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

OFFICE OF PREVENTION,
PESTICIDES, AND TOXIC SUBSTANCES

DATE: June 5, 2006

ACTION MEMORANDUM

SUBJECT: Inert Reassessments: One Exemption from the Requirement of a Tolerance for Diethyl Phthalate (CAS Reg. No. 84-66-2)

FROM: Pauline Wagner, Chief Pauline Wagner 6/8/06
Inert Ingredient Assessment Branch
Registration Division (7505P)

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

I. FQPA REASSESSMENT ACTION

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

Chemical: Diethyl phthalate

CFR: 40 CFR part 180.930

CAS Registry Number and Name: 84-66-2, 1,2-Benzenedicarboxylic acid, diethyl ester

Use Summary: Diethyl phthalate used is as a plasticizer in a wide variety of consumer products, including plastic packaging films, automotive components, toys, cosmetic formulations, toiletries, medical tubing, solid rocket propellants, and as an ingredient in aspirin coating. As an inert ingredient in pesticides, diethyl phthalate is exempt from the requirement for a tolerance when used as a solvent, cosolvent in pesticide formulations applied to animals.

List Reclassification Determination: The current List Classification for diethyl phthalate is 2. Because EPA has determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to diethyl phthalate when used as an inert ingredient in pesticide formulations, the List Classification for these chemicals will change from List 2 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 Diethyl phthalate (CAS Reg. No. 84-66-2), and with the List reclassification determination, as described above. I consider the one exemption established in 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 A. Rossi

Lois A. Rossi, Director
Registration Division

June 12, 2002

Date:

cc: Debbie Edwards, SRRD
Joe Nevola, SRRD

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

OFFICE OF PREVENTION,
PESTICIDES, AND TOXIC SUBSTANCES

June 7, 2006

MEMORANDUM

SUBJECT: Reassessment of the One Exemption from the Requirement of a Tolerance for Diethyl Phthalate (CAS Reg. No. 84-66-2)

FROM: Nancy McCarroll Karen Angulo/for
Toxicology Branch
Health Effects Division (7509C)

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

BACKGROUND

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

EXECUTIVE SUMMARY

This document evaluates diethyl phthalate, a pesticide inert ingredient for which one exemption from the requirement for a tolerance exists. Diethyl phthalate is also approved for use by the U.S. Food and Drug Administration (USFDA) as an indirect food additive for use only as a component of adhesives (21 CFR 175.105). As a plasticizer, it is found in a variety of consumer products, cosmetics and medical tubing.

The toxicology data base for diethyl phthalate is relatively complete and consists of acute, subchronic and chronic toxicology studies in animals as well as studies in genetic toxicology, carcinogenicity, developmental and reproductive effects. No relevant neurotoxicity or immunotoxicity studies have been found in the open literature.

Available acute toxicology studies indicate that diethyl phthalate is minimally toxic via the oral or dermal routes. It is only mildly to slightly irritating to the skin or eyes and

is not a dermal sensitizer in humans or animals (generally rats and/or mice). In short-term exposure (up to 17 weeks) studies, diethyl phthalate was largely nontoxic via the oral or dermal route up to doses in excess of the limit dose of 1000 mg/kg/day. Similarly, the only finding of toxicological relevance seen in chronic oral or dermal studies was slightly decreased body weight in rats; no adverse effects were seen in mice. Diethyl phthalate is neither mutagenic nor carcinogenic; there was no evidence of increased susceptibility in a rat reproduction study. Although increased incidence of extra ribs was seen in separate developmental studies, this variation occurred at maternally toxic doses. Should diethyl phthalate be ingested, it is likely to be absorbed and hydrolyzed via known metabolic pathways to form monoethyl phthalate and further hydrolyzed to phthalic acid and excreted or conjugated and then excreted.

Diethyl phthalate is exempt from the requirement for a tolerance when used as a solvent, cosolvent in pesticide formulations applied to animals. Dietary and residential exposures of concern are not anticipated from its use in pesticide products.

Taking into consideration all available information on diethyl phthalate, it has been determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to diethyl phthalate when considering exposure through food commodities and all other non-occupational sources for which there is reliable information. Therefore, it is recommended that the two exemptions from the requirement of a tolerance established for residues of diethyl phthalate] when used as a solvent, cosolvent or stabilizer can be considered reassessed as safe under section 408(q) of the FFDCA.

I. Introduction

This report provides a qualitative assessment for diethyl phthalate, a pesticide inert ingredient with one tolerance exemption under 40 CFR 180.930.

II. Use Information

A. Pesticides

The tolerance exemption for diethyl phthalate is provided in Table 1.

Table 1. Tolerance Exemption Being Reassessed in this Document

Citation as it Appears in the CFR				CAS Registry Number and Name
40 CFR	Tolerance Exemption Expression	Limits	Uses	
180.930 [a]	Diethylphthalate	---	Solvent, cosolvent	84-66-2 1,2-Benzenedicarboxylic acid, diethyl ester (9CI)

[a] 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

The major use of diethyl phthalate is as a plasticizer in a wide variety of consumer products, including plastic packaging films, automotive components, toys, cosmetic formulations, toiletries, medical tubing, solid rocket propellants, and as an ingredient in aspirin coating. As shown in Table 2, diethyl phthalate is approved for use by the U.S. Food and Drug Administration (US FDA) as an indirect food additive but only as a component of adhesives.

Table 2. FDA Direct Food Additive Uses for Diethyl phthalate

Name	21 CFR	Use Pattern
Diethyl phthalate	175.105	Indirect food additive for use only as a component of adhesives

III. Physical and Chemical Properties

Some of the physical and chemical characteristics of diethyl phthalate structure and nomenclature are found in Table 3.

Table 3. Physical and Chemical Properties of Diethyl Phthalate

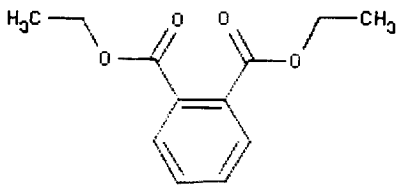
Parameter	Value	Reference
Structure		http://chem.sis.nlm.nih.gov/chemidplus
CAS #	84-66-2	ATSDR, 1995
Empirical Formula	$C_{12}H_{14}O_4$	ATSDR, 1995
Molecular Weight	222.23	ATSDR, 1995
Common Names	Neantine; Palatinol A; Phthalol; Placidol E; Solvanol; Unimoll DA; Anozol; Eastol 1550	HSTB 1994 (as cited in ATSDR, 1995)
Physical State	Colorless, oily liquid	CICAD 52, 2003
Melting Point	-40.5 ° C	HSTB 1994 (as cited in ATSDR, 1995)
Boiling Point	295-302° C	HSTB 1994 (as cited in ATSDR, 1995)
Water Solubility at 25° C	1000 mg/L	CICAD 52, 2003
Other Solubility	Soluble in alcohol, ether , acetone, and benzene; vegetable oils; ketones, esters,	HSTB 1994 (as cited in ATSDR, 1995)

Table 3. Physical and Chemical Properties of Diethyl Phthalate		
Parameter	**Value**	**Reference**
	aromatic hydrocarbons and aliphatic solvents	
Relative Density (water=1) at 25° C	1.120 g/mL	ATSDR, 1995
Vapor Pressure at 20 ° C	3.45×10^{-4} mmHg	ATSDR, 1995
Vapor Pressure at 25° C	1.65×10^{-3} mmHg	ATSDR, 1995
log K_{ow}	1.4-3.3	ATSDR, 1995
Henry's Law Constant	7.8×10^{-7} atm m^3/mol	ATSDR, 1995

IV. Hazard Assessment

Diethyl phthalate is sponsored under EPA's High Production Volume (HPV) Challenge Program (http://www.epa.gov/chemrtk/volchall.htm). The goal of the HPV program is to collect and make publicly available a complete set of baseline health and environmental effects data on those chemicals that are manufactured in, or imported into, the United States in amounts equal to or exceeding one million pounds per year. Industry sponsors volunteer to evaluate the adequacy of existing data and to conduct tests where needed to fill the gaps in the data, and EPA (and the public) has an opportunity to review and comment on the sponsors' robust summary report. The industry sponsor has not submitted a robust summary for diethyl phthalate.

A. Hazard Profile

Diethyl phthalate is being evaluated as part of the US EPA's tolerance reassessment process of inert ingredients. A summary of the relevant scientific information on the potential human health and/or environmental effects (Concise International Chemical Assessment Document 52, CICAD) was prepared by the World Health Organization (WHO) in 2003. CICAD 52 was based primarily on the existing environmental health criteria document published by the Agency for Toxic Substances and Disease Registry (ATSDR) in 1995. The current document was developed from extracts of the above documents as well as information found in the open literature.

B. Toxicological Data

Acute Toxicity

As shown in Table 4, diethyl phthalate has minimal acute toxicity via the oral, or dermal routes (Category IV). It is mild or slightly irritating to the skin or eyes and is generally not a dermal sensitizer.

Table 4. Summary of Acute Toxicity Data for Diethyl phthalate

Parameter	Toxicity Value/Toxicity Category	Reference
Oral LD_{50} rat	9200-9500 mg/kg/IV	CICAD 52,2003
Oral LD_{50} mouse	8600 mg/kg/IV	CICAD 52, 2003
Dermal LD_{50}, rabbit	ND	
Dermal LD_{50}, rat	>11 g/kg/IV	Api, 2001
Inhalation LC_{50}, rat	ND	
Eye Irritation, rabbit	Minimal Irritation/III	Api, 2001
Skin Irritation, rabbit	Mild or slight irritation/IV	Api, 2001
Dermal Sensitization, guinea pig	Not reported to be a dermal sensitizer	Api, 2001

ND = No data

Subchronic Toxicity

No adverse effects were observed in studies of short-term duration (1-17 weeks, of oral exposure or 4 weeks of dermal exposure). There is weak evidence suggesting that diethyl phthalate is a peroxisome proliferator (e.g., liver weight increases, increased peroxisome activity, increased lipid peroxidation) at doses well in excess of the limit doses (1000 mg/kg/day) for subchronic oral or dermal studies.

Oral Exposure

In a dietary study, 10 male Wistar rats received 2% diethyl phthalate (≈2,000 mg/kg/day) in the diet for 1 week. Results only showed a significant and 12% increase in relative liver weight; no effects were noted on kidney or testes. No other examinations were reported.

In an oral gavage study with four male Fisher rats dosed with 2% (1,753 mg/kg/day) diethyl phthalate for 3 weeks, there was a significant decrease in serum triglycerides but no difference in the serum cholesterol levels. Absolute liver weights were significantly lower than control but there was only a 4.4% difference. Enzymes associated with peroxisome activity were slightly increased. For example, catalase activity was increased 1.2-fold (52 ±5.5 U/mg protein vs. 44 ±2.7 U/mg protein in control); and carnitine acetyltransferase was increased 3-fold (8.0±0.6 U/mg protein vs. 2.7 ±0.5 U/mg protein in control). Additionally, there was a slight change in the ratio of mitochondria to peroxisome ratio (5:2 vs. 5.1 in control). Although the difference in this ratio is very slight, it is noteworthy that a "well known peroxisome proliferators" showed a ratio of 5:4. No histology was performed. The no observed adverse effect level (NOAEL) was 1,753 mg/kg/day, which exceeds the limit dose of 1,000 mg/kg/day for

subchronic oral studies; the lowest observed adverse effect level (LOAEL) can not be determined for this study.

Groups of 15 male and 15 female CD rats were exposed to diethyl phthalate at dietary levels of 0, 0.2, 1.0 or 5.0% [≈ 0, 150, 770 or 3160 mg/kg/day (♂); 0, 150, 750 or 3710 mg/kg/day (♀)] for 16 weeks (Brown et al., 1978). There were no adverse effects on hematology, serum enzyme or urinalysis. Effects on high-dose body weights were primarily associated with poor feed consumption rather than the toxic action of the test agent. By contrast, >30% increase in relative liver weight was seen in high-dose males and females at weeks 2, 6 and 16. Increased relative organ weights were also reported for the stomach, small intestine and kidneys. In agreement with the previously discussed oral subchronic studies, organ weight increases were not associated with abnormal histological findings. In a subsequent experiment by the same authors, groups of 6 male and 6 female rats received diets containing either 0 or 5 % diethyl phthalate for 16 week. The authors reported that rats consumed more food (1-5%) but gained less weight than the controls (7-10%). The weight decrement was significant. Combining the data from both studies, the LOAEL was the 5.0% dose for both sexes (3160 mg/kg/day), based on significantly decreased body weight in both sexes. The NOAEL is 750 mg/kg/day.

Finally, groups of six male Sprague Dawley rats were administered 50 mg diethyl phthalate, 5% ethyl alcohol or a combination of both in drinking water for 120 days. No significant differences in body weight, liver weight, or water consumption were noted in rats treated with diethyl phthalate alone or in combination with ethanol. Significant increases in parameters used to measure lipid peroxidation (i.e., increased glycogen, triglyceride and cholesterol storage in the liver) were seen in these treatment groups.

Dermal

In a National Toxicology Program (NTP) dermal study, groups of 10 male and 10 female rats were exposed to 0, 37.5, 75, 150 or 300 µL [≈ 0, 200, 400, 800 or 1600 mg/kg/day (♂); ≈ 0, 300, 600, 1200 or 2500 mg/kg/day (♀)] respectively, applied to clipped skin 5 days/week for 4 weeks. Groups of 10 male and 10 female mice were similarly dosed with 0, 12.5, 25, 50 or 100 µL [≈ 0, 560, 1090, 2100 or 4300 mg/kg/day (♂);≈ 0, 630, 1250, 2500 or 5000 mg/kg/day (♀)], respectively. No adverse effects on clinical chemistry parameters measuring kidney or liver function were observed. Similarly, there were no adverse effects on histopathology of the heart, lung, liver, kidney, esophagus, gallbladder (mouse only), large or small intestines, stomach, or bladder of rats or mice. The only finding was increased relative liver weights (≈ 10%) in high dose male and female rats and high dose female mice and female rats receiving 100 µL. Accordingly, the NOAEL for rats is 1,600 mg/kg/day (♂); 2,500 mg/kg/day

(♀) and is 1,600 mg/kg/day (♂); 2,500 mg/kg/day (♀);I the NOAEL for mice is 4,300 mg/kg/day (♂); 5,000 mg/kg/day (♀). All of these values exceed the limit dose for 21- or 90- day dermal studies.

Chronic Toxicity/Carcinogenicity

The chronic oral or dermal administration of doses in excess of the limit dose of diethyl phthalate caused slightly decreased body weight in rats. No adverse toxicological effects were seen in mice dermally administered diethyl phthalate up to doses in excess of the limit dose. There was no clear evidence of a carcinogenic effect following oral exposure of rats or dermal exposure of rats or mice.

Oral

The only effect seen in a 2-year dietary study with groups of 15 male and 15 female rats receiving diethyl phthalate at dietary levels of 0, 0.5 2.5 or 5.0% (≈ 0, 250, 1250 or 2500 mg/kg/day) was "slightly" decreased body weight gain in the absence of reduced food intake. This effect was confined to the high-dose group. Accordingly, the LOAEL is 2,500 mg/kg/day and the NOAEL is 1,250 mg/kg/day; both levels are in excess of the limit dose for chronic studies (1,000 mg/kg/day). CICAD 52 (2003) considered the study inadequate for the evaluation of carcinogenicity because of the small sample size.

An oral chronic toxicity/carcinogenicity study was not found for mice.

Dermal

In a chronic NTP study, male and female F344/N rats (60/sex/group) were dermally administered 100 or 300 μL diethyl phthalate [≈ 0, 320 or 1010 mg/kg/day (♂); ≈ 0, 510 or 1560 mg/kg/day (♀)], respectively, 5 days/week for 2 years. There were no effects on survival, hematological or clinical chemistry parameter, no neoplasms, or non-neoplastic lesions. The only adverse effect was a slight decrease in body weight gain, decreased mean body weight for high dose males (4-9%), and a treatment-related minimal to mild epidermal acanthosis at the application site for high-dose males and females The latter was considered to be a "subtle adaptive response to local irritation" by CICAD 52 (2003).

In another chronic study, groups of 60 male and female $B6C3F_1$ mice received dermal applications of 0, 7.5, 15 or 30 μL diethyl phthalate [≈ 0, 280, 540 or 1020 mg/kg/day (♂); ≈ 0, 280, 550 or 1140 mg/kg/day (♀)}, respectively, in acetone, 5 days/week for 2 years. No effects on survival, body weights or hematological or clinical chemistry parameters or

dermatological lesions at the application site were observed. Although an 18% increase (9/50 vs. 0/50 control) in non-neoplastic proliferative lesions (i.e., basophilic foci) was seen in the liver of male mice at 15 μL, the effect was confined to this level and this sex. Combined incidences of hepatocellular adenomas/ carcinomas (primarily adenomas) were 9/50, 14/50, 14/50 and 18/50 in the male mice and 7/50, 16/51, 19/50 and 12/50 in the female mice at 0, 7.5, 15, and 30 μL, respectively. These values did not show pairwise significance but the trend in males was significant (p=0.04). NTP considered these results to be equivocal because of the lack of a dose-related trend in females and the unusually low incidence in the concurrent control group compared to historical controls. This position is shared by Health Effects Division (HED) toxicologists within the Office of Pesticides Programs (OPP) at the EPA. As stated in the EPA's 2005 Guidelines for Carcinogen Risk Assessment (USEPA, 2005), for common tumors, such as tumors of the mouse liver, showing an increase in one species, one sex, with only one significant result, the level of statistical significance must be at the 1% level to be considered meaningful.

In an initiation/promotion assay conducted by NTP, groups of 50 male Swiss CD mice were treated dermally with 0.1 mL diethyl phthalate ("neat") as the initiator followed by 12-O-tertadecanoylphorbol-13-acetate (TPA; 0.05 mg/mL for 8 weeks then 0.025 mg/mL) as the promoter starting from week 2 for 1 year. The promotion potential of diethyl phthalate was also assayed in a similar manner using 7,12-dimethylbenz(a)anthracene (DMBA) as the initiator. DMBA and TPA also served as the positive controls. No initiation or promotion potential was observed for diethyl phthalate.

Immunotoxicit/Neurotoxicity

No adverse immunological or neurological effects were reported in general toxicity studies.

Mutagenicity

Conflicting results have been reported in the *Salmonella typhimurium* mammalian microsome reverse gene mutation assays. Several investigators have shown positive results in S. typhimurium TA1535 and/or TA100 but only in the absence of S9 activation. By contrast, the NTP-sponsored Ames preincubation modification to the standard tests conducted by two independent laboratories using coded test compounds found diethyl phthalate at concentrations ranging from 10 to 10,000 μg/plate without S9 or in the presence of rat or hamster S9, to be a confirmed negative(Zeiger, 1985). The monoester, monoethyl phthalate is also negative for gene mutations in *Salmonella* and *Escherichia coli.*

Similarly, diethyl phthalate was negative for chromosome aberrations in Chinese hamster ovary (CHO) cells and in Chinese hamster lung fibroblasts (V79). There was, however, a concentration-related increase in sister chromatid exchanges (SCEs) in CHO cells. This response is associated with DNA damage but it appears that this damage is not manifested as gene mutations or chromosome aberrations *in vitro.* No studies were found in the open literature regarding the potential genotoxic effects of diethyl phthalate in whole animals.

Reproductive Toxicity

As stated in ASTRD (1995) and as reiterated by CICAD 52 (2003), "several investigators have studied the effects of diethyl phthalate on male reproductive function in rats, since other phthalic esters have been shown to be toxic to the male reproductive system". Based on these findings, it was concluded that diethyl phthalate has no adverse effect on the histopathology or the organ weight of testes or other associated accessory glands. Additionally, diethyl phthalate had no effect on progesterone binding to testes microsomes, testicular cytochrome P-450, or testicular steroidogenic enzyme activity. Administration of 2% (≈2000 mg/kg/day) diethyl phthalate to male Wistar rats (5 weeks old) for 1 week decreased testosterone concentrations in testes and serum (≈40% for both). The relevance of this decrease in testosterone is not clear since other phthalate esters, which are toxic to the male reproductive system, increase testosterone. Nevertheless, "...mitochondrial swelling, smooth endoplasmic reticulum focal dilation and vesiculation, and increased interstitial macrophage activity associated with the surface of Leydig cells ..." was observed in male Wistar rats receiving 2000 mg/kg/day diethyl phthalate via oral gavage for 2 days.

In a continuous breeding NTP study, Swiss CD-1 mice (10-12 weeks old), were fed diets containing 0, 0.25, 1.25 or 2.5 % diethyl phthalate (≈0, 340, 1770 or 3640 mg/kg/day, respectively) for 14 weeks beginning 1 week before mating. In the F_0 generation, no systemic effects or adverse effects on fertility or reproductive performance, the number of litters, number or viability of live pups, or pup body weight were observed. For the second generation, only the high-dose and control groups were continued on study. High-dose F_1 males weighed 12% less than controls, liver (18%↑) and prostate (32%↑) weights were significantly increased and epididymal sperm concentration was reduced by 30% but the percentage of motile sperm and the proportion of abnormal sperm were unaffected by treatment. Additionally, increased liver and pituitary weights were recorded in high-dose females; however, these organs were not subjected to a histopathologic examination. Organ weight differences for reproductive tissue were not associated with histopathology in the gonads,

uterus, prostate or seminal vessels. F_1 litters had fewer pups (14% less) than control but there were no adverse effects on fertility. Similarly, when adjusted for litter size, neither viability nor pup body weight were affected Since only the high dose was continued through the second generation, a NOAEL could not be established; the LOAEL was 3640 mg/kg/day, based on body weight reduction in the $F_{1;}$; this value exceeds the limit dose for this type of study.

Developmental Toxicity

In a NTP developmental toxicity study, pregnant CD rats received dietary concentrations of 0, 0.25, 25 or 5 % diethyl phthalate (≈0, 200, 1900 or 3200 mg/kg/day, respectively) on gestation days 6-15. Significantly lower than control body weights were recorded for the mid and high-dose dams on day 9 and days 9 to 18, respectively; body weights returned to normal at sacrifice. No effects were seen on absolute or relative liver or kidney weights. Fertility indices, number of corpora lutea/dam, number of implants and absorptions/liter, number of dead and live fetuses/liter, body weight of fetuses and the ratio of males to females were unaffected by exposure. There were no externally visible visceral or skeletal malformations. A significantly higher ($p=0.05$, 21%) incidence of fetuses with an extra rib was noted in the high-dose group. CICAD 52 concluded that the relevance of this increased incidence was unclear because of the high incidence of skeletal variations in the controls and because of maternal toxicity due to reduced food and water consumption of the high-dose dams early in gestation. Based on the decreased body weight in the dams, the LOAEL was 5% and the NOAEL was 2.5% (≈1900 mg/kg/day); based on the increased incidence of fetuses with an extra rib, the LOAEL was 5% and the NOAEL was 2.5% (≈1900 mg/kg/day), which also exceed the limit dose for developmental toxicity studies.

To determine if diethyl phthalate affects the male reproductive tract, Gray et al (2000 as cited in CICAD 52, 2003) dosed 3 pregnant Sprague Dawley rats with 750 mg/kg/day diethyl phthalate by oral gavage from gestation day 14 to postnatal day 3. Treatment did not cause maternal toxicity or reduce litter sizes. Evaluation of only the male offspring revealed no changes in pup body weight, no increases in the incidence of malformations and no effects on the genital organs, liver, pituitary, or adrenal glands. Similarly, there were no effects on pubertal development.

C. Metabolism and Pharmacokinetics

In the rat, 24% of dermally applied diethyl phthalate was excreted within 24 hours and 11% of the dose was excreted in the next 24 hours; a cumulative total of 50% was excreted by 7 days. Distribution was

considered wide but very little of the ^{14}C label was found in the tissue within 1 week; the amount of label found in the brain, lung, spleen, small intestines, kidney, testis, spinal cord or blood was 0.5% of the administered dose. The amount in adipose tissue, muscle and skin accounted for 0.03, 0.14 and 0.06%, respectively; 34% remained in the area of application and 5% remained in the plastic cup used to protect the application site. In studies cited in ATSDR (1995), diethyl phthalate is first hydrolyzed to the monoester derivative in nonrodents, rodents and nonhuman primates. Once formed, the monoester derivative can be further hydrolyzed to phthalic acid and excreted or conjugated to glucuronide and excreted. Another possibility is the formation of an alcohol, which can be successively oxidized to an aldehyde, ketone or carboxylic acid and then excreted.

D. Special Considerations for Infants and Children

In acute, subchronic or chronic studies, diethyl phthalate has been demonstrated to be of low toxicity. In rat reproduction toxicology studies, no evidence of increased susceptibility was seen in either generation; the LOAEL was 3640 mg/kg/day based on body weight reduction in the F_1 (this value exceeds the limit dose for this type of study). Similarly, testicular effects were seen only at the limit dose (2000 mg/kg/day). Administration of diethyl phthalate to pregnant rats or rabbits during the period of organogenesis did not adversely affect embryo or fetal development. Although there was an increase in the incidence of extra ribs in separate developmental rat studies, this variation occurred at maternally toxic doses; the LOAEL was 5% for the increased incidence of fetuses with an extra rib and the NOAEL was 2.5% (≈1900 mg/kg/day), which exceed the limit dose for developmental toxicity studies.

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

V. Environmental Fate Characterization and Drinking Water Considerations

According to CICAD 52 (2003), diethyl phthalate has a water solubility of 1g/L, low volatility (vapor pressure of 4.6×10^{-2} Pa at 20° C), a low Henry's law constant (4.3×10^{-8}), and a moderate log octanol/water partition coefficient (log K_{OW} 2.47). Release to water would not be expected to lead to volatilization to the atmosphere because of the low vapor pressure. The extent of partitioning within aquatic media is not entirely clear. Modeling suggests that a low to moderate proportion of the total diethyl phthalate will partition to sediment (10-30%); measurements have shown some sediment enrichment with diethyl phthalate.

Accordingly, the overall conclusion is that there is moderate partitioning to particulates, with much of the diethyl phthalate remaining in the water column.

Abiotic degradation is not expected to be a significant component of the breakdown of diethyl phthalate in the environment. Biotic degradation occurs in soil, surface waters and sewage treatment plants. There is some field evidence suggesting that degradation is less in the field than would be predicted from laboratory experiments. Biodegradation takes place under aerobic and anaerobic conditions. Given the uncertainties about the extent of biodegradation, diethyl phthalate is expected to persist in the environment for a period ranging from a few days to a few weeks. Bioaccumulation is moderate experimentally, consistent with the reported log K_{OW}.

There are limited data on measured concentrations of diethyl phthalate in surface waters (rivers, lakes, treated wastewater). But no data on field concentrations in the soil are available.

VI. Exposure Assessment

Diethyl phthalate is used as a plasticizer in a wide variety of consumer products, including plastic packaging films, toothbrushes, cosmetics, detergents, and skin care products. Diethyl phthalate is used as an inert ingredient in pesticide products applied to animals used for food (e.g., cattle). Therefore, residential exposures and contributions to drinking water are not expected. Dietary exposure through consumption of treated animals is expected to be below the level of concern considering diethyl phthalate's rate of excretion in the urine of animals.

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 diethyl phthalate, 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 diethyl phthalate as an inert ingredient in pesticide formulations.

VIII. Cumulative Exposure

Section 408(b)(2)(D)(v) of FFDCA requires that, when considering whether diethyl phthalate 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 diethyl phthalate and any other substances and, this material 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 diethyl phthalate 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

Diethyl phthalate is used as a plasticizer in a wide variety of consumer products, including plastic packaging films, toothbrushes, cosmetics, detergents, and skin care products. Diethyl phthalate is used as an inert ingredient in pesticide products applied to animals used for food. Dietary and residential exposures of concern are not anticipated from its use in pesticide products.

Available acute toxicology studies indicate that diethyl phthalate is minimally toxic via the oral or dermal routes. It is only mildly to slightly irritating to the skin or eyes and is not a dermal sensitizer in humans or animals (generally rats and/or mice). In short-term exposure studies, diethyl phthalate was largely nontoxic via the oral or dermal route up to doses in excess of the limit dose of 1000 mg/kg/day. Similarly, the only finding of toxicological relevance seen in chronic oral or dermal studies was slightly decreased body weight in rats; no adverse effects were seen in mice. Diethyl phthalate is neither mutagenic nor carcinogenic; there was no evidence of increased susceptibility in a rat reproduction study. Although increased incidence of extra ribs was seen in separate developmental studies, this variation occurred at maternally toxic doses.

Taking into consideration all available information on diethyl phthalate, it has been determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to diethyl phthalate when considering exposure through food commodities and all other non-occupational sources for which there is reliable information. Therefore, it is recommended that the one exemption from the requirement of a tolerance established for residues of diethyl phthalate when used as solvent, cosolvent in pesticide formulations under 40 CFR 180.930 can be considered reassessed as safe under section 408(q) of the FFDCA.

X. Ecotoxicity and Ecological Risk Characterization

An overview of ecological risks from diethyl phthalate is provided in CICAD 52 (2003), as follows: "Risk for aquatic organisms, based largely on lethal end-points, is therefore considered low. The only exposure data for soils come from National Priorities List sites in the USA, where 4% of samples contained diethyl phthalate at a mean concentration of 0.039 mg/kg soil. This compares with toxicity values of greater than 100 mg/kg for plant growth, suggesting very low risk. Effects were seen on soil microorganisms at greater than 1000 mg/kg soil, also suggesting low risk, except following spills. The toxicity value for earthworms (550 mg/cm2) is based on exposure on filter paper and cannot be used for risk estimation. Overall, the risks for terrestrial soil organisms appear to be low."

REFERENCES:

Api, AM (2001). Toxicology profile of diethyl phthalate: a vehicle for fragrance and cosmetic ingredients. Food and Chem Toxicol 39:97-108.

ATSDR (1995) Toxicology profile for diethylphthalate. Atlanta, GA, UP Dept. of Health and Human Services, Agency for Toxic Substances and Disease Registry.

Brown, D. Buterworth, KR, Gaunt, IF, Grasso, P, Gangolli, SD (1978). Short-term oral toxicity study of diethyl phthalate in the rat. Food and Cosmetics Toxicology 16(5): 415-422.

CICAD 52 (2003). Diethyl phthalate. Concise International Chemical Assessment Document 52. World Health Organization, Geneva, SZ.

NTP. 1995. NTP technical report on the toxicology and carcinogenesis studies of diethylphthalate (CAS No. 84-66-2) in F344/N rats AND B6C3F1 mice (dermal studies) and dermal initiation/promotion study of diethyl phthalate and dimethylphthalate (CAS No. 131-11-3) in male Swiss (CD-1) mice. Research Triangle Park, NC, US Dept of Health and Human Services, National Institutes of Health, National Toxicology Program (NTP TR 429).

US EPA. 1993. Integrated Risk Information System: Diethyl phthalate (CASRN 84-66-2). Washington, DC, US Environmental Protection Agency, at website http://www.epa.gov/iris/subst/0226.hmt.

U.S. EPA. 2005. Guidelines for Carcinogen Risk Assessment, EPA/630/P-03/001F, March 2005, (http://www.epa.gov/cancerguidelines)

Zeiger, E, Haworth, S, Speck, S, Mortelmans, K (1982). Phthalate ester testing in the National Toxicology Program's environmental mutagenesis test development program. Environ Health Perspectives 45:99-101.