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

OFFICE OF PREVENTION,
PESTICIDES, AND TOXIC SUBSTANCES

June 5, 2006

ACTION MEMORANDUM

SUBJECT: Inert Reassessment -- One Exemption from the Requirement of a Tolerance for Triethyl Phosphate (CAS Reg. No. 78-40-0)

FROM: Pauline Wagner, Chief Pauline W agner 6/6/06
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 ingredient tolerance exemption "as-is."

Chemical: Triethyl phosphate

CFR: Triethyl phosphate has a tolerance exemption in 40 CFR part 180.920.

CAS Registry Number and Name: 78-40-0; Phosphoric acid, triethyl ester.

Use Summary: Triethyl phosphate is used as an industrial catalyst, a desensitizing agent for peroxides, an ethylating agent, a plasticizer for resins, plastics, and gums. It is also used in small amounts as a solvent, a flame retardant, an anti-foaming agent, and an intermediate in the production of various chemicals. As an inert ingredient in pesticide products, triethyl phosphate is used as a stabilizer in formulations applied before a crop emerges from the soil.

List Reclassification Determination: The current List Classification for triethyl phosphate 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 triethyl phosphate when used as inert ingredient in pesticide formulations, the List Classification for triethyl phosphate 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 triethyl phosphate (CAS Reg. No. 78-40-0), and with the List reclassification determination, as described above. I consider the one tolerance exemption for triethyl phosphate established in 40 CFR part 180.920 to be reassessed for purposes of FFDCA's section 408(q) as of the date of my signature, below. A Federal Register Notice regarding this tolerance exemption reassessment decision will be published in the near future.

Lois A. Rossi, Director
Registration Division

Date: June 8, 2006

cc: Debbie Edwards, SRRD
Joe Nevola, SRRD

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MEMORANDUM

SUBJECT: Reassessment of the One Exemption from the Requirement of a Tolerance for Triethyl Phosphate

FROM: Karen Angulo
Inert Ingredient Assessment Branch (IIAB)
Registration Division (7505P)

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

Background

Attached is the science assessment for triethyl phosphate. Triethyl phosphate has one exemption from the requirement of a tolerance under 40 CFR 180.920 when used as an inert ingredient (stabilizer) in pesticide formulations applied to growing crops only, before the crop emerges from soil. This assessment summarizes available information on the use, physical/chemical properties, toxicological effects, exposure profile, environmental fate, and ecotoxicity of triethyl phosphate. The purpose of this document is to reassess the one existing exemption from the requirement of a tolerance for residues of triethyl phosphate when used as an inert ingredient (stabilizer) in pesticide formulations as required under the Food Quality Protection Act (FQPA).

Executive Summary

This report evaluates triethyl phosphate, a pesticide inert ingredient for which one exemption from the requirement of tolerance exists when used as a stabilizer in pesticide formulations applied to growing crops only under 40 CFR 180.920. Applications of the pesticide formulations containing triethyl phosphate are restricted to before the crop emerges from the soil. Triethyl phosphate is also used as an industrial catalyst, a desensitizing agent, an ethylating agent and as a plasticizer for resins, plastics, and gums. In small amounts, triethyl phosphate is used as a solvent, a flame retardant, an anti-foaming agent, and an intermediate in the production of various chemicals.

Sufficient toxicity data and information are available to assess the hazard of triethyl phosphate. This hazard assessment was developed using information from various sources, including the Organization for Economic Cooperation and Development (OECD) High Production Volume Chemicals Program. A qualitative assessment for all pathways of human exposure is appropriate given the minimal human health concerns associated with the low levels of exposure expected from the use of triethyl phosphate as an inert ingredient in pesticide formulations.

Available toxicological information indicates the low toxicity of triethyl phosphate. With the exception of reduced litter size after exposure to high concentrations of the chemical, no other reproductive or developmental effects are reported. All of these effects occurred at concentrations higher than that expected from triethyl phosphate's use as an inert ingredient in pesticide formulations. In addition, no neurotoxicity has been observed. Triethyl phosphate is also negative for genotoxicity and is not expected to be carcinogenic.

Dietary and residential exposures of concern are not anticipated from the use of triethyl phosphate in pesticide formulations due to the limited number of applications that are permitted for pesticide products containing this inert ingredient. Potential exposure is greatly reduced because triethyl phosphate can only be applied before a crop emerges from the soil, which means only a minimal number of applications could occur (possibly only one). Ecological risk concerns are not likely to occur. Triethyl phosphate is not toxic to aquatic or terrestrial organisms, and bioconcentration in aquatic organisms is not expected to be significant.

Taking into consideration all available information on triethyl phosphate, it has been determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to triethyl phosphate 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 triethyl phosphate when used on growing crops under 40 CFR 180.920 can be considered reassessed as safe under section 408(q) of the Federal Food, Drug, and Cosmetic Act (FFDCA).

I. Introduction

This report provides a qualitative assessment for triethyl phosphate, a pesticide inert ingredient for which one exemption from the requirement of tolerance exists when used in pesticide formulations applied to growing crops only under 40 CFR 180.920.

II. Use Information

A. Pesticide Uses

Triethyl phosphate is used as a stabilizer in pesticide formulations applied before a crop emerges from the soil. The one tolerance exemption for this chemical is presented below in Table 1.

Table 1. Pesticide Uses of Triethyl Phosphate

CFR Citation				CAS Reg. No. CAS Name
40 CFR §	**Inert Ingredients**	**Limits**	**Uses**	
180.920*	Triethyl phosphate	---	Stabilizer for formulations used before crop emerges from soil	78-40-0 Phosphoric acid, triethyl ester

*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.

B. Other Uses

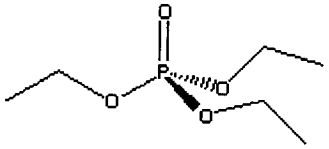
Triethyl phosphate is used as an industrial catalyst, a desensitizing agent for peroxides, an ethylating agent, and as a plasticizer for resins, plastics, and gums. It is also used in small amounts as a solvent, a flame retardant, an anti-foaming agent, and an intermediate in the production of various chemicals.

Triethyl phosphate is approved by the U.S. Food and Drug Administration (FDA) under 40 CFR 175.105 for use as an "indirect" food additive as a component of adhesives.

III. Physical and Chemical Properties

The physical and chemical characteristics of triethyl phosphate, along with its structure and nomenclature, are found in Table 2.

Table 2. Physical and Chemical Properties of Triethyl Phosphate

Parameter	Value	Reference
Structure		ChemFinder, 2006
CAS Number	78-40-0	HSDB, 2006

Parameter	Value	Reference
Molecular Formula	C6-H15-04-P	HSDB, 2006
Molecular Weight	182.16	HSDB, 2006
Synonyms	Ethyl phosphate; Phosphoric acid, triethyl ester; TEP	ChemFinder, 2006
Odor	Mild	HSDB, 2006
Physical State	Colorless liquid	HSDB, 2006
Melting Point	-56.4°C	HSDB, 2006
Boiling Point	215-216°C	HSDB, 2006
Water Solubility	5×10^5 mg/L	HSDB, 2006
Other Solubility	Miscible with most organic liquids	HSDB, 2006
Vapor Density	6.28 (air = 1)	HSDB, 2006
Vapor Pressure	0.39 mm Hg @ 25°C	HSDB, 2006
Log K_{ow}	0.80	HSDB, 2006
K_{oc}	3 and 65*	HSDB, 2006
Henry's Law Constant	1.5×10^{-6} atm-m^3/mole @ 20°C	HSDB, 2006
Specific Gravity	1.0725 @ 19°C	HSDB, 2006

*Determined from experimental values for water solubility and log K_{ow}, respectively.

IV. Hazard Assessment

A. Hazard Profile

This hazard assessment of triethyl phosphate was developed using the Screening Information Data Set (SIDS), which was submitted by Germany to the Organization for Economic Cooperation and Development (OECD) under the SIDS High Production Volume Chemicals Program. Based on the data submitted, the SIDS Initial Assessment Profile (SIAP) and Report (SIAR) concluded that triethyl phosphate is of "low current priority for further work" (OECD, 1998). Other sources of information used in this assessment include the Hazardous Substances Data Bank (HSDB, 2006), Patty's Industrial Hygiene and Toxicology (Clayton and Clayton, 1994), and the Toxicology Data Network (TOXNET, 2006).

B. Toxicological Data

Acute Toxicity:

Available acute toxicological information indicates the low toxicity of triethyl phosphate. Triethyl phosphate is only slightly toxic by the oral, inhalation, and dermal routes of exposure. Triethyl phosphate was shown to be a slight skin irritant in a study with guinea pigs, but in other studies with experimental animals, the chemical was classified as non-irritating to the skin. Quantitative data from various acute toxicity studies are summarized in the following table:

Table 3. Summary of Acute Toxicity Data for Triethyl Phosphate

Study Type (Species)	Toxicity Value	Reference
Oral LD_{50} (rat, mouse, rabbit)	Rat: LD_{50} = 1131 to 1600 mg/kg Mouse: LD_{50} > 1500 mg/kg Rabbit: LD_{50} ~ 1600 mg/kg	OECD SIDS, 1998 Clayton and Clayton, 1994
Inhalation LC_{50} (rat)	LC_{50} > 8817 mg/m^3	OECD SIDS, 1998
Dermal LD_{50} (guinea pig, rabbit)	Guinea Pig: LD_{50} > 21,400 mg/kg Rabbit: LD_{50} > 20,000 mg/kg	OECD SIDS, 1998 Clayton and Clayton, 1994
Dermal irritation (guinea pig)	Slight skin irritant	Clayton and Clayton, 1994

Repeated Dose Toxicity:

The OECD SIDS (OECD, 1998) reported that subchronic and subacute toxicity studies indicate that effects on body weight, organ weights, and liver metabolism are likely following prolonged or repeated exposure to triethyl phosphate. Depressive effects on the central nervous system and slight inhibition of brain cholinesterase have also been observed following exposure to sufficiently high doses (see Neurotoxicity below).

In an subchronic oral toxicity study, rats were exposed to triethyl phosphate at doses up to 6700 mg/kg. Reduced body weight gain, and increased liver and adrenal weights were observed. The estimated no-observable-effect level (NOEL) was 670 mg/kg.

Increased liver metabolism was observed in Wistar rats following the oral administration of triethyl phosphate for 28 days. A NOEL of 100 mg/kg was determined in this study, but because an increase in liver metabolism is not considered toxicologically significant, a no-observable-adverse-effect level (NOAEL) of 1000 mg/kg was derived.

Two additional animal studies also indicate the low toxicity of triethyl phosphate. In a 4-week oral study conducted with mice, a NOAEL of 274 mg/kg was derived. In rats, a NOEL of 366 mg/m^3 was determined following inhalatory exposure (5 hr/day for 12 days). (OECD, 1998)

Neurotoxicity:

A depressive effect on the central nervous system (producing anesthetic-like effects with considerable muscle weakness) and slight brain cholinesterase inhibition (with no cumulative action) have occurred following exposure to relatively high doses of triethyl phosphate. However, studies have so far failed to show neurotoxic effects. This is partly confirmed by studies with the neurotoxin antidote pyridine-2-aldoxime methylchloride, whereby triethyl phosphate was not hydrolyzed *in vitro* (HSDB, 2006).

Chickens, a sensitive species for delayed neurotoxicity, were exposed to triethyl phosphate and gave no indication of neurotoxicity (OECD, 1998). Inhalation of 28,000 ppm of triethyl phosphate for 6-hours by rats resulted in weakness, gasping respirations and 100 percent mortality (HSDB, 2006). After single administration of high doses (rat, mouse $\geq$ 300 mg/kg; dog oral 250 mg/kg), triethyl phosphate caused narcosis and cholinesterase inhibition, which was slight compared to other phosphoric esters (OECD, 1998).

Genotoxicity:

Results of genotoxicity tests conducted with triethyl phosphate have been predominantly negative. Based on the genotoxicity data, a mutagenic effect of triethyl phosphate is not likely.

Triethyl phosphate has tested negative in several Ames test. In an *in vitro* Salmonella/microsome preincubation assay conducted using four *Salmonella typhimurium* strains at 100-10,000 µg/plate, triethyl phosphate was negative both with and without metabolic activation (HSDB, 2006). However, triethyl phosphate was reported to induce gene mutations without metabolic activation in *S. typhimurium* his c117, some bacteria, viruses, and a yeast strain in other studies (OECD, 1998). In an *in vitro* HPRT test in V79 cell cultures, conducted to clarify the gene mutation endpoint, triethyl phosphate was negative for genotoxicity, both with and without metabolic activation (OECD, 1998).

In an *in vitro* chromosomal aberration test on rat hepatocytes, triethyl phosphate showed no DNA-damaging effects (OECD, 1998). The results for *Drosophila melanogaster* in recessive-lethal tests were contradictory, while *in vivo* studies on the mouse (cytogenetics in the bone marrow and dominant lethal test) were negative. In male mice, 300 mg/kg injected intraperitoneally did not produce chromosome damage (TOXNET, 2006).

Carcinogenicity:

Data are not available to evaluate the carcinogenicity of triethyl phosphate. Based on the results of the available genotoxicity studies, triethyl phosphate is not expected to be carcinogenic.

Reproductive/Developmental Toxicity:

In a combined repeat dose and reproductive study, male and female rats were exposed (with no signs of parental toxicity) to triethyl phosphate at doses up to 6700 mg/kg . Litter size was reduced starting at 670 mg/kg and the NOEL for effects on litter size was 335 mg/kg. No effects on testicular weight were noted and histopathological examination of the testes revealed no remarkable findings. A 28-day study with doses of up to 1000 mg/kg of triethyl phosphate also showed no effect on testicular weight (OECD, 1998).

In a developmental toxicity study, exposure to 625 mg/kg of triethyl phosphate resulted in a reduction in body weight gain, food consumption, and feces excretion (OECD, 1998). There was no evidence of developmental toxicity, including teratogenic potential. The NOEL for maternal toxicity was 125 mg/kg and the NOEL for developmental toxicity was 625 mg/kg, the highest dose tested. Therefore, no quantitative susceptibility was observed.

C. Metabolism and Pharmacokinetics

Only limited information was available to assess the metabolism and pharmacokinetics of triethyl phosphate. The OECD SIDS states that triethyl phosphate administered orally or intraperitoneally is eliminated rapidly and to an appreciable extent (90% within 16 hours) (OECD, 1998).

D. Special Considerations for Infants and Children

Triethyl phosphate exhibits a low order of toxicity for human health effects. With the exception of a reduced litter size at a relatively high dose (670 mg/kg), no other reproductive or developmental effects have been reported in animal studies in doses up to 6700 mg/kg. There is no indication of quantitative susceptibility from the available reproductive and developmental studies based on the developmental toxicity NOEL of 625 mg/kg and the maternal toxicity NOEL of 125 mg/kg. Based on this information there is no concern, at this time, for increased sensitivity to infants and children to triethyl phosphate 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

If released to the ambient atmosphere, triethyl phosphate is expected to degrade by reaction with photochemically formed hydroxyl radicals with an estimated half-life of about 7 hours. (HSBD, 2006)

Triethyl phosphate is expected to have very high to high mobility in soil based on estimated Kocs of 3 and 65. Studies using activated sludge and thermophilic fungi indicate that triethyl phosphate is classified as not readily biodegradable in the environment. However, primary degradation may occur within days and ultimate degradation (mineralization) within weeks under acclimated conditions. Volatilization from dry soils may be possible, but from moist soils it is expected to be less. Limited photodegradation on soil surfaces is also possible. (HSDB, 2006)

Triethyl phosphate will hydrolyze very slowly from water, unless the pH is above 11. An experimental Henry's Law constant of 1.5×10^{-6} atm-m^3/mol indicates that this chemical is essentially non-volatile from water surfaces. In addition, the estimated K_{oc}s

and measured BCF values of 2.4 to 22 in aquatic organisms indicates that triethyl phosphate will not absorb to sediments or particulate matter in the water column, or biodegrade (HSDB, 2006). There were no data located on transformation products and their fate.

VI. Exposure Assessment

Triethyl phosphate is used in the manufacture of consumer products as a solvent, lacquer remover, plasticizer, flame-retardant, and softening agent in carpet polyurethane foam backing. Triethyl phosphate is also used as an "indirect" food additive as a component of adhesives used in packaging, transporting, or holding food.

As an inert ingredient, triethyl phosphate is used as a stabilizer in pesticide formulations that are applied before the crop emerges from the soil, which typically equates to one application of the product. This limitation on use significantly reduces the likelihood of residues on food or of residential exposures (inhalation or dermal), and contributions to drinking water are not anticipated.

VII. Aggregate Exposures

In examining aggregate exposure, the 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 triethyl phosphate, 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 the low levels of exposure to this chemical when used as an inert ingredient in pesticide formulations.

VIII. Cumulative Exposure

Section 408(b)(2)(D)(v) of FFDCA requires that, when considering whether triethyl phosphate 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 triethyl phosphate 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 triethyl phosphate 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

Available toxicological data indicate the low acute toxicity of triethyl phosphate. Subchronic and subacute toxicity studies indicate that effects on body weight, organ weights, and liver metabolism are likely following prolonged or repeated exposure to triethyl phosphate. Effects on the central nervous system, such as muscle weakness, and slight inhibition of cholinesterase may occur following exposure to high concentrations. No neurotoxicity has been observed. With the exception of a reduced litter size at a relatively high dose (670 mg/kg), no other reproductive or developmental effects have been reported in animal studies in doses up to 6700 mg/kg. There is no indication of quantitative susceptibility from the available reproductive and developmental studies based on the developmental toxicity NOEL of 625 mg/kg and the maternal toxicity NOEL of 125 mg/kg. All of these effects occured at concentrations higher than the exposure expected from triethyl phosphate's use as an inert ingredient in pesticide formulations. Data are not available to evaluate carcinogenicity, but based on the negative genotoxic activity and a negative *in vitro* cell transformation test, triethyl phosphate is not expected to be carcinogenic.

As an inert ingredient, triethyl phosphate is used as a stabilizer in pesticide formulations that are applied before the crop emerges from the soil, which typically equates to one application of the product. This limitation on use significantly reduces the likelihood of residues on food or of residential exposures, and contributions to drinking water are not anticipated. Therefore, dietary and residential exposures of concern are not likely from the use of triethyl phosphate as an inert ingredient in pesticide formulations.

Taking into consideration all available information on triethyl phosphate, it has been determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to triethyl phosphate when considering dietary exposure (through food commodities and drinking water) 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 triethyl phosphate when used on growing crops can be considered reassessed as safe under section 408(q) of the FFDCA.

X. Ecotoxicity and Ecological Risk Characterization

Data are available to evaluate the effects of triethyl phosphate on aquatic and terrestrial animals. Available information indicates low toxicity to both aquatic and terrestrial organisms (OECD, 1998). Acute toxicity tests have determined LC_{50}s for a variety of freshwater fish. The 48-hr LC_{50} for the Ide and the Japanese Medaka was 2140 mg/L and greater than 500 mg/L, respectively. Two 96-hr LC_{50}s determined for the fathead minnow were greater than 100 mg/L and greater than 1000 mg/L. Results from

acute toxicity tests (EC_{50}) with the aquatic invertebrate *Daphnia magna* range from greater than 100 mg/L up to 2705 mg/L. The lowest definitive EC_{50} was 350 mg/L. A chronic 21-day reproduction test with *Daphnia magna* resulted in an EC_{50} of 729 mg/L and a NOEC of 31.6 mg/L.

In tests for acute toxicity with other aquatic invertebrates (amphipod, flatworm, snail, mudworm, and sowbug), the 96-hr LC_{50} values were all greater than 106 mg/L. Low toxicity was also evident in tests conducted with aquatic plants (*Scenedesmus subspicatus,* 72-hr LC_{50} = 900 mg/L) and microorganisms (*Pesudomonas putida*, EC_{10} (30 min) = 3000 mg/L). The results of the various tests indicate that triethyl phosphate is practically non-toxic to aquatic fish, invertebrates, and plants, as well as microorganisms and terrestrial plants.

Bioconcentration in aquatic organisms is not expected to be significant and the predicted environmental concentration under a worst case scenario is 196 µg/L. Therefore, no long-term environmental impacts are expected and ecological risk concerns are not likely to occur from the use of triethyl phosphate as an inert ingredient in pesticide formulations.

Based on available mammalian data as a surrogate for all terrestrial phase organisms, potential exposures following use of triethyl phosphate as an inert ingredient is not expected to pose risks to mammals, birds and taxa represented by these animals.

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