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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: **June 8, 2006**

ACTION MEMORANDUM

SUBJECT: Inert Reassessments: γ-Butyrolactone (CAS Reg. No. 96-48-0)

FROM: Pauline Wagner, Chief Pauline Wagner 6/8/06
Inert Ingredient Assessment Branch

TO: Lois A. Rossi, Director
Registration Division

I. FQPA REASSESSMENT ACTION

Action: Reassessment of one inert ingredient exemption from the requirement of a tolerance. Current exemption is to be maintained.

Chemical: γ-Butyrolactone
CFR: 40 CFR 180.920 formerly 40 CFR 180.1001(d)
CAS #: 96-48-0

Table 1. Tolerance Exemptions Expression

40 CFR	Inert Ingredients	Limits	Uses (Pesticidal)	CAS Reg. No. and 9 CI Name
180.920	γ - Butyrolactone	(none)	Solvent	96-48-0 2(3H)-Furanone, dihydro-(8CI, 9CI)

Use Summary: γ-Butyrolactone is used as a chemical intermediate in the manufacture of various chemicals, vitamin B1, and the rubber additive thiodibutyric acid. It is a constituent of paint removers, textile aids, drilling oils, hairwave compositions, sun lotions, pharmaceuticals, and printing inks. γ-Butyrolactone is also used as a solvent for polymers and nail polish removers, as a polymerization catalyst, as an extractant in the petroleum industry, and as a cosolvent for capacitor electrolytes and electronic photoresists. γ-Butyrolactone is found

naturally in raw earth almonds and in chickpeas, and has been detected in several other foodstuffs. It is also a synthetic flavoring agent approved by the US FDA. γ-Butyrolactone is also used as a solvent in a variety of pesticide products, as a nematocide, and as an intermediate in the production of pesticides, herbicides, and plant growth regulators.

II. MANAGEMENT CONCURRENCE

I concur with the reassessment of the one exemption from the requirement of a tolerance for the inert ingredient γ-Butyrolactone (CAS Reg. No. 96-48-0). I consider the one exemption established in 40 CFR 180.920 [formerly 40 CFR 180.1001(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: June 12, 2006

CC: Debbie Edwards, SRRD
Joe Nevola, SRRD

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OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

June 8, 2006

MEMORANDUM

SUBJECT: Reassessment of the One Exemption from the Requirement of a Tolerance for γ-Butyrolactone (CAS Reg. No. 96-48-0)

FROM: R. Tracy Ward, Biologist R. Tracy Ward
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 γ-butyrolactone (CAS Reg. No. 96-48-0). γ - Butyrolactone has one exemption from the requirement of a tolerance under 40 CFR 180.920 when used as an inert ingredient (solvent) in pesticide formulations applied to growing crops only. This assessment summarizes available information on the use, physical/chemical properties, toxicological effects, exposure profile, environmental fate, and ecotoxicity of γ-butyrolactone. The purpose of this document is to reassess the one existing exemption from the requirement of a tolerance for residues of γ-butyrolactone when used as an inert ingredient (solvent) in pesticide formulations as required under the Food Quality Protection Act (FQPA).

Executive Summary

This report evaluates γ-butyrolactone, an inert ingredient for which one exemption from the requirement of tolerance exists when used as a solvent in pesticide formulations applied to growing crops only under 40 CFR 180.920.

γ-Butyrolactone is an aliphatic lactone used as an intermediate in the manufacture of various chemicals, herbicides, growth regulators, vitamin B1, and the rubber additive thiodibutyric acid. It is a constituent of paint removers, textile aids, drilling oils, hairwave compositions, sun lotions, pharmaceuticals, and printing inks. γ-Butyrolactone is also used as a solvent for polymers and nail polish removers, as a polymerization catalyst, as an extractant in the petroleum industry, and as a cosolvent for capacitor electrolytes and electronic photoresists.

γ-Butyrolactone is found naturally in raw earth almonds and in chickpeas, and has been detected in alcoholic beverages, tobacco smoke, coffee and several foodstuffs (HSDB, 2005).

The γ-Butyrolactone Consortium (2003) sponsored γ-butyrolactone under EPA's High Production Volume (HPV) Challenge Program (http://www.epa.gov/chemrtk/hpvrstp.htm). The goal of the HPV Challenge 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 1 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. A robust summary has been submitted for γ-butyrolactone and the relevant information has been used in this assessment.

The 1998 Safety Evaluation of Certain Food Additives and Contaminants for aliphatic lactones prepared by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), the Hazardous Substances Data Bank, and the TSCA Test Submissions Databank were also used to prepare this assessment. 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 γ-butyrolactone as an inert ingredient in pesticide formulations.

Available toxicological information indicates the low acute toxicity of γ-butyrolactone. γ-Butyrolactone is only slightly toxic by the oral, inhalation, and dermal routes of exposure, but is a severe eye irritant. Transient minor sedation has also been observed following subchronic repeat dose exposure to γ-butyrolactone, but no target organs have been identified in subchronic or chronic toxicity studies. In addition, no neurotoxicity has been observed. Outside of reduced testicular weight at high doses, there were no other effects reported in reproductive and developmental studies. γ-Butyrolactone is also negative for genotoxicity and is not considered to be carcinogenic.

Residential (inhalation and dermal) exposures of concern are not anticipated from the inert ingredient use of γ-butyrolactone because concentrations of residues are not expected at levels or at the number of repeat doses that produced toxicity in animal studies. The chemical has low vapor pressure and is readily biodegraded in the environment, and upon exposure, has limited uptake through the skin and rapid elimination from the body. Dietary exposures of concern from food and drinking water are also not likely because of its physical-chemical and fate properties.

γ-Butyrolactone is not toxic to aquatic organisms and bioconcentration in aquatic organisms is not expected to be significant, therefore, ecological risk concerns are not likely to occur from the inert ingredient use of this chemical in pesticide products.

Taking into consideration all available information on γ-butyrolactone, it has been determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to γ-butyrolactone 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 γ-butyrolactone when used on growing crops 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 γ -butyrolactone, 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

The inert ingredient γ-butyrolactone is used as a solvent in pesticide products, as a nematocide, and as an intermediate in the production of pesticides, herbicides, and plant growth regulators (HSDB, 2005). There are no active ingredient uses for γ-butyrolactone registered by the EPA. The one tolerance exemption for this chemical is presented below in Table 1.

Table 1. Pesticide Uses of γ-Butyrolactone

CFR Citation				CAS Reg. No. 9CI CAS Name
40 CFR §	Inert Ingredients	Limits	Uses	
180.920*	γ - Butyrolactone	None	Solvent	96-48-0 2(3H)-Furanone, dihydro-

*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.

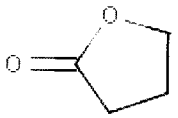
B. Other Uses

γ-Butyrolactone is used as a chemical intermediate in the manufacture of various chemicals (e.g., pyrrolidones), vitamin B1, and the rubber additive thiodibutyric acid. It is a constituent of paint removers, textile aids, drilling oils, hairwave compositions, sun lotions, pharmaceuticals, and printing inks. γ-Butyrolactone is also used as a solvent for polymers and nail polish removers, as a polymerization catalyst, as an extractant in the petroleum industry, and as a cosolvent for capacitor electrolytes and electronic photoresists (HSDB, 2005; BPPD Consortium, 2003).

III. Physical and Chemical Properties

Physical and chemical characteristics of γ-butyrolactone, along with its structure and nomenclature, are found in Table 2.

Table 2. Physical and Chemical Properties of γ-Butyrolactone

Parameter	Value	Reference
Structure		ChemIDPlus, 2004
CAS Number	96-48-0	HSDB, 2005
Molecular Formula	C4-H6-O2	HSDB, 2005
Molecular Weight	86.09	HSDB, 2005
Synonyms	6480; gamma-6480; gamma BL; BLO; butanoic acid, 4-hydroxy-, gamma-lactone; 1,2-butanolide; 1,4-butanolide; 4-butanolide; butyric acid lactone; gamma-butyrolactone; 4-butyrolactone; butyryl lactone; 4-deoxytetronic acid; dihydro-2-furanone; 2(3H)-furanone, dihydro-; 4-hydroxybutanoic acid lactone; gamma-hydroxybutyric acid cyclic ester; gamma-hydroxybutyric acid lactone; 3-hydroxybutyric acid lactone; 4-hydroxybutyric acid lactone; gamma-hydroxybutyrolactone; tetrahydro-2-furanone	HSDB, 2005
Odor	Pleasant, faint	HSDB, 2005
Physical State	Colorless, oily liquid	HSDB, 2005
Melting Point	-43.53°C	HSDB, 2005
Boiling Point	204°C	HSDB, 2005
Water Solubility	1×10^6 mg/L, Miscible	ChemIDPlus, 2004; HSDB, 2005
Other Solubility	Soluble in methanol, ethanol, acetone, ether, and benzene.	HSDB, 2005
Vapor Pressure	0.45 mm Hg @ 25°C	HSDB, 2005
Log K_{ow}	-0.64	HSDB, 2005
K_{oc}	7*	HSDB, 2005
Henry's Law Constant	5.3×10^{-8} atm-m^3/mole*	HSDB, 2005
Specific Gravity	1.1284 @ 16°C	HSDB, 2005

*Estimated values.

IV. Hazard Assessment

A. Hazard Profile

This hazard assessment of γ-butyrolactone was developed using, as primary sources, the test plan and robust summaries for γ-butyrolactone submitted under the EPA HPV Challenge Program by the BPPD Consortium (2003) and the 1998 Safety Evaluation of Certain Food Additives and Contaminants for aliphatic lactones prepared by the Joint FAO/WHO Expert Committee on Food Additives (JECFA; WHO, 1998). Additional sources of information used in this assessment include the Hazardous Substances Data Bank (HSDB, 2005) and the TSCA Test Submissions (TSCATS) Database (TSCATS, 2005).

B. Metabolism and Pharmacokinetics

γ-Butyrolactone is rapidly and completely absorbed when administered orally. Only approximately ten percent of the dose is absorbed following dermal application (BPPD Consortium, 2003).

The metabolic pathway for γ-butyrolactone involves rapid conversion to γ-hydroxybutyrate by a lactonase enzyme in the plasma and liver, followed by production of carbon dioxide and urinary metabolites (BPPD Consortium, 2003). This metabolic conversion to γ-hydroxybutyrate, which affects the central nervous system, is responsible for the weak narcotic effects observed following administration of γ-butyrolactone.

C. Toxicological Data

Acute Toxicity:

Available acute toxicological information indicates the low toxicity of γ-butyrolactone. γ-Butyrolactone is only slightly toxic by the oral, inhalation, and dermal routes of exposure. Administration of γ-butyrolactone has been shown to cause a weak narcotic or sedative effect in experimental animals (BPPD Consortium, 2003). There is limited information regarding the skin irritation potential of γ-butyrolactone, but it produced some irritation when applied to the skin of guinea pigs, and no irritation when applied to the skin of rabbits (HSDB, 2005). Severe eye irritation has also been reported in rabbits (HSDB, 2005). Quantitative data from various acute toxicity studies are summarized in the following table:

Table 3. Summary of Acute Toxicity Data for γ-Butyrolactone

Study Type (Species)	Toxicity Value	Reference
Oral LD_{50} (rat, mouse, guinea pig)	Rat: LD_{50} = 1580 to 1920 mg/kg Mouse: LD_{50} = 1245 mg/kg Guinea Pig: LD_{50} = 500 to 1690 mg/kg	BPPD Consortium, 2003; WHO, 1998; HSDB, 2005
Inhalation LC_{50} (rat)	LC_{50} > 300 ppm (1056 mg/m^3)	BPPD Consortium, 2003
Dermal LD_{50} (guinea pig)	LD_{50} = 5640 mg/kg	BPPD Consortium, 2003
Dermal irritation (guinea pig, rabbit)	Guinea pig: mild skin irritation Rabbit: no irritation	HSDB, 2005
Eye irritation (rabbit)	Severe irritant	HSDB, 2005

Repeated Dose Toxicity:

Available subchronic and chronic toxicity studies indicate few adverse effects following repeated oral exposure to γ-butyrolactone. Transient minor sedation has been observed following subchronic exposure to moderate doses, but no specific target organs have been identified in these studies.

In oral subchronic gavage studies conducted by the U.S. National Toxicology Program (NTP), groups of 10 rats of each sex were exposed to γ-butyrolactone at doses of 0, 56, 112, 225, 450, or 900 mg/kg/day and groups of 10 mice of each sex received doses of 0, 65, 131, 262, 525, or 1050 mg/kg/day, 5 days/week for 13 weeks (1992, as cited in BPPD Consortium, 2003). Mortality was observed at the high dose treatment level in both mice (1050 mg/kg/day) and rats (900 mg/kg/day). Final body weights and mean body weight gains of male rats and mice fed high doses were lower than those of control animals. No body weight effects were noted in dosed females. During the first weeks of the study, animals dosed with ≥ 225 mg/kg/day of γ-butyrolactone showed signs of sedation that diminished in intensity with continued dosing. In all dosed rats, there was an increased incidence of focal inflammation of the nasal mucosa, but this was considered to be a non-specific effect of administration of a volatile agent via gavage. No gross or macroscopic lesions occurred in mice. The no-observed-adverse-effect level (NOAEL) was 225 mg/kg for male rats (body weight gain), 450 mg/kg/day for female rats (one mortality), and 525 mg/kg/day for male and female mice (body weight and mortality). No specific target organs were identified.

NTP also conducted 2 year studies in mice and rats (1992, as cited in BPPD Consortium, 2003). Groups of 50 rats of each sex were administered γ-butyrolactone by gavage 5 days/week for up to 103 weeks. Male rats received 0, 112 or 225 mg/kg/day and female rats received 0, 225, or 450 mg/kg/day. No body weight or mortality effects were noted in the male rats. In the female rats, a reduction in body weight gain was observed at the high dose. Survival was similar in all female groups. The NOAEL for male or female rats was 225 mg/kg. No non-neoplastic toxic lesions or increased incidences of neoplasms were observed in any of the male or female dosed animals. No adverse effects in survival were noted in this study.

In a similar NTP study in which 50 mice of each sex received 0, 262, 525, or 1,050 mg/kg/day of γ-butyrolactone by gavage, lethargy and inactivity were observed in high-dose males shortly after dosing, resulting in an increase in fighting-related trauma, and decreased body weights and survival compared to the controls (1992, as cited in BPPD Consortium, 2003). Body weights were lower in high-dosed mice than in controls. In addition, there was a statistically significant increased incidence of focal hyperplasia of the adrenal medulla in low-dosed males (262 mg/kg) only. No specific target organs were identified. The NOAEL for both sexes in mice was 525 mg/kg/day with a LOAEL of 1,050 mg/kg/day (decreased body weight and survival).

Neurotoxicity:

Administration of γ-butyrolactone at dose levels of approximately 225 mg/kg and above has been associated with weak narcotic or anesthetic-like effects (weakness, unconsciousness and increased depth of respiration) in animal studies. These effects are likely due to the rapid metabolic conversion of γ-butyrolactone to γ-hydroxybutyrate, which is a central nervous system depressant (BPPD Consortium, 2003). However, no other neurotoxic effects have been reported in the available studies.

Genotoxicity:

γ-Butyrolactone has been extensively studied in *in vitro* and *in vivo* genotoxicity tests. Results of these tests have been primarily negative. On the basis of all the data on genotoxicity, a mutagenic effect of γ-butyrolactone is not assumed.

In an *in vitro* reverse mutation assay conducted using four *Salmonella typhimurium* strains at 33-10,000 μg/plate, γ-butyrolactone was negative both with and without metabolic activation (BPPD Consortium, 2003). Other *in vitro* gene mutation tests with *Salmonella typhimurium* strains and *E. Coli* have shown similar results (WHO, 1998). Mitotic gene conversion, mitotic crossing-over and cell growth inhibition tests in yeast with γ-butyrolactone have also been negative. In addition, negative results have been reported for γ-butyrolactone in tests such as forward mutation (*S. typhimurium*), microtiter fluctuation (*S. typhimurium, E. Coli*), differential killing assay (*E. Coli*), and clastogenic activity (rat liver cell line), among others (WHO, 1998). However, γ-butyrolactone tested positive at high concentrations and in the presence of metabolic activation in an *in vitro* chromosomal aberration test with Chinese hamster ovary (CHO) cells. Concentrations of 2580 to 3990 μg/mL γ-butyrolactone caused significant increases in aberrations with no evidence of cell cycle delay. In a sister chromatid exchange (SCE) test, high concentrations (3010 to 5010 μg/mL) of γ-butyrolactone also produced a significant increase in SCEs in CHO cells in the presence of metabolic activation. However, these positive results have been attributed to the high doses used and the presence of metabolic activation and are not considered to be evidence of genotoxicity since *in vivo* studies have not shown γ-butyrolactone to be mutagenic (see below) (BPPD Consortium, 2003; WHO, 1998).

γ-Butyrolactone has tested negative for genotoxicity in various *in vivo* genotoxicity tests. In a mouse micronucleus assay, two intraperitoneal doses of γ-butyrolactone, each equal to 80% of the 7-day LD_{50}, did not produce an increase in the frequency of micronuclei (BPPD Consortium, 2003). Other micronucleus tests described in the literature also failed to provide evidence of genotoxicity. In addition, a sex-linked recessive test in *Drosophila melanogaster* was negative for genotoxicity at doses of 20,000 or 28,000 mg/kg (diet) or 15,000 mg/kg (injection) (WHO, 1998).

Reproductive/Developmental Toxicity:

The only potentially relevant reproductive effect following exposure to γ-butyrolactone reported in animal studies was reduced testicular weight in adults. On the other hand, γ-

butyrolactone has not been shown to be a developmental toxicant by the inhalation or oral routes of exposure.

In the subchronic toxicity studies conducted with rats and mice by NTP, no adverse effects on fertility or other reproductive function were found at doses up to 1000 mg/kg (BPPD Consortium, 2003). In another published study, γ-butyrolactone administered orally to male rats at 500 to 1000 mg/kg reduced gonadal development resulting in significantly reduced testicular weights (HSDB, 2005).

The developmental toxicity of γ-butyrolactone has been investigated in studies conducted with rabbits and rats (BPPD Consortium 2003). No evidence of maternal or fetal toxicity was noted in rabbits exposed via inhalation to γ-butyrolactone at concentrations up to 5.0 mg/L (5,000 mg/m^3) for 6 hrs/day on days 9 to 17 of gestation. No reproductive, embryonic or fetal parameters were affected. Both the developmental and maternal NOAEL was 5.0 mg/L (5,000 mg/m^3). In rats, administration of γ-butyrolactone by oral gavage at concentrations of 10, 50, 125, 250, or 500 mg/kg/day on days 6 to 15 of gestation did not result in embryotoxicity or malformations in the fetuses. Placental weights were significantly reduced at all doses and fetal weights were significantly increased in the 50, 125, and 250 mg/kg groups. The maternal and developmental NOAEL was 500 mg/kg/day. A LOAEL was not determined.

Carcinogenicity:

Results of two-year carcinogenicity studies in experimental animals were equivocal.

In the NTP 2-year oral gavage studies described previously (see Repeated Dose Toxicity), there was no evidence of carcinogenic activity of γ-butyrolactone in male rats administered up to 225 mg/kg/day or in female rats administered up to 450 mg/kg/day of the chemical (BPPD Consortium, 2003). There was equivocal evidence of carcinogenic activity of γ-butyrolactone in male mice based on marginally increased incidences of adrenal medulla pheochromocytomas and hyperplasia in the low-dosed group (262 mg/kg) only. The sensitivity of the study in male mice to detect a carcinogenic effect was reduced by the low survival of the high-dose group (525 mg/kg) associated with fighting. No evidence of carcinogenicity was observed in female mice administered up to 525 mg/kg/day of γ-butyrolactone. In addition, a decreased incidence of hepatocellular neoplasms and harderian gland adenoma in dosed male mice and decreased incidences of mammary gland fibroadenomas/cysts and pituitary cysts in female rats were associated with the administration of γ-butyrolactone.

The International Agency for Research on Cancer (IARC) lists γ-butyrolactone in Group 3, not classifiable as to its carcinogenicity in humans. In its evaluation, IARC notes that the evidence in humans is inadequate, while there is evidence suggesting lack of carcinogenicity in experimental animals. Carcinogenicity tests conducted in mice and rats via oral administration, skin application or subcutaneous injection have not resulted in carcinogenic effects (IARC, 1999; HSDB, 2005).

D. Special Considerations for Infants and Children

γ-Butyrolactone exhibits a low order of toxicity for human health effects. With the exception of reduced testicular weights at high doses in adults, no other reproductive or developmental effects have been reported in animal studies at doses up to and including 500 mg/kg/day. Based on this information there is no concern, at this time, for increased sensitivity to infants and children to γ-butyrolactone 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

γ-Butyrolactone's production and subsequent use may result in its release to the environment. If released to the ambient atmosphere, γ-butyrolactone is expected to exist solely in the vapor-phase. Vapor-phase γ-butyrolactone will degrade by reaction with photochemically-formed hydroxyl radicals with an estimated half-life of 5 to 7 days (HSDB, 2005)

γ-Butyrolactone is expected to have very high mobility in soil based on an estimated K_{oc} of 7. Volatilization from moist soils is not likely to occur based on an estimated Henry's Law constant of 5.3×10^{-8} atm-m^3/mol. γ-Butyrolactone is not expected to evaporate from dry soils. Available biodegradation studies suggest that γ-butyrolactone is readily biodegradable under aerobic conditions.

If released into water, γ-butyrolactone is not expected to absorb to suspended soils or sediments. Volatilization from water surfaces may occur; however, it is not expected to be an important fate process based upon the chemical's estimated Henry's Law constant. γ-Butyrolactone's half-life in neutral aqueous solution is approximately 14 to 28 days at 20°C. It can be hydrolyzed rapidly to γ-hydroxybutyrate, especially at high pH levels. An estimated bioconcentration factor (BCF) of 3.2 indicates that the potential for bioconcentration in aquatic organisms is low.

Considering that γ-butyrolactone will not adsorb to sediments or particulates in the water column or volatilize significantly, γ-butyrolactone may be present in drinking water sources. However, given γ-butyrolactone's potential to hydrolyze and biodegrade in the environment, it is not expected to be present in water in significant concentrations as a result of its use as an inert ingredient in pesticide formulations.

VI. Exposure Assessment

Dietary exposures of concern from food and drinking water are not likely from the use of γ-butyrolactone in pesticide formulations due to the inert ingredient's physical-chemical and fate properties, including low vapor pressure and ready biodegradation. Residential (inhalation and dermal) exposures are possible from the inert ingredient use of γ-butyrolactone in pesticide formulations, but inhalation exposures may be limited by its low vapor pressure.

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 (ground water or surface water) and exposure through pesticide use in gardens, lawns, or buildings (residential and other indoor uses).

For γ-butyrolactone, 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 γ-butyrolactone as an inert ingredient in pesticide formulations.

VIII. Cumulative Exposure

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

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to γ-butyrolactone 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 γ-butyrolactone 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

γ-Butyrolactone is used as a solvent in pesticide formulations applied to growing crops. There are no current limits on its use in pesticide formulations as an inert ingredient.

Available toxicological information indicates the low acute toxicity of γ-butyrolactone. γ-Butyrolactone is only slightly toxic by the oral, inhalation, and dermal routes of exposure, but is a severe eye irritant. Transient minor sedation has also been observed following subchronic repeat dose exposure to γ-butyrolactone, but no target organs have been identified in subchronic or chronic toxicity studies. In addition, no neurotoxicity has been observed. Outside of reduced testicular weight at high doses, there were no other effects reported in reproductive and developmental studies. γ-Butyrolactone is also negative for genotoxicity and is not considered to be carcinogenic.

Residential (inhalation and dermal) exposures of concern are not anticipated from the inert ingredient use of γ-butyrolactone because concentrations of residues are not expected at

levels or at the number of repeat doses that produced toxicity in animal studies. The chemical has low vapor pressure and is readily biodegraded in the environment, and upon exposure, has limited uptake through the skin and rapid elimination from the body. Dietary exposures of concern from food and drinking water are also not likely because of its physical-chemical and fate properties.

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

X. Ecotoxicity and Ecological Risk Characterization

In available ecotoxicity data from the Agency's Ecotox Database (http://www.epa.gov/ecotox), freshwater fish exposed to ≥ 5000 μg/L (5 mg/L) of γ-butyrolactone for 24 hours exhibited stress behavior. Available information indicates that γ-butyrolactone has low toxicity to aquatic invertebrates and algae (BPPD Consortium, 2003). An acute toxicity test with the aquatic invertebrate *Daphnia magna* produced a 48-hr EC_{50} that was greater than 500 mg/L. A 96-hr toxicity test in green algae determined an EC_{50} of 79 mg/L.

Bioconcentration in aquatic organisms is not expected to be significant. Therefore, no long-term environmental impacts are expected and ecological risk concerns are not likely to occur from the use of γ-butyrolactone as an inert ingredient in pesticide formulations.

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