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

OFFICE OF PREVENTION,
PESTICIDES, AND TOXIC SUBSTANCES

DATE: April 4, 2006

ACTION MEMORANDUM

SUBJECT: Inert Reassessment -- Ethylene Glycol Monobutyl Ether (EBGE) (CAS Reg. No. 111-76-2)

FROM: Pauline Wagner, Chief Pauline Wagner 4/5/06
Inert Ingredient Assessment Branch
Registration Division (7505C)

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

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: Ethylene Glycol Monobutyl Ether (EGBE)

CFR: 40 CFR part 180.920

CAS Registry Number and Name: CAS Reg. No. 111-76-2; CAS Name: Ethanol, 2-butoxy- (8CI, 9CI)

Use Summary: The predominant use of this chemical is in consumer products, including household products such as spot removers, cosmetics, paints. It is used as an intermediate in chemical production, and is found in brake fluids and printing ink. EGBE has direct food additive uses approved by FDA. It is also used as an inert ingredient in pesticide products applied to growing crops and in antimicrobial pesticide formulations used on food processing equipment and utensils [180.940(c)].

List Reclassification Determination: The current List Classification for EGBE 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 EGBE used as inert ingredients in pesticide formulations, the List Classification for EGBE 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 ethylene glycol monobutyl ether (EBGE) (CAS Reg. No. 111-76-2) and with the List reclassification determination(s), as described above. I consider the one exemption 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

4/6/06
Date:

cc: Debbie Edwards, SRRD
Joe Nevola, SRRD

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

OFFICE OF PREVENTION,
PESTICIDES, AND TOXIC SUBSTANCES

March 30, 2006

MEMORANDUM

SUBJECT: Reassessment of One Tolerance Exemption for Ethylene Glycol Monobutyl Ether

FROM: Kit Farwell, D.V.M.
Reregistration Branch 1
Health Effects Division (7509C)

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

BACKGROUND

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

EXECUTIVE SUMMARY

This document evaluates ethylene glycol monobutyl ether (EGBE), a pesticide inert ingredient for which an exemption from the requirement of a tolerance exists. As an inert pesticide ingredient, EGBE is exempt from the requirement of a tolerance in pesticide formulations (40 CFR 180.920).

EGBE is also approved by EPA for use in antimicrobial pesticide formulations used on food processing equipment and utensils [180.940(c)]. It also has indirect food additive uses approved by FDA as an adhesive or defoaming agent for material used in packaging food; as a solvent used for resins for food contact surfaces; as a sanitizing solution used on food-processing equipment; and for use in washing fruits and vegetables.

EGBE is also used in household products such as spot removers, and cosmetics. It is used as a solvent in surface coatings in paints; as a coupling agent in metal and household cleaners; as an intermediate in chemical production; and is also found in brake fluids and in printing ink.

The toxicity data base for EGBE is extensive: there are subchronic oral studies in rats and mice and subchronic and chronic inhalation studies in rats and mice, metabolism studies, genetic toxicity studies, and developmental and reproductive toxicity studies.

Studies in laboratory animals have found that the toxicity of EGBE is due to damage to the red blood cell. *In Vitro* tests with blood samples showed that humans are much less sensitive than laboratory animals to this toxicity with EGBE. Liver tumors in male mice, and forestomach tumors in female mice were found not to be caused by a genotoxic mechanism. Developmental toxicity occurred only at the same or greater dose as severe maternal toxicity. Reproductive toxicity (a slight decrease in pup body weight) occurred at a lower dose than did parental toxicity in this study, however, this dose was greater than the dose causing hematological changes in other studies. There are no concerns for potential sensitivity of infant and children because exposure is expected to be much lower than that at which the marginal sensitivity occurred in rats.

Exposure to EGBE as a result of its use as an inert ingredient in pesticidal products is possible through the dietary (food and/or drinking water) or residential (dermal and inhalation) routes of exposure.

The low toxicity of EGBE and the low potential for bioaccumulation limit the potential for risk to human health. Therefore, risks to human health as a result of the consumption of residues of EGBE are likely to be low. Taking into consideration all available information on EGBE, it has been determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to EGBE when considering exposure through dietary exposure and all other non-occupational sources for which there is reliable information. Therefore, it is recommended that the exemption from the requirement of a tolerance established for residues of EGBE when used as an inert ingredient in pesticide formulations applied to growing crops under 40 CFR part 180.920 can be considered reassessed as safe under section 408(q) of the FFDCA.

I. Introduction

This report provides a qualitative assessment for EGBE, a pesticide inert ingredient with tolerance exemption under 40 CFR 180.920. There is sufficient information to conduct this assessment.

II. Use Information

A. Pesticides

The tolerance exemption for EGBE when used as an inert ingredient in pesticide formulations is shown below in Table 1.

Table 1. Tolerance Exemptions Being Reassessed in this Document

Citation as it Appears in the CFR				CAS Registry Number and Name
40 CFR 180[a]	Tolerance Exemption Expression	Limits	Uses	
920	Ethylene glycol monobutyl ether	---	---	111-76-2 Ethanol, 2-butoxy- (8CI, 9CI)

a. 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

EGBE is used in household products such as spot removers, and cosmetics. It is used as a solvent in surface coatings in paints, as a coupling agent in metal and household cleaners, as an intermediate in chemical production, and is also found in brake fluids and in printing ink.

Table 2 shows indirect food additive uses approved by FDA.

Table 2. FDA Indirect Food Additive Uses for EGBE

Name	21 CFR	Use Pattern
Ethylene glycol monobutyl ether	175.105	Adhesive for use in packaging, transporting, or holding food.
Monobutyl ether of ethylene glycol	176.210	Defoaming agent used in manufacture of paper and paperboard for use in packaging, transporting, or holding food.
Ethylene glycol monobutyl ether	177.1650	Solvent used for resins for food contact surface of articles intended for packaging, transporting, holding, or contacting dry food.
Ethylene glycol monobutyl ether	178.1010	Sanitizing solution used on food-processing equipment, utensils, and other food-contact articles.
Ethylene glycol monobutyl ether	178.315	Chemicals used in washing or to assist in the peeling of fruits and vegetables.

III. Physical and Chemical Properties

Some of the physical and chemical characteristics of EGBE, along with its structure and nomenclature, are found in Table 3.

Table 3. Physical and Chemical Properties of Ethylene Glycol Monobutyl Ether

Parameter	Value	Reference
Structure		NTP
CAS #	111-76-2	NTP
Empirical Formula	$C_6H_{14}0_2$	Merck
Molecular Weight	118.2	NTP
Other Names	2-butoxyethanol	NTP
Physical State	colorless liquid	NTP
Melting Point	-74.8^0 C	NTP
Boiling Point	168.4^0 C	NTP
Relative Density (water=1)	0.9	NTP
Vapor Pressure	0.88	NTP
log Kow	0.83	NTP
Henry's Law Constant	1.6×10^{-6}	NTP

IV. Hazard Assessment

EGBE is being evaluated as part of the US EPA's tolerance exemption reassessment process of inert ingredients.

A number of toxicity studies with EGBE were conducted by the National Toxicology Program: subchronic oral and inhalation studies in rats and mice, inhalation carcinogenicity studies in rats and mice, metabolism/pharmacokinetic studies in rats, genetic toxicology studies, developmental toxicity studies in rats, and a reproductive study in mice.

The principal source of toxicity information for this document was a comprehensive toxicological review conducted by EPA's National Center for Environmental Assessment (NCEA, Jeffrey Gift, 1999). The NCEA document reviewed the NTP studies as well as studies from the open literature and was performed for the EPA's Office of Air to remove EGBE from a list of hazardous air pollutants (Angela Howard, EPA, personal communication).

Other sources of information included reviews by the World Health Organization, CDC's National Institute for Occupational Safety and Health (NIOSH) and CDC's Agency for Toxic Substances and Disease Registry (ATSDR) and Pubmed and Toxline literature reviews conducted for this assessment.

A. Hazard Profile

Acute toxicity: EGBE is of generally low acute toxicity by the oral route of exposure in rats, mice, and guinea pigs (tox category III). Rabbits appear to be more sensitive (tox category II), although no details about this study were available. EGBE is in tox category II by the dermal route (rabbits) and is in tox category IV by the inhalation route of exposure. EGBE was reported to be a severe eye irritant causing conjunctival edema and hyperemia. The skin sensitization test in guinea pigs was negative. See Table 4.

Subchronic and chronic toxicity: Toxicity is similar for subchronic and chronic durations regardless of the route of exposure. The main target for EGBE is the red blood cell, which is damaged by the metabolite, 2,-butoxyacetic acid (BAA). The BAA metabolite damages the red blood cell membrane, causing hemolysis, or rupture of the red blood cell. This type of anemia is called a "responding" anemia, which means the body responds by producing more red blood cells in the bone marrow, and in the case of laboratory animals, in the spleen. Similar hemolytic effects occur by oral, dermal, and inhalation exposure.

Toxicity in other tissues from EGBE exposure is generally secondary to the red blood cell hemolysis. The increased iron from hemolyzed red blood cells results in liver and kidney toxicity. Liver toxicity is shown by increased liver weight and microscopic liver changes (hepatocellular degeneration) which have been shown to be due to increased iron in the liver's Kuppfer cells. The increased iron (hemosiderin) causes oxidative damage to the liver, though there is possibility of liver damage by some other unknown mechanism.

Increased kidney weights and microscopic kidney changes (tubular degeneration) also result from EGBE treatment. These changes are accompanied by accumulation of hemoglobin in the cells. The liver and kidney changes generally return to normal after a recovery period of 2 to 3 weeks.

One type of toxicity which was not caused by red blood cell hemolysis was ulceration of the forestomach in mice. Because the ulcers are believed to be caused by prolonged storage of food in the forestomach, and humans do not have a forestomach, this toxicity is of limited relevance to humans.

Female rats are consistently more sensitive to the hemolytic effect than are males, and older rats are more sensitive than young rats. These differences are believed to be due to less efficient elimination of the BAA metabolite in the urine of females and older rats. Tolerance to EGBE develops with time, although as rats age, the tolerance diminishes.

Humans are much less sensitive than rats to the hemolytic toxicity of the toxic metabolite, BAA. *In vitro* studies with blood samples have shown that hemolysis in rat blood occurs at a concentration approximately 15 times less than that causing a comparable effect in a human blood sample. Furthermore, testing of blood samples from potentially sensitive humans (elderly and human patients with sickle cell anemia or hereditary spherocytosis) found that their red blood cells were also less sensitive than rat blood cells to the toxic metabolite, BAA. This comparative testing of blood samples was performed by treating blood samples after they were drawn and did not include dosing of humans or animals with EGBE or BAA.

Metabolism and pharmacokinetics: EGBE is eliminated primarily as BAA (2-butoxyacetic acid) in the urine regardless of the route of exposure. This metabolite has been found to be responsible for hemolytic effects.

Genetic toxicology: EGBE was evaluated in a battery of genotoxicity tests for the potential to induce cytogenetic damage in vitro and in vivo. The data did not support a mutagenic or clastogenic potential for EGBE. One laboratory reported a weak genotoxic response at toxic doses, but the data were questionable.

Cancer: This cancer assessment section was based upon a review of EGBE's carcinogenic potential prepared by EPA/ORD/NCEA (Jeffrey Gift, February, 2005). EGBE treatment resulted in a marginal increase in hemangiosarcomas of the liver in male mice, and forestomach squamous cell papillomas or carcinomas in female mice. Previously EPA had classified EGBE as a "possible human carcinogen". NCEA later evaluated the mode-of-action involved in these tumors and concluded that non-linear modes of action were likely responsible for these tumors and quantitation of cancer risk was not required.

The hemangiosarcomas were believed to be due to excess iron from hemolyzed red blood cells which caused oxidative stress. Because humans are much less sensitive to the hemolytic effects of EGBE, it was concluded that a non-linear mode of action was relevant for this tumor.

The forestomach tumors in female mice were believed to be due to sustained cytotoxicity and cell regeneration from prolonged storage in the mouse forestomach. Because this effect occurred at relatively high doses, and because humans lack a forestomach for storage, it was concluded that a non-linear mode of action was appropriate for this tumor.

Developmental toxicity: There are several developmental studies in rats and rabbits. In rats, developmental toxicity (increased resorptions, reduced number of viable fetuses) occurred at greater doses than did maternal toxicity (clinical signs and mortality). In other rat and rabbit studies, retarded skeletal ossification occurred at the same dose as maternal toxicity (clinical

signs, hematological effects). Executive summaries for these studies follow in the Toxicological Data section.

Reproductive toxicity: Slightly decreased pup weight occurred at a lower dose than did parental toxicity (maternal mortality). At a higher dose, decreased litter size and decreased number of litters occurred at the same dose as maternal mortality.

Although structurally related ethers (ethylene glycol methyl ether and ethylene glycol ethyl ether) have caused toxicity to testes and sperm, similar effects were not noted in this reproductive study in mice with EGBE nor in the developmental studies with rats. An executive summary for the reproductive toxicity study follows in the Toxicological Data section.

B. Special considerations for infants and children

EGBE is of generally low toxicity at doses less than a lethal dose. Besides effects noted in the developmental and reproductive studies above, toxicity is due to injury to the red blood cell, or due to secondary effects from the red blood cell effects. Because the young are less sensitive than older individuals, there are no concerns for potential sensitivity of offspring to the hematological effects of EGBE when used as an inert formulation.

Developmental toxicity occurred only at the same or greater dose as severe maternal toxicity. Reproductive toxicity (a very slight decrease in pup body weight) occurred at a lower dose than did parental toxicity in this study, however, this dose was greater than the dose causing hematological changes in a number of other studies. There are no concerns for potential sensitivity of infant and children because exposure is expected to be much lower than that at which the marginal sensitivity occurred in rats. For this reason, a safety factor analysis has not been used to assess risk and the 10-fold safety factor for protection of infants and children is not needed.

V. Environmental Fate Characterization/Drinking Water Considerations

According to an assessment previously prepared by the Office of Air, concern for dietary exposure via drinking water is likely to be low.

"Once in soil, EGBE is further decomposed through biotic processes, but it has been estimated that as much as 35 percent of the EGBE deposited on soil can eventually move to water." Due to its physico-chemical properties, "EGBE tends to remain dissolved until it biodegrades (half life = 1 to 4 weeks). It has a low bioconcentration factor, therefore, it is not anticipated to accumulate in the environment or in food stuffs. Its relatively rapid biodegradation in water indicates that humans are unlikely to be exposed to significant amounts of EGBE in drinking water." (68 FR 65648; FRL-7587-5)

VI. Exposure Assessment

EGBE is used as an inert ingredient in pesticide formulations and is also used in household and industrial cleaners, cosmetics, paints, brake fluid, and printing ink. EGBE also had indirect food additive uses approved by the US FDA (21 CFR 175.105, 177.1650, 176.210, 178.1010).

Human exposure to residues of EGBE may occur via dietary (food and drinking water) and/or residential pathways of exposure. Dietary exposure to residues of EGBE would be via the oral route, by consumption of raw agricultural commodities to which pesticide products containing EGBE have been applied, and/or by consumption of drinking water. Based on the environmental fate properties of EGBE, it is expected to biodegrade readily and does not bio-accumulate in the environment. Exposure to EGBE in drinking water is likely to be low.

Exposure may also occur via the residential pathway of exposure (dermal and inhalation routes of exposure), through the use of residential pesticide products containing EGBE as an inert ingredient.

VII. Aggregate Exposures

For 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 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 EGBE, 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 EGBE 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 EGBE and any other substances, and this material does not appear to produce toxic metabolites produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that EGBE 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/.

IV. Human Health Risk Characterization

The principal toxicity of EGBE is anemia caused by damage to the red blood cell membrane. There is also toxicity to liver and kidney caused by accumulation of iron from the red blood cells in those organs. Liver tumors in male mice, and forestomach tumors in female mice were found not to be caused by a genotoxic mechanism.

Developmental toxicity occurred only at the same or greater dose as severe maternal toxicity. Reproductive toxicity (a slight decrease in pup body weight) occurred at a lower dose than did parental toxicity in this study, however, this dose was greater than the dose causing hematological changes in other studies. There are no concerns for potential sensitivity of infant and children because exposure is expected to be much lower than that at which the marginal sensitivity occurred in rats.

Exposure to EGBE as a result of its use as an inert ingredient in pesticidal products is possible through the dietary (food and/or drinking water) or residential (dermal and inhalation) routes of exposure. Exposure may also occur as a result of its FDA-approved use as a indirect food additive. The FDA allows for EGBE to be added to food as an adhesive or solvent.

The low toxicity of EGBE and the low potential for bio-accumulation limit the potential for risk to human health. Therefore, any risks to human health as a result of the consumption of residues of EGBE are likely to be low. Taking into consideration all available information on EGBE, it has been determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to EGBE when considering exposure through dietary exposure and all other non-occupational sources for which there is reliable information. Therefore, it is recommended that the exemption from the requirement of a tolerance established for residues of EGBE when used as an inert ingredient in pesticide products can be considered reassessed as safe under section 408(q) of the FFDCA.

V. Ecotoxicity and Ecological Risk Characterization

In a study looking at mortality of carp exposed to EGBE for 48 hours no established trend could be determined, an approximate LC50 of between 1395 and 1575 mg/L was reported. In a study looking at goldfish mortality during a 24 hour static study, the LC50 was reported to be 1700 g/L. Bluegill sunfish exposed to EGBE for 96 hours under static conditions had an LC50 of 1490 g/L. Inland silverside exposed for 96 hours under static conditions showed an LC50 of 1250 g/L. In a 24 hour study looking a behavior effects looking at mobility on *Daphnia magna,* the EC50 was determined to be 1815 mg/L (EC0 = 1283, EC100 2500). In a second 24 hour study looking at mortality under static conditions, the LC50 was reported to be 1700 g/L. In a study looking at sand shrimp over 96 hours under static conditions, the LC50 was reported to be 775 g/L. In a second study looking a brine shrimp, the LC50 was reported to be 1 g/L. Blue green algae showed population effects at 35 g/L following an 8-day exposure regimen under static conditions. In a second study looking at a different variety of blue-green algae, population effects were observed at 900 g/L. Several studies looking a flagellates and ciliates, important

prey items in aquatic environments, population effects were observed at 91 to 463 g/L. No chronic data were available in Ecotox.

REFERENCES

EPA:

Toxicological review of ethylene glycol monobutyl ether (EGBE) (CAS no. 111-76-2) in support of summary information on the Integrated Risk Information System
EPA/ORD/NCEA. Jeffrey S. Gift, Ph.D. October, 1999.
http://www.epa.gov/IRIS/toxreviews/0500-tr.pdf

An Evaluation of the Human Carcinogenic Potential of Ethylene Glycol Butyl Ether
EPA/ORD/NCEA. Jeffrey S. Gift, Ph.D. February, 2005).
http://oaspub.epa.gov/eims/eimscomm.getfile?p_download_id=441874

Ethylene glycol monobutyl ether (EGBE)(2-Butoxyethanol) (CASRN 111-76-2
IRIS. December 30, 1999.
http://www.epa.gov/iris/subst/0500.htm

EPA Office of Air:
40 CFR, vol. 69, No. 228, 11/29/04, Rules and Regulations
40 CFR, vol. 68, No. 225, 11/21/03, Proposed Rules

Department of Health and Human Services:

Toxicological Profile for 2-Butoxyethanol and 2-Butoxyethanol Acetate
Agency for Toxic Substances and Disease Registry (ATSDR), August, 1998
http://www.atsdr.cdc.gov/toxprofiles/tp118.html#bookmark03

NIOSH Criteria Documents: Criteria for a Recommended Standard: Occupational Exposure to Ethylene Glycol Monobutyl Ether and Ethylene Glycol Monobutyl Ether Acetate
DHHS (NIOSH) Publication No. 90-118. September 1990
http://www.cdc.gov/niosh/90-118.html

Toxicity studies with EGBE conducted by the National Toxicology Program
http://ntp.niehs.nih.gov/index.cfm?objectid=0710F259-0908-74C6-847A3D2AA4D90E19

World Health Organization:

Concice International Chemical Assessment Document 67. Selected alkoxyethanols. 2-Butoxyethanol. World Health Organization. Philip Copestake. 2005. http://www.who.int/ipcs/publications/cicad/cicad_67_2_butoxyethanol.pdf

PubMed and TOXNET literature searches

Developmental and Reproductive Studies:

Hardin, BD; Goad, PT; Burg, JR. (1984) Developmental toxicity of four glycol ethers applied cutaneously to rats. Environ Health Perspect 57:69-74.

Heindel, JJ; Gulati, DK; Russell, VS; et al. (1990) Assessment of ethylene glycol monobutyl and monophenyl ether reproductive toxicity using a continuous breeding protocol in Swiss CD-1 mice. Fundam Appl Toxicol 15:683-696.

Nelson, BK; Setzer, JV; Brightwell, WS; et al. (1984) Comparative inhalation teratogenicity of four glycol ether solvents and an amino derivative in rats. Environ Health Perspect 57:261-271.

Sleet, RB; Price, CJ; Marr, MC; et al. (1989) Teratologic evaluation of ethylene glycol monobutyl ether administered to Fischer 344 rats on either gestational days 9-11 or days 11-13. Final Report. Research Triangle Institute/National Toxicology Program. NTP-CTER-86-103.

Tyl, RW; Millicovsky, G; Dodd, DE; et al. (1984) Teratologic evaluation of ethylene glycol monobutyl ether in Fischer 344 rats and New Zealand white rabbits following inhalation exposure. Environ Health Perspect 57:47-68.

Wier, PJ; Lewis, SC; Traul, KA. (1987) A comparison of developmental toxicity evident at term to postnatal growth and survival using ethylene glycol monoethyl ether, ethylene glycol monobutyl ether, and ethanol. Teratog Carcinog Mutag 7:55-64.

TOXICOLOGICAL DATA:

Table 4. Summary of Acute Toxicity Data for EGBE

Parameter	Toxicity Value	Reference
Oral LD50	2500 mg/kg rat 1400 mg/kg mice 1200 mg/kg guinea pig 320 mg/kg rabbit	WHO
Dermal LD50 - rabbit	404 mg/kg	WHO
Inhalation LD50 - rat	2200 mg/m3 rat	WHO
Eye Irritation - rabbit	"severe eye irritant"	WHO
Skin Irritation - rabbit	"mild irritant"	WHO
Skin Sensitization - guinea pig	Negative	WHO

NA = Not Available.

Executive summaries for developmental studies:

In a developmental toxicity study (Wier, 1987) EGBE was administered by gavage to 6 CD-1 mice per dose group on days 8-14 of gestation at doses of 0, 350, 650, 1,000, 1,500, or 2,000 mg/kg/day. Maternal toxicity included mortality of 3/6 animals in the 1,000 mg/kg-day group and 6/6 in the 2,000 mg/kg-day group. The maternal LOAEL was 350 mg/kg/day, the lowest dose tested based on clinical signs (lethargy and abnormal breathing). The developmental NOAEL was 650 mg/kg/day and the LOAEL was 1000 mg/kg/day based on an increased number of resorptions and a reduced number of viable fetuses.

In a developmental toxicity study (Sleet, 1989) EGBE was administered by gavage to groups of 28-35 F344 rats at doses of 0, 30, 100, or 200 mg/kg-day on gestation days 9-11, or doses of 0, 30, 100, or 300 mg/kg-day on gestation days 11-13. The maternal NOAEL was 30 mg/kg/day and the LOAEL was 100 mg/kg/day based on marked reductions in body weight, increases in kidney and spleen weights, and severe hematological effects. There was reduced viability of embryos at 200 mg/kg/day but not at 300 mg/kg/day and the study authors reported that the developmental NOAEL was 100 mg/kg/day. In a developmental toxicity study (Nelson, 1984) SD rats (15/group) were exposed to 0, 150, or 200 ppm EGBE via inhalation for 7 hours/day for days 7-15 of gestation. Rats in the 200 ppm group had of hematuria on only the first day of exposure. The maternal NOAEL was 100 ppm and the LOAEL was 200 ppm for slight maternal toxicity. The developmental NOAEL was 100 ppm, the highest dose tested.

In a developmental toxicity study (Tyl et al., 1984) F344 rats (36/group) were exposed to 0, 25, 50, 100, or 200 ppm EGBE via inhalation for 6 hours/day on gestational days 6-15. The maternal NOAEL was 50 ppm and the LOAEL was 100 ppm based on reduced red blood cell count, blood or hemoglobin in the urine, decreased weight gain, and reduced food consumption. The developmental NOAEL was 50 ppm and the LOAEL was 100 ppm retarded skeletal ossification of vertebral arches or centra, sternebrae, or phalanges.

In a developmental toxicity study (Tyl et al., 1984) New Zealand white rabbits (24/group) were exposed to 0, 25, 50, 100, or 200 ppm EGBE via inhalation for 6 hours/day on gestational days 6-18. The maternal NOAEL was 100 ppm and the LOAEL was 200 ppm based on clinical signs and decreased weight gain. The developmental NOAEL was 100 ppm and the LOAEL was 200 ppm based on retarded skeletal ossification of sternebrae and rudimentary rib. There was also reduced gravid uterine weight at 200 ppm.

In a developmental toxicity study (Hardin, 1984), EGBE was administered to SD rats on gestation days 6-15 of gestation by the dermal route of exposure, four times per day at 1,800 and 5,400 mg/kg-day. In the highest dose group, 10/11 rats died between days 3 and 7 of treatment. Signs associated with treatment included red-stained urine, ataxia, inactivity, rough coats, and necrosis of the tail tip. At the lower dose, body weight was slightly reduced and there was no evidence of embryo- or fetotoxicity, nor were any gross malformations or variations noted.

Executive summary for reproduction study: In a 2-generation reproduction study (Heindel et al., 1990) EGBE was administered in drinking water to Swiss CD-1 mice for 7-days premating and 98 days after mating. There were 20 mice per sex per dose group and doses were 0, 700, 1300, or 2000 mg/kg/day. Maternal mortality occurred in the 2 higher dose groups: 6/20 mid-dose and 13/20 high-dose females died; no males were reported to have died. Other toxicity in the 1300 and 2000 mg/kg/day groups included decreased body weight gain, increased kidney and liver weights, and decreased water consumption. The 1300 and 2000 mg/kg/day groups had a decrease in the number of litters produced per pair and in the size of each litter. The 700 mg/kg/day group had a reduction (5%) of live pup weight. No adverse effect on fertility was observed in the 700 mg/kg-day dose group. A crossover mating trial suggested that fertility effects were primarily due to effects in females. There were too few mice in the two higher dose groups to assess fertility in the second generation, but there was no effect on fertility when offspring in the 700 mg/kg/day group were mated. The NCEA document reported a NOAEL of 700 mg/kg/day for maternal effects; the LOAEL was 1300 mg/kg/day based on maternal mortality, decreased weight gain, and increased kidney and liver weight. The NOAEL for reproductive effects was 700 mg/kg/day and the LOAEL was 1300 mg/kg/day based on decreased litter size and decreased number of litters. The offspring LOAEL was 700 mg/kg/day, the lowest dose tested, based on very slight decreases in pup weight.