



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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: June 1, 2005

ACTION MEMORANDUM

SUBJECT: Inert Reassessment – Valeric acid (CAS Reg. No.109-52-4)

FROM: Dan Rosenblatt, Chief
Minor Use, Inerts, and Emergency Response Branch

TO: Lois A. Rossi, Director
Registration Division

I. FQPA REASSESSMENT ACTION

Action: Reassessment of one inert exemption from the requirement of a tolerance. The exemption is being reassessed without any changes.

Chemical: Valeric acid (CAS Reg. No.109-52-4)
CFR: 40 CFR part 180.920 [formerly 40 CFR180.1001(d)]
CAS #: CAS Reg. No.109-52-4

Use Summary: Valeric acid is used as a stenching agent or odorant, with a limit of not more than 2% in pesticide formulations. Valeric acid is also used as an intermediate in the manufacture of flavors and perfumes, ester type lubricants, plasticizers and vinyl stabilizers. It is a food additive used as a synthetic flavoring substance and adjuvant.

List Reclassification Determination: Based on the expected low levels of exposure, this inert ingredient can be reclassified from List 3 to List 4B with current restrictions maintained.

II. MANAGEMENT CONCURRENCE

I concur with the reassessment of the one exemption from the requirement of a tolerance for the inert ingredient valeric acid (CAS Reg. No.109-52-4, and with the List reclassification determination, as described above. I consider the one exemption established in 40 CFR part 180.920 [formerly 40 CFR180.1001(d)] 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

Date: 6/9/05

CC: Debbie Edwards, SRRD
Joe Nevola, SRRD



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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

June 1, 2005

SUBJECT: Science Assessment for Valeric Acid

FROM: Princess Campbell, D.V.M. Environmental Specialist
Minor Use, Inerts, and Emergency Response Branch (MUIERB)
Registration Division (RD) (7505C)

TO: Pauline Wagner, Special Assistant *Pauline Wagner 6/1/05*
Dan Rosenblatt, Branch Chief, MUIERB
Registration Division

Background:

Attached is the science assessment for valeric acid. This assessment summarizes available information on the use, physical/chemical properties, toxicological effects, and exposure profile for valeric acid. The purpose of this document is to evaluate for reassessment the existing exemption from the requirement of a tolerance for residues of this inert ingredient as required under the Food Quality Protection Act (FQPA). In performing this assessment, EPA's Office of Pesticide Programs (OPP) has utilized reviews performed by the Department of Energy's Oak Ridge National Laboratory (ORNL) on behalf of EPA, a Structure Activity Relationship (SAR) assessment performed by the Structure Activity Team (SAT) in the Office of Pollution Prevention and Toxics (OPPT), and the WHO report of 1998.

Executive Summary:

Valeric acid is a colorless liquid, also known as pentanoic acid, valerianic acid, propylacetic acid, or butanecarboxylic acid. A tolerance exemption for valeric acid is established in 40 CFR 180.920 as a stenching agent or odorant for use on growing crops only, at not more than 2% in pesticide formulations.

The predominant use of valeric acid is as an intermediate in the manufacture of flavors and perfumes, ester type lubricants, plasticizers and vinyl stabilizers. It is a food additive used as a synthetic flavoring substance and adjuvant. The use of valeric acid as an inert ingredient in pesticide products is a very small part of the production volume.

The acute oral rat LD₅₀ for valeric acid is 1720 mg/kg (female (F)) and < 2000 mg/kg (male (M)). It is a strong skin irritant in humans and is corrosive to rabbit skin and eyes (HSDB). The TSCA Section 8(e)-4884 submission reported that valeric acid was a strong skin irritant in mice.

Effects were noted in the acute oral study. The liver, spleen, adrenal glands and lungs were the target organs. In a rat single dose level developmental study both maternal and fetal toxicity were observed at a dose of 750 mg/kg/day administered by oral intubation on GD 6- 15. However, another study did not report adverse developmental effects at 100 mg/kg/day, although maternal toxicity was observed (decreased body weight, respiratory distress). Valeric acid showed mixed results when tested for genotoxicity with positive results in chromosome aberration and sister chromatid exchanges assays, but was negative in the gene mutagenicity assay. Results of a two-year mouse dermal skin painting study indicated the occurrence of benign tumors in 8% of the treated animals and malignant tumors in approximately 16% of the treated animals at 25 mg/kg, the only dose tested. Other chemicals with such irritating and corrosive properties, have shown similar results. These tumors were most probably due to prolonged, exposure induced irritation. No absorption data were available, but the SAT predicted that valeric acid would be absorbed by all routes.

Valeric acid is not expected to be persistent in the environment. It is not expected to reach ground water since the estimated time for complete ultimate aerobic biodegradation is on the order of days (EPA 12/08/04).

Based on the high dose levels that were needed to elicit effects of concern following oral exposure in the valeric acid toxicity studies, valeric acid's high vapor pressure which indicates it will readily volatilize from food crops, thus reducing residues, and the lack of persistence in the environment, it is recommended that the exemption from the requirement of a tolerance established for residues of valeric acid on growing crops at not more than 2% in pesticide formulations can be considered reassessed as safe under Section 408(q) of the FFDCA.

I. Introduction

This assessment summarizes available information on the use, physical/chemical

properties, toxicological effects, and exposure profile for valeric acid (CAS Reg. No.109-52-4), a pesticide inert ingredient for which an exemption from the requirement of a tolerance exists in 40 CFR 180.920, as a stenching agent or odorant for use on growing crops only at not more than 2% in pesticide formulations.

Valeric acid is also known as pentanoic acid, valerianic acid, propylacetic acid or butanecarboxylic acid.

II. Use Information

a. Non-pesticidal:

Valeric acid is used as an intermediate in the manufacture of flavors and perfumes, ester type lubricants, plasticizers and vinyl stabilizers. It is a food additive used as a synthetic flavoring substance and adjuvant.

b. Pesticidal:

Table 1. Tolerance Exemptions Being Reassessed in this Document				
Tolerance Exemption Expression	CAS No.	40 CFR ◇	Use Pattern (Pesticidal)	List Classification
Valeric acid, normal	109-52-4	180.920	Stenching agent or odorant Limit: not more than 2% in pesticide formulations	3

Residues listed in 40 CFR §180.920 [formerly 40 CFR§ 180.1001(d)] are exempted from the requirement of a tolerance when used as inert ingredients in pesticide formulations when applied to growing crops only.

III. Physical/ Chemical Properties

Empirical formula: C₅ H₁₀ O₂

Structure:

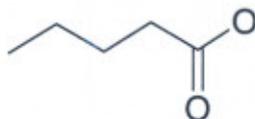


Table II. Physical/Chemical Properties of Valeric Acid

CASRN	MW	VP mm Hg @ 25 °C	BP (°C)	MP (°C)	Log K _{ow}	Specific gravity @ 20°C	Solubility @ 25 °C
109-52-4	102.15	1.96x10 ⁻¹	186.1	-34.5	1.39	0.939	24 g/L

IV. Hazard Assessment

A. Toxicological Profile:

Valeric acid is of low oral acute toxicity. It is a strong irritant to skin and eyes. In repeated dose dermal studies valeric acid was reported to be corrosive to rabbit skin. In a single dose level study, approaching the limit dose, both developmental and maternal effects were noted in a rat oral embryo/fetal toxicity and teratology screening study. Valeric acid showed mixed results in mutagenicity studies and in a two year skin painting study in mice squamous cell carcinomas, papillomas, and fibrosarcomas were seen.

B. Toxicological Data:

The toxicity database for valeric acid consists of studies submitted to the Agency under TSCA (Toxic Substances Control Act) Section 8 (e). Under this Section of the Act any person who manufactures, processes, or distributes in commerce a chemical substance or mixture and obtains information which concludes that the substance presents a substantial risk of injury to health or the environment shall immediately inform the Agency. Also, a review of valeric acid (as part of a review of several carboxylic acids used as flavorings) was conducted by the WHO (World Health Organization).

Acute

The acute oral rat LD₅₀ for valeric acid is 1720 mg/kg (F) and < 2000 mg/kg (M). Effects to the liver, spleen, adrenal gland, and lungs occurred during the oral LD₅₀ study. It is reported to be a strong skin irritant in humans and is corrosive to rabbit skin and eyes. (HSDB) TSCA Section 8(e)-4884 reported that valeric acid was a strong skin irritant in mice.

Subchronic

Rats fed 5% valeric acid (about 2500 mg/kg bw per day) in a rice diet for 115-150 days had papillomatous growths in the forestomach (Mori, 1953 as cited in WHO 1998). These effects are not considered to be relevant to the human ingestion of this substance as a flavoring agent in foods, or as inert ingredient in pesticide products since the effect occurred only in an organ for which there is no human equivalent.

In a 28-day dermal toxicity study in rabbits (5 male, 5 female) severe dermal irritation and corrosion was seen. Rabbits were treated with 0 or 500 mg/kg/day of valeric acid at five applications per week for 2 - 4 weeks. The skin of the animals was either left intact or abraded before treatment and was non-occluded after treatment. Some animals were held for a 2-week recovery. All treated animals exhibited severe erythema, moderate to severe edema, necrosis and eschar formation. There was one death and all animals experienced decreased body weight gain. In the group held for the recovery period, the dermal effects subsided.

Developmental

Female rats given 0, 75 or 100 mg/kg bw per day valeric acid by gavage on days 6 to 15 of gestation exhibited signs of maternal toxicity including respiratory effects and decreased body weight, but no significant developmental toxicity at either dose. (Narotsky *et al.*, 1994 as cited in WHO 1998)

The WHO report of 1998 also stated that when valeric acid was given daily by tracheal intubation on days 6 to 15 of gestation, no evidence of fetotoxicity, developmental toxicity or teratogenicity associated with this carboxylic acid was observed (Narotsky *et al.*, 1994 as cited by WHO). There is no evidence to conclude that, when ingested as flavouring substances, intake of any of the substances in the group of linear saturated aliphatic substances would be associated with reproductive or developmental toxicity.

In a single dose screening developmental toxicity study submitted to the Agency under TSCA, 22 female rats were dosed by gavage at 750 mg/kg/day (a dose which is approaching the limit dose of 1000 mg/kg/day) during gestation days 6 -15. Signs of maternal toxicity which included wheezing, salivation, dyspnea, rough hair coat and reduced body weight gain were seen in the dams. Fetal toxicity was also noted which included dilated renal pelves/ureter and skeletal variants. The skeletal variants included reduced ossification of the bones in the skull, vertebrae, sternebrae, and pelvis.

Mutagenicity

Valeric acid showed mixed results when tested for genotoxicity. Positive results were seen in the *in vitro* chromosome aberrations assay, and in the *in vitro* sister chromatid exchanges assays with activation, but it was negative in the *in vitro* sister chromatid exchange assay without activation (ORNL) and in the gene mutagenicity assay (EPA 12/08/04).

Carcinogenicity

Results of a two-year mouse dermal skin painting study with valeric acid showed benign

tumors in 4/50 of the treated animals and malignant tumors in 8/50 of the treated animals at 25 mg/kg, the only dose tested.

Table III: Toxicity Data:

Study	Species	Dosing	Doses mg/kg	NOAEL	LOAEL	Effects
Developmental Screening	Rat	Gavage, GD 6-15	0, 750	Not observed	<750 mg/kg	Maternal and fetal toxicity
Developmental	Rat	Gavage, GD 6- 15	0, 75, 100	Not reported	Not reported	Maternal toxicity- resp. effects; ↓ body wts
Repeated Dose	Mouse	Dermal 2 years (2x weekly)	25, 50*	Not observed	<25 mg/kg	Dec body wt, benign and malignant skin tumors
Repeated Dose	Rabbit	Dermal 28 days	0, 500	Not observed	500 mg/kg	Dec body wts; skin lesions
Gene Mutation (HGPRT)	CHO					Negative
Sister chromatid exchange	CHO	S9 Activation No activation				Positive Negative
Chromosome aberration	CHO					Positive

* Initial dose concentration was 50 mg/kg, reduced to 25 mg/kg after the first four doses due to dermal toxicity. Applied undiluted.

SAR Assessment

Based on the information provided by OPP and on information in OPPT's TSCA 8(e) files, the SAR assessment rated valeric acid as moderate to high concern for human health.

Valeric acid is expected to be absorbed by all routes with concerns for irritation and possible corrosion to all tissues. The SAT report is included as Appendix A.

Conclusion

Valeric acid is a highly corrosive chemical. Acids must be used carefully, with appropriate protective equipment. End product testing will allow the Agency to specify the personal protective equipment (PPE) for each formulation that contains valeric acid. Additionally, the limitation of 2% in the formulated product will remain in place.

V. Environmental Fate Characterization/ Drinking Water Considerations

The environmental fate of valeric acid will limit its likelihood of reaching either surface or ground water or bioaccumulating in the environment. Valeric acid is expected to degrade rapidly in the environment with ultimate aerobic degradation estimated in days. The chemical is volatile with a measured vapor pressure of 0.196 mm @ 25° C.

OPPT's Modeled estimates for environmental fate indicate that concern for exposures via drinking water is likely to be low. This conclusion is based on valeric acid's volatility from surfaces such as those found under field conditions and its rather rapid primary degradation (estimated to be hours to days). Migration to ground water is expected to be unlikely based again on the rapid biodegradation of valeric acid, despite its low adsorption to soils and sediments.

VI. Exposure Assessment

Valeric acid is used as an intermediate in the manufacture of flavors and perfumes, ester type lubricants, plasticizers and vinyl stabilizers. It is a food additive used as a synthetic flavoring substance and adjuvant. According to the WHO, the human per capita intake of valeric acid as a flavoring substance is approximately 850 µg per day for a 60 kg/bw. At this level of intake the WHO (1998) has concluded that valeric acid posed no safety concern.

The existing tolerance exemption limits the amount of valeric acid that can be in a pesticide product to 2%. Food residues from the use of valeric acid as a pesticidal inert are likely to be low, based on valeric acid's high vapor pressure which indicates it will volatilize readily, and its rapid biodegradation. Thus, the exposure resulting from the use of valeric acid as an inert ingredient in pesticide products will be much smaller than from its use as a food additive.

VII. Aggregate Exposure:

In examining aggregate exposure, section 408 of the FFDCA directs EPA to consider available information concerning exposures from the pesticide residue in food and all other non-

occupational 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 valeric acid a qualitative assessment for all pathways of human exposure (food, drinking water, and residential) is appropriate. Health concerns, such as eye and skin irritation, associated with exposure from the use of valeric acid as a pesticide inert are addressed by appropriate product testing and labeling, and the 2% limitation in the formulated product.

VIII. Cumulative Exposures

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

Unlike other pesticide chemicals 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 valeric acid and any other substances. Valeric acid 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 valeric acid 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/>.

C. Special Considerations For Infants and Children

FFDCA section 408 provides that EPA shall apply an additional tenfold margin of safety for infants and children in the case of threshold effects to account for prenatal and postnatal toxicity and the completeness of the data unless EPA concludes that a different margin of safety will be safe for infants and children. The Agency has reviewed the developmental toxicity studies conducted with valeric acid and concludes that there were no significant developmental effects. Therefore, there is no increased susceptibility for infants and children. Although delayed ossification of several bone structures and an increase in fetuses with dilated renal pelvises/ureters were observed, these effects were at most only borderline statistically significant increases when compared to controls, and were observed at a dose level (750 mg/kg) approaching the limit dose. Also, a second developmental study reported no adverse fetal effects at a dose level of 100 mg/kg, while signs of maternal toxicity were exhibited at 75 mg/kg. EPA has not used a safety factor analysis to assess the risk for valeric acid. For the same reasons the additional tenfold safety factor is unnecessary.

IX. Human Health Risk Characterization

The SAR report indicated that valeric acid would be absorbed via all routes and that valeric acid is possibly irritating and corrosive to all tissues. With the limitation of 2% of valeric acid in the formulated product the use of valeric acid as an inert ingredient in pesticidal formulations will result in exposures far below those expected to produce the irritation and corrosive effects. Valeric acid is also not expected to be persistent in the environment or to reach ground water.

Thus, taking into consideration the available information on valeric acid, there is reasonable certainty that no harm will occur to any population subgroup from the use of valeric acid as an inert ingredient in pesticide formulations, especially with limitations in the pesticide formulations of no more than 2% of the formulated product. Therefore, it is recommended that the exemption from the requirement of a tolerance established for residues of valeric acid in/on raw agricultural commodities can be considered reassessed as safe under section 408(q) of the FFDCa.

X. Ecotoxicity and Ecological Risk Characterization

OPPT's SAT report rated valeric acid as moderately toxic to aquatic organisms. Predicted acute toxicity values were: 96h LC₅₀ for fish 1,000 ppm, 48 h LC₅₀ for daphnid 260 ppm, and 96 h EC₅₀ for green algae 40 ppm. Predicted chronic values were 100 ppm for fish, 40 ppm for daphnid, and 20 ppm for green algae.

Valeric acid exhibits low sorption to soils and sediments, and rapid removal by biodegradation. An estimated time for ultimate removal via biodegradation is on the order of days so valeric acid is not expected to persist or bioaccumulate in the environment. Therefore, based on potential exposures and estimated and measured toxicity to aquatic and terrestrial organisms, ecological concerns for listed and non-listed species are not likely from the use of valeric acid as an inert ingredient in pesticide products unless application rates exceed 200 lbs/acre on a yearly basis.

List Classification- Recommend List 4B with the current limitations.

REFERENCES:

Literature Summary Report for Valeric Acid. Toxicology and Hazard Assessment Group, Life Sciences Division. Oak Ridge National Laboratory, Oak Ridge, TN 37831. 2004.

US EPA OPPT SAT report (Z05-0002). 12/08/04

<http://www.inchem.org/documents/jecfa/jecmono/v040je10.htm>

WHO Food Additives Series 40. World Health Organization, Geneva 1998.

APPENDIX I

CASE NUMBER: Z05-0002

RELATED CASES:

CONCLUSIONS/DISCUSSIONS

TYPE OF CONCERN:	HEALTH	ECOTOX
LEVEL OF CONCERN:	2-3	2

KEYWORDS: IRR/CORR-S,E,MM,L
MUTA DEVEL ONCO
LIVER, SPLEEN, ADRENALS, LUNG (ALL UNCERT)
AQUATOX

SUMMARY OF ASSESSMENT

FATE: Liquid
LogKow = 1.39(M); S (25°C) = 24 g/L(M); H = 4.72E-7(M)
MP (C) = -34(M); BP (C) = 186.1(M); VP @ 25C (mm) = 0.196(M)
LogKoc = 0.61(E); LogBCF = 0.50(E);
POTW removal (%) = 90 via biodeg;
Time for complete ultimate aerobic biodeg ? da
PBT Potential: P1B1T2
Sorption to soils/sediments = low
*CEB FATE: Migration to ground water = negl
Volatilization Halflife Rivers (hr) = 1000; Lake (da) = 570
Atmospheric Oxidation (half-life, hrs) OH = 31

HEALTH: Absorbed all routes. [Note: the majority of the data used in preparing this report were supplied by OPP.] Concern for irritation and possible corrosion to all tissues [HSDB reports that valeric acid is a strong skin irritant in humans and is corrosive to rabbit skin; HSDB reports that valeric acid is a severe irritant to rabbit eyes; in a 28-day dermal study in rabbits there was corrosion of the skin with necrosis at 500 mg/kg (only dose tested); 8E-4884 reports valeric acid was a strong skin irritant in mice]. Concern for mutagenicity [8E-10051: (+) for chromosome aberrations and sister chromatid exchange (SCE) in CHO cells; 8E-1814: (-) in an Ames assay, (+) for SCE in CHO cells, (+) for chromosome aberrations in CHO cells]; oncogenicity [8E-4884: skin painting in mice with valeric acid resulted in 6 squamous cell carcinoma, 2 papillomas, and 3 fibrosarcomas in 50 treated mice; OPP summary: 2-year mouse dermal skin painting LOAEL = 25 mg/kg (only dose tested) with benign (4/50) and malignant (8/50) skin tumors in treated mice]; and developmental toxicity (8E-1532 and 8E-11280: rat oral developmental LOAEL = 750 mg/kg with delayed ossification. Uncertain concern for liver, spleen, adrenal gland, and lung toxicity [8E-15205: rat oral LD₅₀ = 1720 mg/kg (F), <2000 mg/kg

(M) with effects to the liver, spleen, adrenals, lung, and GI tract] SAT judges that the effects on the liver, spleen, and adrenals may be stress related from the high oral dose.

*CEB HEALTH: Moderate high concern

ECOTOX: Predicted (P) and measured (M) toxicity values in mg/L (ppm) are:

fish 96-h LC50	> 1000.0	P
daphnid 48-h LC50	= 260.0	P
green algal 96-h EC50 c	= 40.0	P
fish chronic value	>= 100.0	P
daphnid ChV	= 40.0	P
algal ChV c	= 20.0	P

Predictions are based on SAR-nearest analog method for alkyl carboxylic acid anionic surfactants with 4 linear carbons in the alkyl hydrophobe and pH = 7 with soluble salt; SAR chemical class = surfactant-anionic-carboxylic acid-nC4 hydrophobe; MW102; pH7; effective concentrations based on 100% active ingredients and mean measured concentrations; hardness <150.0 mg/L as CaCO3; and TOC <2.0 mg/L;

moderate concern for toxicity;

assessment factor = 10.0

concern concentration = 1.0 mg/L (ppm)

*CEB ECOTOX: All releases to water with CC = 1000 ppb

SAT Co-chair: Leonard Keifer 564-8916