate, maternal toxicity was seen at 1,500 ppm and no toxicity seen in the offspring.

Based on this information, there is no concern, at this time, for increased sensitivity to infants and children to ethyl and amyl acetate when used as inert ingredients in pesticide formulations. For the same reasons, a safety factor analysis has not been used to assess the risk; therefore, an additional tenfold safety factor for the protection of infants and children is also unnecessary.

V. ENVIRONMENTAL FATE CHARACTERIZATION AND DRINKING WATER CONSIDERATIONS

The following is from a 1986 Agency document (US EPA 1986) prepared by the Office of Research and Development (ORD) to support the Office of Solid Waste and Emergency Response (OSWER) program of listing hazardous constituents (e.g., ethyl acetate) under the Resource Conservation and Recovery Act (RCRA):

> When released to water, microbial degradation and volatilization are likely to be important removal mechanisms. Ethyl acetate has been shown to be readily biodegradable in a number of BOD [biological oxygen demand] studies (using activated sludge and sewage), in a natural water BOD test and under anaerobic conditions (Stover and Kincannon, 1983; Price et al., 1974; Thom and Agg, 1975). The volatilization half-life for a river 1m deep flowing at a speed of 1 m/sec with a wind velocity of 3 m/sec has been estimated to be ~9 hours from the experimentally measured vapor-aqueous solution equilibrium ratio (Hine and Mookerjee, 1975). Hydrolysis will not be important in neutral or acidic water, but may become significant in alkaline water; the respective hydrolysis half-lives at 25°C and pHs 7, 8 and 9 are 2.0 years, 73 days and 7.3 days (Mabey and Mill, 1978). Aquatic oxidation (by HO radical), adsorption to sediment, and bioconcentration are not expected to be important (Anbar and Neta, 1967). If released to the atmosphere, ethyl acetate will react with photochemically produced HO radical with an estimated half-life of 5.5-5.9 days at 19-23°C (Atkinson, 1985). If released to soil, ethyl acetate is likely to be susceptible to significant leaching and biodegradation. Volatilization from dry surfaces is expected to be relatively rapid.

Based on structure activity relationship (SAR), amyl acetate is expected to behave similarly in the environment. Like ethyl acetate, amyl acetate will undergo rapid biodegradation in all media with half-lives similar to, or more rapidly than ethyl acetate. Amyl acetate is classified as readily biodegradable. Hydrolysis reaction rates will be similar and atmospheric reactions with hydroxyl radicals will be more rapid for amyl acetate, with a half-life on the order of several days. Adsorption to sediment will be slightly higher, but not enough to substantially mitigate migration to ground water. Volatilization will be fairly rapid from dry surface, although less so than ethyl acetate. Bioconcentration is not expected to be significant. (US EPA 2006c)

VI. EXPOSURE ASSESSMENT

Ethyl acetate is used as a solvent or cosolvent in pesticide formulations applied to growing crops or to RAC's after harvest. Amyl acetate is used as a solvent, cosolvent, or attractant in pesticide formulations applied to growing crops or to RAC's after harvest. Individuals may be exposed to ethyl and amyl acetate through the oral, dermal, and inhalation routes of exposure. EPA expects that exposure to these acetates would primarily be through the oral route, via consumption of agricultural crops to which this inert ingredient has been applied and exposure through drinking water. Additional exposure may occur through the dermal and inhalation routes from residential use of pesticide products containing ethyl and amyl acetate. Expected food, drinking water, and residential exposures are discussed below.

Food and Drinking Water

Ethyl and amyl acetate are expected to be found in food, but at low levels. Both occur naturally in plants, plant material, and other biomaterials. Ethyl acetate occurs in everything from fruit to nuts to meat products; the highest concentrations reported are in alcoholic beverages—whiskey was found to contain up to 800 ppm ethyl acetate and beer, 50 ppm. Fruit juice was found to have about 2 ppm ethyl acetate. Amyl acetate was identified in a range of foods from fruits and chicken to potato. Because of ethyl and amyl acetate's environmental fate properties, EPA expects that drinking water exposures would be low as they readily biodegrade in soil and water.

Residential

Because of ethyl and amyl acetate's physical and chemical properties (both are expected to undergo rapid biodegradation in all media), EPA expects residues from residential exposure to be low. Additionally, acute dermal and inhalation toxicity studies indicate low hazard.

VII. AGGREGATE EXPOSURES

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

VIII. CUMULATIVE EXPOSURE

Section 408(b)(2)(D)(v) of the FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity."

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to ethyl or amyl acetate and any other substances and, ethyl and amyl acetate do not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that ethyl and amyl acetate have a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

IX. HUMAN HEALTH RISK CHARACTERIZATION

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

The overall acute toxicity of ethyl and amyl acetate is low. Oral LD_{50} values for the rat and rabbit are at least in Toxicity Category III, and eye and skin irritation appears to be slight. At exposure levels expected for the use of ethyl and amyl acetate as inert ingredients in pesticide products, developmental toxicity is not expected and the young are not expected to be more sensitive to its effects than adults. Overall, ethyl acetate does not appear to be mutatgenic.

Any exposure to ethyl and amyl acetate is expected to occur at levels much lower than the levels where any effects were seen in animal studies. Individuals are exposed to ethyl and amyl acetate naturally—the acetates have been detected in

various biological materials. The World Health Organization (WHO) has approved ethyl acetate as a flavoring agent (IPCS 2002) and FDA has classified it as GRAS (generally regarded as safe). Finally, because of the environmental fate properties of ethyl and amyl alcohol, EPA does not expect concentrations of concern to occur in drinking water and for the same reason, any residential exposure is expected to be low.

IX. ECOTOXICITY AND ECOLOGICAL RISK CHARACTERIZATION

The following is from the 1986 Agency document (US EPA 1986) prepared by the ORD to support OSWER's listing hazardous constituents under RCRA:

Ethyl Acetate

> LC_{50} values of 125-270 mg/L were reported for various fish and amphibian species with medaka, *Oryzias latipes* having the lowest LC_{50} (Sloff et al 1983). LC_{50} values of 130-3,950 mg/L were reported for various invertebrates, with the stonefly, Nemoura cinerea, having the lowest value (Sloff et al 1983). The lowest reported acutely toxic concentration for fish or invertebrates was 19.4 mg/L, which inhibited growth of fathead minnows in a 96-hour exposure (Barron and Adelman 1984).
>
> The only chronic toxicity data were provided by a 32-day fathead minnow embryo-larval bioassay in which growth was impaired at concentrations > or equal to 9.65 mg/L (Barron and Adelman 1984). Among aquatic plants and bacteria, Scenedesmus sp. were by far the most sensitive, having a threshold for inhibition of cell multiplication of 15 mg/L (Bringmann and Kuehn 1978; Sloff et al 1983).

A review of the available ethyl acetate effects data in the Agency's ECOTOX Database (USEPA 2006d) supports the summary found in US EPA 1986. Based on these data, ethyl acetate would be classified as practically nontoxic to aquatic organisms. The ECOTOX Database did provide information on effects to aquatic plants and protozoa. Effects concentrations, measuring biomass and/or population growth ranged from 150 mg/L to well in excess of 1,000 mg/L. There were no terrestrial effects data available in ECOTOX. Based on mammalian data as a surrogate for terrestrial phase organisms, ethyl acetate would be considered practically not toxic.

Amyl Acetate

Gangolli (2005) reported the most sensitive fish species tested was mosquito fish (LC_{50} 65 mg/L for 24 to 96 hour). However, it is unclear whether creek chub may be more sensitive given the results of a test that yielded only an LC_{100} (24 hour LC_{100} 120 mg/L exposed to Detroit river water). Other reported results were bluegill sunfish LC_{50} (96 hour) 650 ppm static bioassay in fresh water; inland silverside LC_{50} (96 hour) 180 mg/L static bioassay in synthetic seawater. These results would indicate that amyl acetate is slightly toxic to fish. Invertebrate toxicity was limited to a 48-hour study using *Daphnia magna*, EC_{50} 440 mg/L. Based on these results, invertebrates are classified as practically nontoxic.

A review of the available amyl acetate effects data in the Agency's ECOTOX Database (US EPA 2006d) supports the summary found in Gangolli (2005). The ECOTOX Database did provide information on effects to aquatic plants and protozoa. Effects concentrations, measuring biomass and/or population growth ranged from 63 mg/L to greater than 500 mg/L. There were no terrestrial animal effects data available in ECOTOX. Based on mammalian data as a surrogate for terrestrial phase organisms, amyl acetate would be considered practically not toxic. Several studies on plants indicated no effects at the highest dose tested.

Based on the available environmental fate data which shows ethyl and amyl acetate to degrade rapidly in the environment and the available measured effects data which show effects only a high doses, applications in the environment would have to exceed 100 pounds per acre to have the potential to exceed the Agency's Level of Concern for endangered and threatened species, the Agency's most protective threshold.

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