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

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

May 18, 2005

SUBJECT: **Ethylene Oxide** HED Risk Assessment for Reregistration Eligibility Document (RED) PC Code No 042301; DP Barcode No. D316794

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Attached is Health Effects Division's (HED's) risk assessment of ethylene oxide for purposes of issuing a Reregistration Eligibility Decision (RED) Document for this active ingredient. The disciplinary science chapters and other supporting documentation are incorporated into the risk assessment or included as appendices as follows:

Hazard Identification Assessment; Santhini Ramasamy - Section 4 and Appendix 1
Residue Chemistry Assessment; Jerry Stokes (D313774, 3/31/05)
Occupational and Residential Exposure Assessment; Matthew Crowley (D316796, 5/16/05), D. Smegal, (D309124, 2/15/05)
Dietary Exposure and Risk Assessment; Becky Daiss (D313777, 3/30/05)
Incident Report; Jerry Blondell (D313773, 3/9/05)
Tier II Drinking Water Assessment; Ed Odenkirchen (D279672, 12/12/01)

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1.0 EXECUTIVE SUMMARY

Purpose and Scope

This assessment provides information to support the issuance of a risk management decision document known as a Reregistration Eligibility Decision (RED) Document for ethylene oxide. EPA's pesticide reregistration process provides for the review of older pesticides (those initially registered prior to November 1984) under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) to ensure that they meet current scientific and regulatory standards. The process considers the human health and ecological effects of pesticides and incorporates a reassessment of tolerances (pesticide residue limits in food) to ensure that they meet the safety standard established by the Food Quality Protection Act (FQPA) of 1996. This assessment is limited to ethylene oxide sterilization of herbs, spices, dried vegetables, and walnuts. OPP's Antimicrobial Division is conducting a separate but concurrent assessment of other non-food ethylene oxide sterilization uses.

Use Profile

Ethylene oxide is a fumigant/sterilant used to sterilize medical or laboratory equipment, pharmaceuticals, and aseptic packaging (21CFR §201), or to reduce microbial load on cosmetics, whole and ground spices or other seasoning materials (40 CFR §180) and artifacts, archival material or library objects. Sterilization/fumigation with ethylene oxide must be performed only in vacuum or gas tight chambers designed for use with ethylene oxide. It is applied by commercial applicators only; there are no residential uses of ethylene oxide. Tolerances for residues in/on black walnuts, copra, and spices are established under 40 CFR §180.151. Estimates of ethylene oxide usage performed by HED's Biological and Economical Analysis Division (BEAD) indicate that a maximum of approximately 8.2 million pounds of ethylene oxide are used annually in the U.S. for commercial fumigation/sterilization. Approximately 7.4 million pounds are used annually for sterilization of medical and laboratory items/equipment. Ethylene oxide treatment is the principal method used to reduce bacterial levels in spices/herbs and black walnuts. An estimated maximum of approximately 800,000 pounds are used annually for fumigation of herbs and spices according to BEAD. All other uses account for less than 1% of the total annual usage. (J. Faulkner, 2/22/01).

Regulatory History

Ethylene oxide is a FIFRA List B reregistration pesticide. A Data-Call-In (DCI) Notice for ethylene oxide was issued in 1989 requiring submission of product chemistry, residue chemistry, and toxicology studies. The Phase 4 Review of available residue chemistry data was issued in 1991. Additional DCIs were issued in 1992 to address chemistry data deficiencies outlined in the Phase 4 Reviews. All of the required residue chemistry data have been submitted and reviewed. The majority of the toxicology data requirements have been either waived or reserved pending review of the residue chemistry data on spices. The Occupational Safety and Health Administration (OSHA) regulates worker exposure to ethylene oxide. The OSHA exposure standards include a permissible exposure limit (PEL) of 1ppm and a short-term

excursion limit (STEL) of 5 ppm. EPA approved pesticide product labeling under FIFRA requires adoption of the OSHA exposure standard.

Hazard Identification

Ethylene oxide and its reaction products, ethylene chlorohydrin and ethylene glycol, have been identified as the compounds of concern for this risk assessment.

Ethylene oxide is highly reactive gas and is rapidly taken up via the lungs. It is classified as moderately toxic to less toxic in acute inhalation toxicity studies in several species (Class III or Class IV). There are no studies identified on eye and skin irritation properties. Based on the effects from subchronic and chronic studies, skin and eye irritant effects are not prominent. It is a possible dermal sensitizer. Neurological effects have been reported in several subchronic and chronic studies in animals. Ethylene oxide is mutagenic and genotoxic in almost all available studies. Strong evidence of carcinogenicity was observed in chronic inhalation carcinogenicity studies. Several epidemiological literature studies provide adequate evidence for an association between exposure to ethylene oxide and increased risk for cancers, especially of hematopoietic origin. The overall evidence indicates increased risk of cancers in humans and in animals and positive results on mutagenicity/genotoxicity tests both *in vivo* and *in vitro*. The Agency is currently determining the cancer classification for ethylene oxide.

Ethylene chlorohydrin is very toxic both by oral (Category II) and dermal (Category I and II) routes and less or more toxic by inhalation routes depending upon the species (Category II in rats and mice, Category IV in guinea pigs). It could produce marked eye and dermal irritation in rabbits. Dermal sensitization effects are not identified. The database is inadequate for assessing fetal susceptibility effects since there are no rabbit developmental or two-generation reproduction studies available. There are no oral carcinogenicity studies available in rodents. Two chronic dermal toxicity studies are identified in the literature for rats and mice. No evidence of carcinogenicity was found in either species. Limited epidemiological studies in male workers exposed to ethylene chlorohydrin provide inconsistent results on increased risk for hematopoietic or lymphopoietic or pancreatic cancers. Based on the mutagenicity and genotoxicity test results and lack of evidence of carcinogenicity in rats and mice by dermal route, the potential for carcinogenic effects in animals by oral route thought to be low. However, the chronic toxicity studies in rodents are required before a cancer classification can be concluded for ethylene chlorohydrin.

Ethylene glycol has low acute toxicity in experimental animals following oral (Category III or Category IV), and dermal (Category IV) routes and moderate toxicity by inhalation (Category II). Ethylene glycol causes minimal eye and skin irritation. No study was identified on dermal sensitization. Subchronic and chronic studies indicate the kidney as the target organ for ethylene glycol induced toxicity. Ethylene glycol exhibited no evidence of carcinogenicity based on two year bioassays using rats and mice. It is developmentally toxic, inducing primarily skeletal and external malformations at high doses in rodents. Mouse developmental and reproductive toxicity studies indicate consistent fetal susceptibility at doses lower than that produced maternal toxicity. Since the developmental effects in mice are mostly skeletal

variations, and the effects are seen at high doses (close to the limit dose), there is low degree of concern.

Based on the evidence evaluated, there is no concern for pre- and/or postnatal toxicity resulting from exposure to ethylene oxide, ethylene chlorohydrin, or ethylene glycol. Therefore the special FQPA safety factors were reduced to 1x.

Dose Response Assessment

The primary exposure scenarios for ethylene oxide are dietary and occupational exposure. There are no residential uses of ethylene oxide. However, residential exposure can occur as a result of the use of ethylene oxide as a sterilant for musical wind instruments, and from ambient releases from commercial sterilization sources. Occupational and residential exposure to ethylene oxide occurs primarily by inhalation. Therefore toxicological end points for inhalation are required and were selected for worker and residential exposure scenarios. Ethylene oxide is not considered a residue of concern for dietary exposure because data from a spice sterilization study indicate that ethylene oxide residues disappear rapidly after sterilization and are unlikely to be found in sterilized spices available for consumption. However, the ethylene oxide reaction products, ethylene chlorohydrin and ethylene glycol, are considered residues of concern for dietary exposure due to persistent high levels of these compounds found after sterilization. Therefore, toxicological endpoints were selected for the dietary exposure assessment for these reaction products.

Acute and chronic toxicological endpoints for dietary exposure to ethylene chlorohydrin were selected from a developmental toxicity study in mice and a subchronic oral toxicity in rats respectively. A chronic dietary exposure endpoint was selected for ethylene glycol from a chronic oral toxicity study in rats. No acute reference dose was derived for ethylene glycol since it is toxic only at very high doses under acute conditions. Due to lack of developmental toxicity, reproduction toxicity and chronic combined carcinogenicity study in rats and mice for ethylene chlorohydrin, 10x data base uncertainty factor (UF_{DB}) is deemed necessary when estimating dietary risk for ethylene chlorohydrin. The database is complete for ethylene glycol and no UF_{DB} is deemed necessary.

Cancer and short-, intermediate-, and long-term inhalation toxicity endpoints were selected for occupational exposure to ethylene oxide. The cancer inhalation unit risk factor (URF) was selected based on cancer potency information published by the California Office of Environmental Health Hazard Assessment. The California URF is based on mononuclear cell leukemia in female rats analyzed using a linearized multistage model. EPA's Office of Research and Development (ORD) is currently conducting an assessment of ethylene oxide carcinogenicity. The Agency's cancer assessment has not yet completed internal or external peer review. However, based on preliminary findings, the cancer URF derived by ORD will likely be higher than the California URF and consequently, will result in increased estimates of cancer risk from inhalation exposure to ethylene oxide. Short and intermediate term inhalation endpoints were selected from a subchronic inhalation study in mice. The long-term inhalation endpoint was selected from a two generation reproduction inhalation study in rats. The traditional interspecies factor of 10X is reduced to 3X since the doses are expressed as air concentrations and the pharmacokinetics is assumed similar between animals and humans. The interspecies

factor of 3x is considered sufficient to account for only pharmacodynamic differences between animals and humans. The database for ethylene oxide is considered complete and no UF_{DB} is deemed necessary.

Exposure/Risk Assessment and Risk Characterization

Risk assessments were conducted for dietary and occupational exposure pathways from use of ethylene oxide as a sterilant on spices, herbs, dried vegetables and walnuts. A drinking water exposure assessment was not conducted for this assessment because the Environment Fate and Effects Division (EFED) expects that uses of ethylene oxide for indoor food and nonfood uses will result in insignificant exposure to drinking water resources. Residential handler uses are not supported/available and are therefore not assessed. However, residential exposure can occur as a result of the use of ethylene oxide as a sterilant for musical wind instruments, and from ambient releases from commercial sterilization sources. EPA's Office of Air and Radiation (OAR) has conducted a residual risk assessment for the ethylene oxide commercial sterilization source category as part of its residual risk program. HED is using OAR's assessment to address risk for the residential ambient exposure scenario The OAR assessment is cited and summarized herein. An aggregate assessment of risk is not required because drinking water exposures are not expected and there is not a common chemical exposure for residential and dietary exposure scenarios. A cumulative risk assessment considering risks from other pesticides or chemical compounds having a common mechanism of toxicity has not been conducted for this RED because HED has not yet determined if there are any other chemical substances that have a mechanism of toxicity common with that of ethylene oxide, ethylene chlorohydrin, or ethylene glycol.

Dietary Pathway Exposure and Risk

HED conducted refined acute and chronic dietary exposure analyses using the Dietary Exposure Evaluation Model with the Food Commodity Intake Database (DEEM-FCID™) and the Lifeline model. The dietary assessment for ethylene oxide treated commodities includes only the ethylene oxide reaction products, ethylene chlorohydrin and ethylene glycol. Acute and chronic dietary exposure assessments were conducted for ethylene chlorohydrin. Since ethylene glycol is toxic only at very high doses under acute conditions, no acute dietary exposure assessment was conducted for ethylene glycol. The dietary risk assessment indicates that for all supported commodities, the acute dietary exposure estimates for ethylene chlorohydrin are above HED's level of concern. The chronic dietary exposure estimates for both ethylene chlorohydrin and ethylene glycol are below HED's level of concern.

Occupational and Residential Pathway Exposure and Risk

HED assessed occupational exposures from use of ethylene oxide as a sterilant in the spice industry only. OPP's Antimicrobial Division is conducting a separate but concurrent assessment of exposures and risks from use of ethylene oxide in hospitals, healthcare facilities, and other settings. HED's occupational exposure assessment indicates that cancer risks are of concern at the current regulatory levels established by OSHA (PEL = 1 ppm) and recommended by the National Institute of Occupational Safety and Health (NIOSH) (REL=0.1 ppm). Non-

cancer worker exposure/risk is estimated to be of concern at the OSHA PEL but not of concern at the NIOSH Recommended Exposure Limit.

AD's qualitative screening level assessment of residential exposure from use of ethylene oxide as a sterilant for musical wind instruments indicates that these exposures are not likely to result in adverse health effects. OAR's assessment of residential exposure and risk from ambient air concentrations of ethylene oxide in areas proximate to sterilization facilities indicates that no source poses a lifetime cancer risk to the general population greater than 100 in a million, while approximately half of the modeled sources pose a lifetime cancer risk greater than 1 in a million. The chronic non-cancer assessment indicated that no source emitted ethylene oxide in quantities that resulted in exposures that approached the inhalation reference concentration, indicating that chronic non-cancer effects are unlikely to occur. Results of the acute exposure assessment indicate that estimated acute exposures are not of concern.

2.0 INGREDIENT PROFILE

2.1 Summary of Registered and Proposed Uses

There are 29 active ethylene oxide registrations held by 6 companies based on OPP's most current information. The end use formulations are all gas mixtures of ethylene oxide and inert gases (e.g. carbon dioxide) in varying concentrations. There are also currently two Special Local Needs (SLN) registrations for use as a sterilant for beekeeping equipment and a number of Section 18 emergency exemptions. Table 1 provides available information on registered use sites, application rates, and frequency of application.

Table 1. Ethylene Oxide Summary of Registered Uses

Reg #	%AI	Form	Site	MaxAR/#Apps
7182-1	100	pressurized gas	medical/lab items; phamaceuticals; packaging; spices; seasonings; actifacts, archival material, library objects	NS
10330-16	10	pressurized gas	medical/lab items; phamaceuticals; packaging; spices; seasonings; actifacts, archival material, library objects	NS
10330-18	20	pressurized gas	medical/lab items; phamaceuticals; packaging; spices; seasonings; actifacts, archival material, library objects	NS
10330-21	8.5	pressurized gas	medical/lab items; phamaceuticals; packaging; spices; seasonings; actifacts, archival material, library objects	NS
36736-2	100	Liquid	technical - industrial and/or medical uses	NS
36736-3	80	pressurized gas	medical/lab items; phamaceuticals; packaging; spices; seasonings; actifacts, archival material, library objects	NS
36736-4	10	pressurized gas	medical/lab items phamaceuticals, packaging; spices; seasonings; actifacts, archival material library objects	NS
36736-5	20	pressurized gas	medical/lab items phamaceuticals packaging; spices; seasonings; actifacts, archival material, library objects	NS
36736-6	12	pressurized gas	medical/lab items; phamaceuticals; packaging; spices; seasonings; actifacts, archival material, library objects	NS
36736-7	8.5	pressurized gas	medical/lab items; phamaceuticals; packaging; spices; seasonings; actifacts, archival material, library objects	NS
36736-8	100	pressurized gas	technical - medical/lab items; phamaceuticals; packaging; spices; seasonings; actifacts, archival material, library objects	NS

Table 1. Ethylene Oxide Summary of Registered Uses				
Reg #	**%AI**	**Form**	**Site**	**MaxAR/#Apps**
58779-5	100	pressurized gas	Technical - medical/lab items; phamaceuticals;	NS
67470-1	20	pressurized gas	medical/lab items; phamaceuticals; packaging; spices; cosmetics	NS
67470-2	80	pressurized gas	medical/lab items; phamaceuticals; packaging; cosmetics	NS
67470-3	12	pressurized gas	medical/lab items; phamaceuticals; packaging; spices; cosmetics	NS
67470-4	8.5	pressurized gas	medical/lab items; phamaceuticals; packaging; spices; cosmetics	NS
67470-5	30	pressurized gas	medical/lab items; phamaceuticals; packaging; cosmetics	NS
67470-6	100	pressurized gas	technical - medical/lab items; phamaceuticals; packaging; spices; cosmetics	NS
67470-7	100	pressurized gas	technical - medical/lab items; phamaceuticals; packaging; spices; cosmetics	NS
67470-8	8.6	pressurized gas	medical/lab items; phamaceuticals; packaging; cosmetics	NS
67470-9	10	pressurized gas	medical/lab items; phamaceuticals; packaging; cosmetics	NS
69340-1	84	pressurized gas	hospital, medical, veterinary	NS
69340-2	97	pressurized gas	hospital, medical, veterinary	NS
69340-4	96	pressurized gas	hospital, medical, veterinary	NS
69340-5	90	pressurized gas	hospital, medical, veterinary	NS
69340-6	96	pressurized gas	hospital, medical, veterinary	NS
70009-1	100	Liquid	technical medical/lab items; phamaceuticals; packaging, spices; seasonings; actifacts, archival material, library objects	NS
ME910005	10	pressurized gas	bee keeping equipment	NS
NC950002	8.5	pressurized gas	bee keeping equipment	NS

* Special Local Needs Registration; NS = not specified

2.2 Structure, Nomenclature and Physical/Chemical Properties

The nomenclature and physicochemical properties of ethylene oxide and its major metabolites are provided in Table 2.

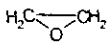
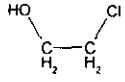
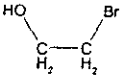
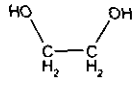
Table 2. Nomenclature and Physical/Chemical Properties for Ethylene Oxide and Reaction Products				
Common name	Ethylene Oxide	Ethylenechlorohydrin	Ethylenebromohydrin	Ethylene Glycol
Chemical structure				
Molecular Formula	C_2H_4O	C_2H_5ClO	C_2H_5BrO	$C_2H_6O_2$
Molecular Weight	44.053 g/mol	80.514	124.965	62.068
IUPAC name	Oxirane	2-chloroethanol	2-bromoethanol	
CAS name	Oxirane	2-chloroethanol	2-bromoethanol	Ethylene glycol
CAS #	75-21-8	107-07-3	540-51-2	107-21-1
PC Code	042301	NA	NA	NA

Table 2. Nomenclature and Physical/Chemical Properties for Ethylene Oxide and Reaction Products				
Melting point/range C	-111.6	-89	-80	-13
Boiling point C	10.4	130	150	195
Density or specific gravity	1.80 g/L at 25 C	1.2015-1.2025	1.494 20C	1.1155
Water solubility (20°C)	miscible in water	miscible. ≥10 g/100 mL	Miscible 1-5 g/100mL	miscible. ≥10 g/100 mL at 17.5C
Solvent solubility	217 mg/g in dioctyl phthalate at 40 C soluble in ethanol & ether	NA	NA	NA
Vapor pressure at 20°C	1095 torr; 1.4 bar	5mm	2.06 mmHg 25C	0.06
Dissociation constant)	NA	NA	NA	NA
Octanol/water partition coefficient (K_{ow}) 25C	-0.26-0.30	Log P_{ow} –0.06	0.23	NA
UV/vis absorption spectrum	NA	NA	NA	NA

NA = not available

3.0 METABOLISM ASSESSMENT

3.1 Comparative Metabolic Profile

Absorption of ethylene oxide via inhalation is limited by the air concentrations and the ventilation rate. Once absorbed, ethylene oxide is distributed to body tissues and metabolized to ethylene glycol and its glutathione conjugates. Labeled ethylene oxide is primarily excreted in urine and a half-life of approximately 10 min was estimated for the first-order clearance of ethylene oxide in rodents.

Limited evidence suggests that ethylene chlorohydrin is rapidly absorbed in rats and a majority of the administered radioactivity (77-80%) was eliminated in urine within 24 hours of ingestion. About 90% of the radioactivity in the urine was in the form of thiodiacetic acid and thionyldiacetic acid. Less than 5% of the administered radioactivity in total is excreted in feces and in expired air. Peak levels of radioactivity were found in blood 1 hour after administration and the radioactivity was reduced to 50% after approximately 4 hours.

Ethylene glycol is shown to be readily absorbed from the gastrointestinal tract. Once absorbed, it is also rapidly cleared with half-lives ranging 1-4 h in rodents, monkeys and dogs. The reported half-lives in humans range from 2.5h (in children) to 8.4 h (in adults) following acute ingestion. Ethylene glycol is oxidized by alcohol dehydrogenase in animals as well as in humans in successive steps to glycoaldehyde, then to glycolic acid glyoxylic acid and oxalic acid (refer to diagrams Appendix 3.0).

Ethylene oxide residues disappear rapidly after sterilization and are unlikely to be found in spices available for consumption. Ethylene chlorohydrin and ethylene bromohydrin have been shown to result from fumigation of foods with ethylene oxide due to interaction with natural chlorides and bromides present in the crop. At high sterilization concentrations, ethylene oxide reacts with moisture to form ethylene glycol and, in the presence of sugars, glycol derivatives. Spice sterilization study data indicate persistent high levels of the reaction products ethylene chlorohydrin and ethylene glycol in treated spices and herbs and walnuts. Ethylene bromohydrin residues are also found in treated commodities but are minimal relative to ethylene chlorohydrin.

3.2 Nature of the Residue in Foods

3.2.1 Plants

The qualitative nature of ethylene oxide residues in plants is adequately understood. The HED risk assessment team has determined that the residues of potential concern in plants are ethylene chlorohydrin and ethylene glycol because of the high levels of these reaction products present in treated spices and herbs and walnuts. Ethylene oxide is not considered a residue of concern for dietary exposure because data from an ethylene oxide spice sterilization study indicate that it disappears rapidly after sterilization.

Information on the nature of the residue is based primarily on a "Persistence Study of Residues of Ethylene Oxide and Reaction Products in Spices and Black Walnuts", conducted by McCormick Technical Resource Center (1994). The purpose of the study was to quantify the amount and persistence of ethylene oxide and its reaction products ethylene chlorohydrin, ethylene bromohydrin, and ethylene glycol in whole and ground spices and black walnuts treated post harvest with ethylene oxide. C^{14} uniformly labeled in the ethylene carbon atoms of ethylene oxide was used in the residue identification study. A total of 29 whole and ground spices were evaluated to represent spices in the three major categories of leaves, seeds and classical spices. Commodities were treated in commercial chambers and stored under conditions representative of actual handling practices in the spice and black walnut industries.

Levels of ethylene oxide, ethylene chloro- and bromohydrin and ethylene glycol in general are significantly higher in ground versus whole herbs and spices. Ethylene oxide residues in treated spices and black walnuts were found to disappear rapidly after treatment and during storage. Total radioactive residue (TRR) 36 - 2400 ppm at day 0 dissipated to < 0.5-37 ppm by two weeks and to <0.5-1 ppm by two months post-treatment for all treated commodities. There was no consistent TRR decline trend for ethylene chlorohydrin. Initial TRRs in herbs and spices were generally higher (100-4700 ppm) than those for ethylene oxide and levels tended to stabilize after two weeks to two months (250-4550 ppm at two weeks and 215-4650 ppm at two months). Most of the treated spices and nuts contain about 100 ppm or less of ethylene bromohydrin throughout the analysis period. There was also no consistent decline trend for TRR of ethylene glycol. Levels of ethylene glycol in various treated spices appeared to stabilize within the 2 week to 2 month period (100-3700 ppm at two weeks and 100-5100 at two weeks). (J. Stokes, D 313774, 3/31/05)

3.2.2 Livestock

Based on the post harvest use of ethylene oxide on spices and black walnuts, there are no expected residues in livestock commodities.

3.3 Environmental Fate

The Environment Fate and Effects Division expects that uses of ethylene oxide for indoor food and nonfood uses will result in insignificant exposure to drinking water resources. EFED has neither required nor received environmental fate and ecological effects data for ethylene

oxide. In the November 1, 1990 Phase IV package review for ethylene oxide EFED indicated that no environmental fate data were required because the chemical's uses are limited to indoor environments. Although EFED has not received submission of nor performed formal review of environmental fate and effects data for ethylene oxide, there are publically available sources of such information. EFED has not conducted a formal review of such sources, but presents the following for informational purposes only. Conway et al. (1983) maintain that ethylene oxide is not persistent in the environment because it is reactive and degrades by biotic and abiotic processes. Biochemical oxidation, reactivity, and volatilization are likely to limit ethylene oxide concentrations in soil and water. Ethylene oxide is quickly biodegraded under aerobic conditions (Berglund 1988, Rajagopalan et al. 1998). The ethylene oxide Henry's Law Constant is 1.4×10^{-4} atm-m^3/mole, suggesting a tendency for volatile loss from water or soil (Conway et al. 1983). Hydrolysis of ethylene oxide to glycols at ambient temperatures requires weeks for completion with a half-life of 14 days (Conway et al. 1983). (E. Odenkirchen, D279672, 12/12/01)

3.4 Reaction Products

A summary of ethylene oxide and its reaction products is provided in Table 3.

Table 3.Ethylene Oxide, Ethylene Chlorohydrin, Ethylene Bromohydrin, and Ethylene Glycol Residues in Spices/Herbs/Walnuts

Commodity	ETO Residues, ppm (mean)		ECH Residues, ppm, (mean)		EBH Residues, ppm, (mean)		ETG Residues, ppm (mean)	
	0 day	2 mo	0 day	2-6 mo	0 day	2-6 mo	0 day	2-6 mo
SPICES HERBS								
Classical								
black pepper (w)	318	<0.5	150	126	<100	<100	<100	<100
black pepper (w)*	116	<0.5	425	206	<100	<100	253	143
black pepper (g)	569	0.9	1216	1096	<100	<100	562	759
black pepper (g)*	889	1	1793	1573	<100	<100	771	1121
capsicum (w)	731	<0.5	1416	412	<100	<100	961	943
capsicum (w)*	785	<0.5	1805	850	<100	<100	1551	2240
capsicum (g)	710	<0.5	1294	1055	112	<100	1374	1004
capsicum (g)*	1434	<0.5	1595	2079	112	<100	1033	1582
cassia (w)	747	<0.5	124	166	<100	<100	513	656
cassia (g)	1482	<0.5	208	216	<100	<100	966	674
ginger (w)	458	<0.5	259	430	<100	<100	312	121
ginger (g)	877	<0.5	1161	1165	<100	<100	1344	1965
turmeric (w)	95	<0.5	126	101	<100	<100	<100	<100
turmeric (g)	357	<0.5	1595	1688	<100	<100	810	773
Leafy								
Basil (w)	393	1	5869	1459	05	103	1275	1494
Basil (w)*	411	1	6250	2318	210	<100	1690	1994
Basil (g)	59	<0.5	4707	560	370	<100	973	1246
Basil (g)*	36	2	6275	809	244	<100	1282	1335
oregano (w)	252	<0.5	1005	285	<100	<100	2349	1155
oregano (g)	783	<0.5	600	193	<100	<100	892	958
Sage (w)	1063	<0.5	478	483	<100	<100	511	588
Sage (g)	1313	<0.5	890	745	<100	<100	1030	5104
Seeds								
caraway (w)	439	<0.5	104	<100	<100	<100	247	220
caraway (g)	2042	<0.5	355	442	<100	<100	851	1359

Table 3.Ethylene Oxide, Ethylene Chlorohydrin, Ethylene Bromohydrin, and Ethylene Glycol Residues in Spices/Herbs/Walnuts								
Commodity	ETO Residues, ppm (mean)		ECH Residues, ppm, (mean)		EBH Residues, ppm, (mean)		ETG Residues, ppm, (mean)	
	0 day	2 mo	0 day	2-6 mo	0 day	2-6 mo	0 day	2-6 mo
celery (w)	253	<0.5	856	506	<100	<100	262	241
celery (w)*	298	<0.5	1174	664	<100	<100	496	365
celery (g)	438	<1.0	1618	815	<100	<100	570	723
celery (g)*	720	<1.0	2400	712	125	<100	992	920
coriander (w)	399	1	618	870	<100	<100	230	353
coriander (g)	2399	<0.5	1164	2257	<100	<100	695	1079
cumin (w)	273	1	716	409	<100	<100	188	546
cumin (w)*	277	<0.5	1696	354	<100	<100	940	530
cumin (g)	981	<0.5	893	787	<100	<100	511	730
cumin (g)*	1000	<0.5	1850	1105	<100	<100	1197	1171
fennel (w)	68	<0.5	1409	134	<100	<100	696	419
fennel (g)	1046	<0.5	2197	1478	<100	<100	1036	917
nutmeg (w)	658	<0.5	241	186	<100	153	564	676
nutmeg (w)*	862	<0.5	355	200	<100	138	118	994
nutmeg (g)	1948	<0.5	257	344	<100	175	1281	1809
nutmeg (g)*	741	<0.5	253	366	<100	140	2323	2544
sesame (w)	221	<0.5	<100	<100	<100	<100	1320	116
Black Walnuts								
Ice cream pieces	517	<0.5	<100	<100	<100	<100	<100	107
Large fancy	318	<0.5	<100	<100	<100	<100	<100	100
Medium fancy	457	<0.5	<100	<100	<100	<100	100	<100

* two treatments

3.5 Summary of Residues for Tolerance Expression and Risk Assessment

A summary of parent and reaction products included in the risk assessment and tolerance expression is provided in Table 4. A tabular summary of ethylene oxide tolerance reassessments is provided in Table 5.

Table 4. Compounds to be included in the Risk Assessment and Tolerance Expression			
		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plant	Primary Crop	ethylene chlorohydrin, ethylene glycol	ethylene oxide ethylene chlorohydrin
	Rotational Crop	Not Applicable	Not Applicable
Livestock	Ruminant	Not Applicable	Not Applicable
	Poultry	Not Applicable	Not Applicable
Drinking Water		Not Applicable	Not Applicable

Table 5 - Tolerance Reassessment for Ethylene Oxide				
Tolerances Established Under 40 CFR §180.114				
	Ethylene Oxide		Ethylene Chlorohydrin	
Commodity	Current Tolerance (ppm)	Reassessed Tolerance (ppm)	Current Tolerance (ppm)	Reassessed Tolerance (ppm)
basil	--	50	--	5000
spices/herbs (except basil)	50	50	--	2000

Table 5 - Tolerance Reassessment for Ethylene Oxide				
Tolerances Established Under 40 CFR §180.114				
	Ethylene Oxide		Ethylene Chlorohydrin	
Commodity	Current Tolerance (ppm)	Reassessed Tolerance (ppm)	Current Tolerance (ppm)	Reassessed Tolerance (ppm)
dried bulb vegetables	--	50	--	5000
Black walnut	50	50	--	50

4.0 HAZARD CHARACTERIZATION/ASSESSMENT

4.1 Hazard Characterization

Ethylene oxide and its reaction products, ethylene chlorohydrin and ethylene glycol, have been identified as the compounds of concern for this risk assessment.

The toxicology database for ethylene oxide is adequate. The toxicology database for ethylene glycol is considered sufficient. The toxicology database for ethylene chlorohydrin is incomplete; no guideline studies are available and there are very limited studies (acute toxicity studies, subchronic toxicity studies in rats, dogs, and monkeys, developmental toxicity studies in mice and chronic dermal carcinogenicity study in rats and mice) identified in literature.

Based on the available data, no special FQPA Safety Factor is required (i.e.,1X) for the three chemicals since there are no residual uncertainties for pre-and/or post-natal toxicity. However, a database uncertainty factor of 10X is applied for ethylene chlorohydrin since the toxicology database is incomplete for this reaction product.

4.1.1 Ethylene oxide

Ethylene oxide is a colorless, highly reactive gas and is rapidly taken up via the lungs. The absorption from inhalation is limited by the air concentration of ethylene oxide and the ventilation rate. Once absorbed, ethylene oxide is distributed to body tissues and metabolized to ethylene glycol and to glutathione conjugates. Labeled ethylene oxide is primarily excreted in urine and a half-life of approximately 10 min was estimated for the first-order clearance of ethylene oxide in rodents. It is classified as moderately toxic to less toxic in acute inhalation toxicity studies in several species (Class III or Class IV). There are no studies identified on eye and skin irritation properties. Based on the effects from subchronic and chronic studies, skin and eye irritant effects are not prominent. Dermal sensitization is possible in guinea pigs.

FOB (Functional Observational Battery) alterations such as drooping eyelids, low arousal and no response to touch, ataxia, decreased hind-limb grip strength, landing foot splay and decreased motor activity have been identified in neurotoxicity studies using rodents. Demyelination of sciatic nerve has been reported in monkeys (n=2) treated with ethylene oxide for two years. Peripheral neuropathy, impaired hand-eye coordination and memory loss have been reported in workers exposed to ethylene oxide for longer periods.

Ethylene oxide is an electrophilic agent and alkylates nucleophilic groups in macromolecules such as hemoglobin and DNA. The protein adducts such as hydroxyethyl valine and DNA adducts such as hydroxyl ethyl guanine adducts are identified and are used as biomarkers of exposure to ethylene oxide in humans.

In the available subchronic and chronic studies only limited findings are reported on hematological, clinical chemistry and organ weight changes. There is qualtitative (but not quantitative) susceptibility following in utero exposures in rats or after post-natal exposure in the two-generation reproduction study in rats. There are no residual uncertainties for pre and/or post-natal toxicity. Based on the available data, there is no need for a Special FQPA Safety Factor (i.e., 1X) for pre and/or post-natal toxicity.

Ethylene oxide is mutagenic and genotoxic in almost all available studies. Gene mutations, DNA damage, and cytogenetic effects have been observed routinely in bacterial, rodent and human cells exposed *in vitro* to ethylene oxide. Gene mutations and chromosomal aberrations are also evident in somatic cells of rodents exposed to ethylene oxide *in vivo*. In rodents and not in humans, ethylene oxide has been shown to produce dominant lethal mutations and heritable translocations in germinal cells.

Positive evidence of carcinogenicity was observed in chronic inhalation carcinogenicity studies. In Fischer 344 rats, there was a dose-related increase in the incidences of mononuclear cell leukemia, peritoneal mesotheliomas and brain tumors. In mice, the incidences of lung carcinomas, malignant lymphomas, uterine adenocarcinomas, mammary adenocarcinomas and adenosquamous carcinomas and Harderian cystadenomas were increased compared to controls.

Several epidemiological studies available in the literature provide adequate evidence for an association between exposure to ethylene oxide and increased risk for cancers, especially of hematopoietic origin. The reports by NIOSH on a large cohort follow-up of men and women from sterilization plants and spice treatment facilities (n=18235) indicate a positive trend for increased risk from hematopoietic cancers in males and breast cancer in females when cumulative exposures with 15 or 20 year lag period were considered.

The overall evidence indicates increased risk of cancers in humans and in animals along with positive findings on mutagenicity genotoxicity tests both *in vivo* and *in vitro*. Agency is currently determining the classification of carcinogenicity for ethylene oxide.

4.1.2 Ethylene Chlorohydrin

The acute toxicity studies indicate ethylene chlorohydrin is very toxic both by oral (Category II) and dermal (Category I and II) routes and less or more toxic by inhalation routes depending upon the species (Category II in rats and mice and Category IV in guinea pigs). Evidence suggests that ethylene chlorohydrin could produce marked eye and dermal irritation in rabbits. Dermal sensitization effects are not identified for ethylene chlorohydrin.

There are no rabbit developmental or two-generation reproduction studies available for ethylene chlorohydrin. Based on the mice developmental study, a qualitative susceptibility was

evident due to increased incidence of 14th rib at dose level that produced significant maternal toxicity (there was 61% decrease in maternal body weight at the 100 mg/kg/day that induced the 14th rib). The incidence of 14th rib is not considered as a major malformation. For ethylene chlorohydrin a 10X database uncertainty factor is applied due to the incomplete toxicity database.

Limited evidence suggests that ethylene chlorohydrin is rapidly absorbed in rats and majority of the administered radioactivity (77-80%) was eliminated in urine within 24 hours of ingestion. About 90% of the radioactivity in the urine was in the form of thiodiacetic acid and thionyldiacetic acid. Less than 5% of the administered radioactivity in total is excreted in feces and in expired air. Peak levels of radioactivity were found in blood 1 hour after administration and the radioactivity was reduced to 50% after approximately 4 hours (Grunow and Altmann, 1982, as cited in NTP, 1985).

Several studies indicate that ethylene chlorohydrin is a weak base pair substitution mutagen in bacteria and the mutagenicity in bacteria is enhanced in the presence of rat liver S9 extract Ethylene chlorohydrin tested negative in the mutagenicity tests using mammalian cell cultures (*in vitro*) or rodents (*in vivo*). However, in one test, ethylene chlorohydrin induces DNA repair in human fibroblasts *in vitro*. Ethylene chlorohydrin tested negative for dominant-lethal mutations or heritable translocations in mouse.

There are no chronic combined carcinogenicity studies available in rodents via the oral route of exposure. Two chronic studies are identified in the literature for rats and mice receiving ethylene chlorohydrin via the dermal route. No evidence of carcinogenicity was found in both species. Limited epidemiological studies in male workers exposed to ethylene chlorohydrin provided inconsistent results on increased risk for hematopoietic or lymphopoietic or pancreatic cancers.

Based on the mutagenicity and genotoxicity test results and lack of evidence of carcinogenicity in rats and mice by dermal route, the potential for carcinogenic effects in animals by the oral route is low. However, the chronic toxicity studies in rodents are required before a cancer classification can be concluded for ethylene chlorohydrin.

4.1.3 Ethylene Glycol

Ethylene glycol has low acute toxicity in experimental animals following oral (Category III or Category IV), and dermal (Category IV) routes and moderate toxicity by inhalation (Category II). Ethylene glycol causes minimal eye and skin irritation. No study was identified on dermal sensitization.

The toxicity of ethylene glycol is believed to be mediated through metabolites, glycolate and oxalate. In several acute poisoning conditions, the toxic effects of ethylene glycol are controlled by the administration of alcohol dehydrogenase inhibitors.

Subchronic and chronic studies indicate kidney as the target organ for ethylene glycol induced toxicity. Ethylene glycol exhibited no evidence of carcinogenicity based on two year bioassays using rats and mice.

Ethylene glycol has been shown to cause developmental toxicity, inducing primarily skeletal and external malformations at high doses in rodents. Mouse developmental and reproductive toxicity studies indicate consistent fetal susceptibility effects at doses lower than that produced maternal toxicity. Since the developmental effects in mice are mostly skeletal variations, and the effects are seen at high doses (close to the limit dose), there is low degree of concern. Further, the doses selected for dietary risk assessment are based on renal effects which occur at substantially lower doses than do the developmental effects. Therefore, there are no residual uncertainties for pre- and postnatal toxicity following exposures to ethylene glycol.

Ethylene glycol is shown to be readily absorbed from the gastrointestinal tract. Once absorbed, ethylene glycol is also rapidly cleared with the half-lives ranging 1-4 h in rodents, monkeys and dogs. In humans the reported half-lives range from 2.5h (in children) to 8.4 h (in adults) following acute ingestion. Ethylene glycol is oxidized by alcohol dehydrogenase in animals as well as in humans in successive steps to glycoaldehyde, then to glycolic acid, glyoxylic acid and oxalic acid (IPCS, 2002) (refer to the diagram in Appendix 3.0).

Mutagenicity tests in bacteria and mammalian cells are consistently negative. The chromosomal aberrations tests in Chinese hamster ovary cells and DNA damage in rat hepatocytes are negative. The *in vivo* genotoxicity tests are also negative for dominant lethal mutations in rats and chromosomal aberrations of bone marrow cells in mice exposed to ethylene glycol.

Consistent with mutagenicity and genotoxicity test results, the results from chronic carcinogenicity studies on ethylene glycol indicate no tumor concerns in rodents. Ethylene glycol is not likely to be carcinogenic to humans.

Tables 6 - 8 provide the toxicity profile for ethylene oxide, ethylene chlorohydrin, and ethylene glycol.

Table 6a. Ethylene Oxide – Acute Toxicity

Study/ Species	MRID or Publication	Results	Classification
870.1100 Acute Oral			
Rats	IPCS, 2003	LD_{50} = 330 mg/kg (m)	Category II
Mice	IPCS, 2003	LD_{50} = 365 mg/kg (m) LD_{50} = 280 mg/kg (f)	Category II
Guinea pigs	IPCS, 2003	LD_{50} = 270 mg/kg (m&f)	Category II
870.1200 Acute Dermal, Rabbits	No Study Identified	N/A	N/A
870.1300 Acute Inhalation, Rats	42046601	4h-LC_{50} = 1741 ppm (3.1 mg/L) (m&f)	Category IV
Acute Inhalation, Rats	42429201	1h-LC_{50} =5029 ppm (9.2 mg/L) (m&f)	Category IV
Acute Inhalation, Mice	IPCS, 2003	4h-LC_{50} = 820 ppm (1.5 mg/L)	Category III
Acute Inhalation, Dogs	IPCS, 2003	4h-LC_{50} = 954 ppm (1.8 mg/L)	Category III
870.2400 Primary Eye Irritation, Rabbits	No Study identified		

Table 6a. Ethylene Oxide – Acute Toxicity			
Study/ Species	**MRID or Publication**	**Results**	**Classification**
870.2500 Primary Skin Irritation, Rabbits	No Study Identified		
870.2600 Dermal Sensitization, Guinea Pig	40087801	Sensitization possible	
870.6200 Acute Neurotoxicity	44256402	Doses: 0, 100, 300, 500 ppm **NOAEL:100 ppm** **LOAEL: 300 ppm** Drooping eyelids/half-closed eyes, low arousal, no response to approach	**Acceptable/Guideline**

Table 6b: Ethylene Oxide – Subchronic, Chronic Toxicity Studies			
Study/Species	**MRID or Publication**	**Doses**	**Results/Classification**
Developmental/Reproduction Toxicity			
Developmental Toxicity Rats	42797702	Doses (inhalation): 0, 50, 125, 225 ppm (6h/day, GD 6-15)	**Maternal NOAEL: 50 ppm** **Maternal LOAEL: 125 ppm** Decreased body weight gain on GDs 6-15 and GDs 0-21 **Developmental NOAEL: 50 ppm** **Developmental LOAEL: 125 ppm** Decreased fetal weight, increased litter incidence of delayed ossification in phalanges, metatarsals, metacarpals and sternebrae #4-6 **Acceptable/Guideline**
Developmental Toxicity, Rabbits	41874102	Doses (inhalation) : 0, 150 ppm GD7-19, GD1-19 7h/day	**Maternal and Developmental NOAEL: 150 ppm** **Maternal and Developmental LOAEL: Not Established** **Unacceptable/Guideline** No dose response effects were determined
Two-Generation Reproduction Study, Rats	42788101	Doses (inhalation): 0, 10, 33, 100 ppm 6h/day, 5d/week	**Parental NOAEL: 10 ppm** **Parental LOAEL: 33 ppm** Decreased body weight and/or weight gain in F0 and F1 males during premating **Reproductive NOAEL: 10 ppm** **Reproductive LOAEL: 33 ppm** Increased post implantation loss in F0 generation **Offspring NOAEL: 10 ppm** **Offspring LOAEL: 33 ppm** Decreased mean body weight and weight gain of F1pups on PND 7 and PND 21 **Acceptable/Guideline**
Subchronic Toxicity			
Subchronic Neurotoxicity, Rats, 13 weeks	44359401	Doses (inhalation): 0, 25, 50, 100, 200 ppm	**NOAEL: 100 ppm** **LOAEL: 200 ppm** Decreased body weight gain in both sexes and decreased hindlimb grip strength in females Note: Cancer incidence in all treated groups during 13 weeks recovery period. Malignant glioma in cerebral cortex at 200 ppm (1 male), mononuclear cell leukemia (1 male at 100 ppm), hemangiosarcoma of skin (1 male at 25 ppm) and basal cell carcinoma of the skin (1 female at 50 ppm; 1 female at 200 ppm) **Acceptable/Guideline**
Subchronic Neurotoxicity, Rats, 4 weeks	44256401	Doses (inhalation): 0, 100, 300, 400, 500 ppm	**NOAEL: 100 ppm** **LOAEL: 300 ppm** Decreased body weight, body weight gain, hindlimb grip strength **Range Finding Study**
Subchronic (14 weeks)	NTP (1987)	Doses	**NOAEL: 50 ppm**

Table 6b: Ethylene Oxide – Subchronic, Chronic Toxicity Studies*			
Study/Species	**MRID or Publication**	**Doses**	**Results/Classification**
B6C3F1 Mice		(inhalation): 0, 50, 100, 200, 400, 800 ppm	**LOAEL: 100 ppm** Renal tubular degeneration **Acceptable/Non-Guideline**
Subchronic (10 weeks) B6C3F1 Mice	Snellings et al., 1984	Doses (inhalation): 0, 10, 50, 100, 250 ppm	**NOAEL 10 ppm** **LOAEL 50 ppm** Neurological effects such as altered gait, decreased locomotor activity in females and organ weight changes. **Acceptable/Non-Guideline**
Subchronic (10 weeks) B6C3F1 Mice	Snellings et al., 1984a	Doses (inhalation): 0, 10, 50, 100, 250 ppm	**NOAEL: 10 ppm** **LOAEL: 50 ppm** Neurological effects such as altered gait, decreased locomotor activity in females and organ weight changes. **Acceptable/Non-Guideline**
Chronic Toxicity			
870.4100 Chronic Toxicity Monkeys 2 years	MRID 42159401, Seizer et al., 1996 and IPCS, 2003	Doses (inhalation): 0, 50, 100 ppm 6-7h/day, 5d/wk, 24 months, 12 males/ treatment	**NOAEL: Not Established** **LOAEL: 50 ppm** Eye lesions, demyelination of the sciatic nerve, axonal dystrophy in the nucleus gracilis, decreased sperm counts and motility abnormalities; Decreased mean conduction velocity at 100 ppm Deficiencies: Age of animals unknown; inadequate dose groups, Incomplete study details with regard to study examination, individual gross or histological data, inadequate hematological and clinical parameters etc..); small number of animals tested (only 2 animals were sacrificed after 2 years of exposure). **Acceptable/Non-Guideline Study**
Combined Chronic Carcinogenicity			
Chronic Carcinogenicity Study, Rats 2 years	Snellings et al. (1984b) Garman et al. (1985), Garman and Snellings, (1986)	Doses (inhalation): 0, 10, 33, 100 ppm (7h/day, 5d/week)	**Systemic NOAEL: 10 ppm** **Systemic LOAEL: 33 ppm** Decreased survival and body weight Type of cancer incidence-0, 10, 33, 100 ppm: mononuclear cell leukemia-13/97, 9/51, 12/39, 9/30 (m), 11/116, 11/54, 14/48, 15/26 (f); peritoneal mesothelioma-2/97, 2/51, 4/39, 4/30 (m), brain tumors which include glioma, malignant reticuloses and granular cell tumors-1/181, 1/92, 5/85, 7/87 (m) 1/185, 1/94, 3/92, 4/80 (f) **Acceptable/Non-Guideline Study**
Chronic Carcinogenicity Study, Male Rats	Lynch et al (1984)	Doses (inhalation): 0, 50, 100 ppm (males only) (7h/day, 5d/week)	**Systemic NOAEL: Not Established** **Systemic LOAEL: 50 ppm** Decreased body weight gain, organ weights and non-neoplastic lesions in adrenal cortex, spleen and respiratory tract) Type of cancer incidence-0, 50, 100 ppm: mononuclear cell leukemia-24/77, 38/79, 30/76; peritoneal mesothelioma- 3/78, 9/79, 21/79; mixed cell brain glioma-0/76, 2/77, 5/79 Note: No interim clinical and hematological parameters measurements; inadequate clinical parameter measurements at the termination (NIOSH study) **Acceptable/Non-Guideline Study**
870.4300 Combined Chronic Toxicity/Carcinogenicity Mice	NTP (1987)	Doses (inhalation): 0, 50, 100 ppm (6h/day, 5d/week)	**Systemic NOAEL: 100 ppm** **Systemic LOAEL: Not Established** (Type of cancer incidence, control, 50, 100 ppm): alveolar/bronchiolar carcinoma-6/50, 10/50, 16/50 (m), 0/49, 1/48, 7/49 (f); harderian gland papillary cystadenoma-1/43, 9/44, 8/42 (m), 1/46, 6/46, 8/47 (f); malignant lymphoma of hematopoietic system-9/49, 6/48, 22/49 (f); uterine adenocarcinoma-0/49, 1/47, 5/49 (f), mammary gland adenocarcinoma or adenosquamous carcinoma-1/49, 8/48, 6/49 (f) **Acceptable/Non-Guideline**
Subchronic Dermal Toxicity			
21-Day Dermal Toxicity (Rats)	No Study identified	-	-
Dermal Absorption	No Study	-	-

Table 6b: Ethylene Oxide – Subchronic, Chronic Toxicity Studies*			
Study/Species	**MRID or Publication**	**Doses**	**Results/Classification**
	identified		
Metabolism			
Rat Metabolism	IPCS, 2003	-	Absorption: Very soluble in blood; rapid absorption in several species; limited by the concentration in air and ventilation rate Distribution: In mice greater amount of inhaled ethylene oxide is found distributed in liver, kidneys and lungs with small amounts in spleen, testes and brain. In rats, greater amount of inhaled ethylene oxide is found in urinary bladder, liver, packed blood cells, adrenal glands and lower levels in fat Metabolism: Two pathways are identified. 1) Ethylene oxide is found hydrolyzed to ethylene glycol and subsequently to oxalic acid, formic acid and carbon dioxide. This is predominant in larger species such as rabbits and dogs 2) Conjugation with glutathione. This step is predominant in rats and mice. Excretion: In rats and mice 40-80% of the inhaled dose is eliminated in urine within 48 hours Large amount of the administered ethylene oxide is eliminated in the urine as glutathione conjugates; Small amounts (10%) is eliminated as carbon dioxide and negligible amounts (1%) is eliminated via lungs as the parent compound
Mutation/Genotoxicity			
	IPCS 2003	-	Positive evidence for mutation in bacteria, eukaryotic somatic and germ cells; Increased chromosomal aberrations, sister chromatid exchange and unscheduled DNA synthesis in mammalian cells,, Induction of dominant lethal mutations and heritable translocations in mice. In humans, increased chromosomal aberrations in peripheral blood leukocytes of workers exposed to ethylene oxide.
Human Studies			
	Steenland et al. 2003	-	Breast cancer incidence studied in a cohort of 7576 women. Breast cancer reported in 319 subjects. The standardized incidence ratio (SIR) for incident breast cancer in the whole cohort was below the US population. Trend analysis in SIRs using Poisson regression was positive with increasing exposure (p=0.002) The odds ratios with 15 year lag for cumulative exposure categories, 0 (lagged out), <647, 647-2026, 2026-4919, 4919-14620, >14620 ppm-days were 1.00, 1.06, 0.99, 1.24, 1.42, and 1.87, respectively.
	Steenland et al. 2004	-	In the mortality analysis of a 1998 follow-up study of a large cohort of 18235 men and women, 2852 deaths present. The mortality analysis of the overall cohort indicates no excess risk for hematopoietic cancers combined or of non-Hodgkin's lymphoma. However, internal exposure response analyses conducted using a 15 year lag found positive trends for hematopoietic cancers in males (p=0.02). The odds ratios with 15 year lag for hematopoietic cancer mortality in males were 1.00, 1.23, 2.52, 3.13, and 3.42 for 0 (lagged out), >0-1199, 1200-3679, 3680-13499, >13500 ppm-days, respectively. The trend in hematopoietic cancer was driven by lymphoid tumors (non-Hodgkin's lymphoma, myeloma, lymphocytic leukemia). Although there is no excess overall risk for breast cancer, internal exposure analyses found positive trend for breast cancer using the log of cumulative exposures with a 20 year lag (p=0.01). The odds ratios with 20 year lag for breast cancer mortality correspond to 1.00, 1.76, 1.77, 1.97, and 3.13 for cumulative exposure categories, 0 (lagged out), >0-646, 647-2779, 2780-12321, >12322 ppm-days, respectively.

* 1 ppm = 1.83 mg/m^3 or 1 mg/m3 = 0.55 ppm

Table 7a – Ethylene Chlorohydrin – Acute Toxicity			
Study/ Species	**MRID or Publication**	**Results**	**Classification**
870.1100 Acute Oral, Rats	Lawrence et al. 1971a	**Oral LD_{50} = 71.3 mg/kg (m)** (95% C.L 57.8-88.6)	Category II
Acute Oral, Mice	Lawrence et al. 1971a	**Oral LD_{50} = 81.4 mg/kg (m)** (95% C.L 66.4-99.7)	Category II

Table 7a – Ethylene Chlorohydrin – Acute Toxicity			
Study/ Species	**MRID or Publication**	**Results**	**Classification**
870.1200 Acute Dermal, Rabbits	Lawrence et al. 1971a	**LD_{50} = 67.8 mg/kg (m&f)** (95% C.L 41.2-111.7)	Category I
Acute Dermal, Rats	NTP, 1985	**LD_{50} = 410 mg/kg (f); LD_{50} = Between 360-480 mg/kg (m)**	Category II
Acute Dermal, Mice	NTP, 1985	**LD_{50} = 1324 mg/kg (m), 1858 mg/kg (f)**	Category II
870.1300 Acute Inhalation, Mice	NIOSH, 1975 (As reported in NTP, 1985)	**LC_{50} = 117 ppm (0.39 mg/L)** Duration not known	Category II
Acute Inhalation, Rats	Carpenter et al. 1949 (As reported in NTP, 1985)	**LC_{50} = 32 ppm (0.11 mg/L)** Duration not known	Category II
Acute Inhalation, Guinea pigs	NIOSH, 1977 (As reported in NTP, 1985)	**LC_{50} = 918 ppm (3.0 mg/L)** Duration not known	Category IV
870.2400 Primary Eye Irritation, Rabbits	Lawrence et al. 1971a	Severe Irritation	Category undertermined Inadequate observation period
870.2500 Primary Skin Irritation, Rabbits	Lawrence et al. 1971a	Marked Irritation	Category undertermined Inadequate observation period
870.2600 Dermal Sensitization, Guinea pig	Lawrence et al. 1971b	No Sensitization	
870.6200 Acute Neurotoxicity	No Study	-	-

Table 7b. Ethylene Chlorohydrin Subchronic, Chronic Toxicity Studies			
Study/Species	**MRID or Publication**	**Doses**	**Results/Classification**
Developmental/Reproduction Toxicity			
Developmental Toxicity CD-1 mice	Courtney et al. 1982	Doses: 0, 50, 100, 150 mg/kg GD 6-16 (gavage)	**Maternal NOAEL: 50 mg/kg/day** **Maternal LOAEL: 100 mg/kg/day** Decreased bodyweight gain (↓61%) Note: 75% mortality of dams at 150 mg/kg/day; The remaining 25% mice at the HDT were not pregnant **Developmental NOAEL: 50 mg/kg/day** **Developmental LOAEL: 100 mg/kg/day** Decreased fetal weight and relative liver weight **Acceptable/Non-Guideline**
Developmental Toxicity CD-1 mice	Courtney et al. 1982	**Doses:** 0, 16, 43, 77, 227 mg/kg/day (drinking water)	**Maternal and Developmental NOAEL: 227 mg/kg/day (HDT)** **Maternal and Developmental LOAEL: Not Established** **Acceptable/Non-Guideline**
Developmental Toxicity Rabbit	No Study identified	-	-
Two-Generation Reproduction Study	No Study identified	-	-
Subchronic Oral Toxicity			
Subchronic (13 weeks) Albino Rats (FDRL strain)	Oser et al. 1975	Doses: 0, 30, 45, 67.5 mg/kg/day Gavage	**NOAEL: 45 mg/kg/day** **LOAEL: 67.5 mg/kg/day** Decreased mean body weight in males (34%) and decreased survival in males and females (32% in the HDT vs 100% in control males and 24% in the HDT vs 96% in control females); Labored breathing in animals that died earlier (~ 3 weeks) at the high dose. Gross and histological changes in animals died at the high dose (~ 3 weeks). Dark liver, lungs and

Table 7b. Ethylene Chlorohydrin Subchronic, Chronic Toxicity Studies			
Study/Species	**MRID or Publication**	**Doses**	**Results/Classification**
			hemorrhagic adrenal and pituitary glands; subacute myocarditis, colloid depletion in the thyroid, fatty liver thyroid congestion and a high incidence of congestive pulmonary changes Minimum data reporting **Acceptable/Nonguideline**
Subchronic (13 weeks) Beagle Dogs	Oser et al. 1975	Doses: 0, 600, 900, 1350 ppm gavage Mean chemical intake: 0, 13.3, 18.4, 18.3 mg/kg (m) 0, 16.9, 20.3, 19.3 mg/kg (f)	**NOAEL 18.4 mg/kg/day** **LOAEL: Not Established** No treatment related effects. The chemical intake in the mid and high doses are not different from each other due to emesis and decreased body weight; Limited data reporting **Acceptable/Non-Guideline**
Subchronic (13 weeks) Monkeys	Oser et al. 1975	Doses: 0, 30, 45, 62.5 mg/kg/day Gavage	**NOAEL: 62.5 mg/kg/day (HDT)** **LOAEL: Not Established** No treatment related effects. Note: Limited findings reported. **Acceptable/Nonguideline**
Subchronic Dermal Toxicity			
Subchronic (14 days) Rats	NTP, 1985	Doses: 0, 20, 30, 40, 60, 80 mg/animal dermal, each day 0, 114/147, 172/222, 226/313, 339/451, 442/611 (m/f)	**NOAEL: 313 mg/kg/day** **LOAEL: 451 mg/kg/day** 60% mortality in females, decreased body weight gain (↓41%) **Acceptable/Non-Guideline**
Subchronic (14 days) CD-1 Mice	NTP, 1985	Doses: 0, 2.5, 5, 10, 20, 30, 45, 60 mg/animal, dermal, each day 0, 92/109, 174/225, 377/435, 741/847, 1095/1376, 1411/1875 (m/f)	**NOAEL: 1095 mg/kg/day** **LOAEL: 1411 mg/kg/day** 60% mortality in males and females, decreased body weight in males. **Acceptable/Non-Guideline**
Subchronic (13 week) Rats	NTP, 1985	Doses: 0, 62, 125, 250, 500, 1000 mg/kg 5d/week, dermal	**NOAEL: 125 mg/kg/day** **LOAEL: 250 mg/kg/day** 10% mortality in males and 30% mortality in females **Acceptable/Non-Guideline**
Subchronic (13 week) CD-1 Mice	NTP, 1985	Doses: 0, 5, 10, 20, 30, 45 mg/animal 5d/week, dermal 0, 192/227, 385/455, 769/909, 1154/1304, 1731/1957	**NOAEL: 385 mg/kg/day** **LOAEL: 769 mg/kg/day** 10-30% mortality in one week **Acceptable/Non-Guideline**
Combined Chronic Carcinogenicity			
870.4300 Combined Chronic Toxicity/Carcinogenicity F344 Rats	NTP, 1985	Doses: 0, 50, 100 mg/kg/day dermal, 5d/week	**NOAEL 100 mg/kg/day** **LOAEL Not Established** No change in survival or body weight gain. No evidence of carcinogenicity

Table 7b. Ethylene Chlorohydrin Subchronic, Chronic Toxicity Studies			
Study/Species	**MRID or Publication**	**Doses**	**Results/Classification**
			Acceptable/Non-Guideline
870.4300 Combined Chronic Toxicity/Carcinogenicity CD-1 Mice	NTP, 1985	Doses: 0, 7.5, 15 mg/animal Dermal, 5d/week 0, 253, 630 mg/kg –Wk 1 0, 180, 411 mg/kg –Wk 100 Average 0, 216, 520 mg/kg/day	**NOAEL: 216 mg/kg/day** **LOAEL: 520 mg/kg/day** Low survival at high dose No change in bodyweight gain Marginal increase in the incidence of lymphomas/leukemias combined; alveolar bronchiolar adenomas/carcinomas in low dose males, the incidence in high dose appeared similar to controls; NTP concluded no evidence of carcinogenicity **Acceptable/Non-Guideline**
Mutation/Genotoxicity			
	NTP, 1985	-	Positive for mutagenicity in bacteria and the mutagenicity was enhanced in the presence of rat liver S9 extract. Negative for the mutagenicity tests using mammalian cell cultures (in vitro) or rodents (in vivo). However, in one test, ethylene chlorohydrin induces DNA repair in human fibroblasts in vitro. Negative for dominant-lethal mutations or heritable translocations in the mouse
Metabolism			
	Grunow and Altmann, 1982, as cited in NTP, 1985	-	Limited evidence suggests that ethylene chlorohydrin is rapidly absorbed in rats and majority of the administered radioactivity (77-80%) was eliminated in urine within 24 hours of ingestion and less than 5% of the administered radioactivity in total is excreted in feces and in expired air. Peak levels of radioactivity were found in blood 1 hour after administration and the radioactivity was reduced to 50% after approximately 4 hours. About 90% of the radioactivity in the urine was in the form of thiodiacetic acid and thionyldiacetic acid
Human Studies			
	Olsen et al., 1997	-	1361 male workers from ethylene chlorohydrin factory -minimum of 30 days work experience in the factory in 1940-1992 -No increased risk for pancreatic and lymphopoietic and hematopoietic cancer Dow Chemical Company Report
	Benson and Teta, 1993	-	278 male workers Follow up from 1940-1988 Mean duration of assignment 5.9 years Mean duration of follow up 36.5 years -Increased risk for total cancer pancreatic and lymphatic and hematopoietic cancer with increased duration of assignment to the chlorohydrin unit Union Carbide Corporation Report

Table 8a. Ethylene Glycol Acute Toxicity			
Study/Species	**MRID or Publication**	**Results**	**Classification**
Acute Toxicity			
870.1100 Acute Oral Fischer 344 Rats	Clark et al. 1979 (HSDB, 2005)	LD_{50} = 4000 mg/kg/day (f)	Category III
Wistar Rats	Richardson 1973 (ATSDR, 1997)	LD_{50} = ~12, 900 mg/kg/day (m)	Category IV
Mice	Schuler et al. 1984 (HSDB, 2005)	LD_{50} = >11, 090 mg/kg/day	Category IV
Mice	IPCS, 2002	LD_{50} = 6610 mg/kg/day	Category IV
Guinea-pigs	IPCS, 2002	LD_{50} = 5500-8350 mg/kg/day	Category IV
Dogs	IPCS, 2002	LD_{50} = 5500 mg/kg/day	Category IV
Cats	IPCS, 2002	LD_{50} = 1650 mg/kg/day	Category III

Table 8a. Ethylene Glycol Acute Toxicity			
Study/Species	**MRID or Publication**	**Results**	**Classification**
870.1200 Acute Dermal, Rabbits	IPCS, 2002	LD_{50} = 10600 mg/kg/day	Category IV
870.1300 Acute Inhalation, Rats and Mice	IPCS, 2002	LC_{50} = >200 mg/m^3	Category II
870.2400 Primary Eye Irritation, Rabbits	IPCS, 2002	Minimal conjunctival irritation without permanent corneal damage	-
870.2500 Primary Skin Irritation Rabbits and Guinea pigs	IPCS, 2002	Mild dermal irritation	-
870.2600 Dermal Sensitization, Guinea pigs	No study identified	-	-

Table 8b. Ethylene Glycol Subchronic, Chronic Toxicity Studies			
Study/Species	**MRID or Publication**	**Doses**	**Results/Classification**
Developmental/Reproduction Toxicity			
Developmental Toxicity CD-1 Rats	Neeper-Bradley et al. 1990 and 1995 (NTP-CERHR 2004)	Doses: 0, 150, 500, 1000, 2500 mg/kg/day. (GD6-15), 25/group	**Maternal NOAEL: 500 mg/kg/day** **Maternal LOAEL: 1000 mg/kg/day** Increased relative liver weight. At the HDT increased liver and kidney weights and water intake. **Developmental NOAEL: 500 mg/kg/day** **Developmental LOAEL: 1000 mg/kg/day** Reduced fetal body weight, increased incidence of litters with skeletal malformations (duplicated or missing ribs, centra and arches and poor ossification). At the HDT, increased litter incidences for total malformations, and external, visceral and skeletal malformations. The malformations included gastroschisis, hydrocephaly, lateral ventricle dilation, umbilical hernia, and malformations of the ribs and vertebrae. **Acceptable/Non-Guideline**
Developmental Toxicity CD Rats	Price et al. 1985 (NTP-CERHR 2004)	Doses: 0, 1250, 2500, 5000 mg/kg/day. (GD 6-15) gavage, 27-29/group	**Maternal NOAEL: Not Established** **Maternal LOAEL: 1250 mg/kg/day** Decreased maternal body weight gain, increased relative kidney weight, water intake and post implantation loss per litter, decreased liver weight and number of live fetuses per litter at the HDT **Developmental NOAEL: Not Established** **Developmental LOAEL: 1250 mg/kg/day** Increased incidence of litters with visceral malformations. Increased incidence of litters with skeletal malformations at 2500 mg/kg/day. Decreased fetal body weight per litter and increased number of malformed fetuses per litter and increased litter incidence for skeletal, visceral and external malformations at the HDT. Malformations involved varying degrees of skeletal dysplasia, and clefts of the face, lip or palate. **Acceptable/Non-Guideline**
Developmental Toxicity Fischer 344 Rats	Maronpot et al. 1983 (NTP-CERHR 2004)	Doses: 0, 40, 200, 1000 mg/kg/day. (GD 6-15) diet, ~20/group	**Maternal NOAEL: 1000 mg/kg/day (HDT)** **Maternal LOAEL: Not Established** **Developmental NOAEL: 200 mg/kg/day** **Developmental LOAEL: 1000 mg/kg/day** Increased litter incidence of skeletal variations **Acceptable/Non-Guideline**

Table 8b. Ethylene Glycol Subchronic, Chronic Toxicity Studies			
Study/Species	**MRID or Publication**	**Doses**	**Results/Classification**
Developmental Toxicity CD-1 Mice	Price et al. 1984 and 1985 (NTP-CERHR 2004)	Doses: 0, 750, 1500, 3000 mg/kg/day. (GD 6-15) gavage, 23-25/group	**Maternal NOAEL: 750 mg/kg/day** **Maternal LOAEL: 1500 mg/kg/day** Decreased maternal body weight gain and decreased absolute liver weight Increased post implantation loss /litter at the HDT **Developmental NOAEL: Not Established** **Developmental LOAEL: 750 mg/kg/day** Increased malformed fetuses/litter, and percentage of litters with malformed fetuses (mostly skeletal malformations) and decreased fetal weight. Similar effects at 1500 mg/kg/day. At the HDT, increased percent of live malformed fetuses/litter, increased litter incidence for skeletal, visceral and external malformations, especially neural tube closure defects and craniofascial and axial skeletal dysmorphogenesis. **Acceptable/Non-Guideline**
Developmental Toxicity CD-1 Mice	Neeper-Bradley et al. 1995 and Tyl and Frank, 1989 (NTP-CERHR 2004)	Doses: 0, 50, 150, 500, 1500 mg/kg/day. (GD 6-15)	**Maternal NOAEL: 1500 mg/kg/day (HDT)** **Maternal LOAEL: Not Established** **Developmental NOAEL: 150 mg/kg/day** **Developmental LOAEL: 500 mg/kg/day** Reduced fetal body weight increased incidence of the 14th rib. At the HDT reduced fetal body weight increased incidence of total malformations, fused ribs and arches, poor ossification in thoracic and lumbar centra and 14th rib. **Acceptable/Non-Guideline**
Developmental Toxicity New Zealand white Rabbits	Tyl et al. 1993 (NTP-CERHR 2004)	Doses: 0, 150, 500, 1000, 2000 mg/kg/day. (GD 6-19)	**Maternal NOAEL: 1000 mg/kg/day** **Maternal LOAEL: 2000 mg/kg/day** 42% mortality, three early deliveries, one spontaneous abortion and renal lesions which include intraluminal oxalate, epithelial necrosis, tubular dilatation and degeneration **Developmental NOAEL: 2000 mg/kg/day (HDT)** **Developmental LOAEL: Not Established** **Acceptable Non-Guideline**
Three-Generation Reproduction Study, Fischer 344 Rats	DePass, 1986a and Woodside et al. 1974 (NTP-CERHR 2004)	Doses: 0, 40, 200, 1000 mg/kg/day Diet	**Systemic/Reproductive/Offspring NOAEL: 1000 mg/kg/day** **Systemic/Reproductive/Offspring LOAEL: Not Established** **Acceptable Non-Guideline**
Two-Generation Reproduction Study, CD-1 Mice	Lamb et al. 1985, Morrissey et al. 1989 (NTP-CERHR 2004)	Doses: 0, 0.25, 0.5, 1.0% in drinking water (w/v) Equivalent to 0, 410, 840 and 1640 mg/kg/day	**Systemic NOAEL: 1640 mg/kg/day (HDT).** **Systemic LOAEL: Not Established** **Reproductive NOAEL: 840 mg/kg/day** **Reproductive LOAEL: 1640 mg/kg/day** Decreased number of F1 litters per fertile F0 pair **Offspring NOAEL: 840 mg/kg/day** **Offspring LOAEL: 1640 mg/kg/day** Decreased number of F1 pups/litter and mean F1 pup weight, skeletal effects in F1 pups. **Acceptable/Non-Guideline**
Two-Generation Reproduction Study, CD-1 Mice	Gulati et al. 1986 (NTP-CERHR, 2004)	Doses: 0, 0.5, 1.0, 1.5% in drinking water (w/v) Equivalent to 0, 897, 1798 and 2826 mg/kg/day	**Systemic NOAEL/LOAEL: Not Determined** due to limited reporting on body weight and organ weights in low and mid dose groups in F0 animals. **Reproductive NOAEL: Not Established** **Reproductive LOAEL: 897 mg/kg/day** Decrease in sperm counts, testes and seminal vesicle weights in F1 males. **Offspring NOAEL: Not Established** **Offspring LOAEL: 897 mg/kg/day** Decrease in F1 and F2 pup weights **Acceptable/Non-Guideline**
Subchronic Oral Toxicity			

Table 8b. Ethylene Glycol Subchronic, Chronic Toxicity Studies			
Study/Species	**MRID or Publication**	**Doses**	**Results/Classification**
Subchronic 16 weeks, Wistar Rats	Gaunt et al. 1974 (IPCS, 2002)	Doses: 0, 35, 71, 180, 715 mg kg day (m); 0, 38, 85, 185, 1128 mg/kg/day (f)	**NOAEL: 71 mg/kg/day** **LOAEL: 180 mg/kg/day** Increased urinary excretion of oxalate and increased overall incidence for kidney histopathological effects. The changes include dilation, degeneration, protein casts, and deposition of calcium oxalate crystals in nephrons. **Acceptable/Non-Guideline**
Subchronic 10 days Sprague-Dawley Rats,	Robinson et al., 1990 (IPCS, 2002)	Doses: 0, 0.5 to 4.0 % (w/v) in drinking water Equivalent Doses: 650-5300 mg/kg/day (m); 0, 800-7300 mg/kg/day (f)	**NOAEL: Not Determined** **LOAEL: 650 mg/kg/day**. Alterations in clinical chemistry parameters Severity of histopathological lesions in kidney at high doses (≥ 2600 mg/kg/day in males and at 7300 mg/kg/day in females) **Acceptable/Non-Guideline**
Subchronic 90 days Sprague-Dawley Rats	Robinson et al., 1990 (IPCS, 2002)	Doses: 0, 0.25-2.0 % (w/v) in drinking water Equivalent Doses: 205-3130 mg/kg/day (m); 0, 600-5750 mg/kg/day (f)	**NOAEL: Not Determined** **LOAEL: 205 mg/kg/day** Alterations in hematological parameters in females. Decreased body weight and kidney histopathological effects at high doses (≥ 950 mg/kg/day in males and at 3100 mg/kg/day in females) **Acceptable/Non-Guideline**
Subchronic 13 weeks Fischer 344 Rats	Melnick, 1984 (IPCS, 2002)	Doses: 0, 165, 325, 640, 1300 or 2600 mg/kg/day, diet	**NOAEL: 640 mg/kg/day** **LOAEL: 1300 mg/kg/day.** Reduced body weight and kidney effects **Acceptable/Non-Guideline**
Combined Chronic Carcinogenicity			
Combined Chronic Toxicity/Carcinogenicity, 2 years, Fischer 344 Rats,	DePass et al 1986b	Doses: 0, 40, 200, 1000 mg/kg/day 30 rats/sex/group	**NOAEL: 40 mg/kg/day** **LOAEL: 200 mg/kg/day** **Presence of calcium oxalate crystals in urine of both sexes and possible fatty changes in liver in females** *(Note: IRIS (2004) determined this level as NOAEL in the 1989 revision for cRfD determination)* At the HDT, 100% mortality by 12 months, decreased body weight, changes in clinical chemistry and hematological parameters, organ weight changes, and chronic nephritis in males and mild fatty changes in the liver of females. **Acceptable/Non-Guideline**
Combined Chronic Toxicity/Carcinogenicity, 2 years, Sprague Dawley, Rats	Blood, 1965 (IRIS, 2004)	Doses: 0, 0.1%, 0.2%, 0.5%, 1.0%, 4.0% in Diet Equivalent to 0, 50, 100, 250, 500, 2000 mg/kg/day 16/sex/group	**NOAEL: 100 mg/kg/day** **LOAEL: 250 mg/kg/day** Increased incidence of cytoplasmic crystal deposition in renal tubular epithelium. Increased mortality, decreased growth, increased water consumption, proteinuria and renal calculi at higher doses (500 mg/kg/day males and 2000 mg/kg/day males and females) **Acceptable/Non-Guideline**
CD-1 Mice, 2 years	DePass et al 1986b	Doses: 0, 40, 200, 1000 mg/kg/day 20 mice/sex/group	**NOAEL: 1000 mg/kg/day** **LOAEL: Not Established** **Acceptable/Non-Guideline**
B6C3F1 Mice Diet 2 Years	NTP, 1993 (IPCS, 2002	Doses: 0, 1500, 3000, 6000	**NOAEL: Not Established** **LOAEL: 1500 mg/kg/day**

Table 8b. Ethylene Glycol Subchronic, Chronic Toxicity Studies			
Study/Species	**MRID or Publication**	**Doses**	**Results/Classification**
		mg/kg/day (m); 0, 3000, 6000, 12000 mg/kg/day (f)	Arterial medial hyperplasia in lungs in females. High dose mice and mid dose mice had hyalin degeneration in the liver. Mid and high dose mice had transient kidney damage. No evidence of carcinogenicity at the doses tested **Acceptable/Non-Guideline**
Rhesus monkeys Diet, 3 years	Blood et al. 1962 (IRIS, 2004)	Doses: 0, 0.2, 0.5% Equivalent doses: 0, 100, 250 mg/kg/day (determined assuming 1 ppm is equivalent to 0.05 mg/kg/day)	**NOAEL: 250 mg/kg/day (HDT)** **LOAEL: Not Established** **Acceptable/Non-Guideline**
Mutagenicity/Genotoxicity			
	IPCS, 2002		Mutagenicity tests in bacteria and mammalian cells are consistently negative. The chromosomal aberrations tests in Chinese hamster ovary cells and DNA damage in rat hepatocytes are negative. The in vivo genotoxicity tests are also negative for dominant lethal mutations in rats and chromosomal aberrations of bone marrow cells in mice exposed to ethylene glycol.

4.2 FQPA Hazard Considerations

4.2.1 Adequacy of the Toxicity Database

4.2.1.1 Ethylene Oxide

The toxicity database is considered adequate for ethylene oxide based on the studies submitted to the Agency (acute and subchronic neurotoxicity, developmental toxicity studies in rats, reproduction study in rats, chronic toxicity study in monkeys) and those available in the open (public) literature.

4.2.1.2 Ethylene Chlorohydrin

There are no guideline studies submitted to the Agency for ethylene chlorohydrin. From the open literature, teratogenicity studies in mice and subchronic oral toxicity studies in rats, monkeys and beagle dogs and subchronic and chronic dermal toxicity studies in rats and mice were identified. The teratogenicity study in non-rodents, two-generation reproduction study in rats and chronic toxicity studies in rats and mice are not available and therefore, the toxicity database for ethylene chlorohydrin is considered inadequate.

4.2.1.3 Ethylene Glycol

Although no guideline studies are available for ethylene glycol, there are several open literature studies (on teratogenicity in rodents and non-rodents, reproduction, subchronic and chronic oral toxicity in rodents) available which provide enough confidence to evaluate the

toxicity endpoint for ethylene glycol. The toxicity database for ethylene glycol is considered adequate based on the studies available in the open (public) literature.

4.2.2 Evidence of Neurotoxicity

4.2.2.1 Ethylene Oxide

Guideline Studies

A brief summary of neurotoxicity findings are listed below. The acute and subchronic study details can be found in the Appendix in Section 2.0. In an acute neurotoxicity study (MRID 44256402), groups of ten Sprague-Dawley rats/sex were exposed to 0, 100, 300, or 500 ppm ethylene oxide for six hours by whole body inhalation and observed for 14 days. FOB results indicate increased incidences for drooping eyelids or half-closed eyes, low arousal level and no response to an approaching object in the MDT and HDT as compared to controls. Slightly impaired locomotion was observed in few mid dose males and high dose males and females, on day 1. In mid- and high-concentration males, some evidence of persistent FOB effects was observed on day 8 and 15. No effects were found on fore- and hind-limb grip strengths, landing foot splay, or reflex assessments. Motor activity decreased in mid dose males and high dose males and females. No microscopic lesions were described for the brain, spinal column, or peripheral nerves from any control or high-concentration rat.

In a subchronic neurotoxicity study (MRID 44359401), groups of 15 Sprague-Dawley rats/sex were exposed to 0, 25, 50, 100, or 200 ppm ethylene oxide for six hours/day, five days/week for 14 weeks (at least 65 exposures) by whole body inhalation. Exposure concentrations were selected based on results of a range-finding study, MRID 44256401. To assess the reversibility of any observed effects, ten rats/sex/dose were observed during an additional 13-week recovery period. There was a 25% decrease in hind limb grip strength at 200 ppm. There were no treatment-related effects on motor activity. One male exposed to 100 ppm was found dead during the recovery period (4 weeks after termination of exposure). Antemortem observations included lethargy, paleness, labored breathing, ano-genital staining, decreased fecal volume/no stool, and decreased food consumption.

In a range-finding study (MRID 44256401), groups of five Sprague-Dawley rats/sex were exposed to target concentrations of 0, 100, 300, 400, or 500 ppm ethylene oxide for six hours/day, five days/week for 4 weeks by whole body inhalation. Decreased hindlimb grip strength was noted at 300 ppm and above ($p \leq 0.05$ or 0.01). Decreased landing foot splay was noted at 400 ppm and above ($p \leq 0.05$ or 0.01). One animal died and some animals exhibited lethargy, prostration, emaciation, yellow anogenital staining, moist rales, labored breathing, black/brown stains on the snout, paleness, emaciation in the 500 ppm group. Decreased absolute brain weight was noted in males exposed to 400 (6.8%; $p \leq 0.05$) or 500 ppm (8.9%; $p \leq 0.01$). No treatment-related macroscopic lesions were noted at necropsy. Treatment-related microscopic lesions were noted in all males and females from the 500 ppm group and included minimal to slight vacuolation of the white matter of the thalamus and medulla oblongata.

Studies from Open Literature

Neurological effects in animals have been reported in several subchronic and chronic studies. In a subchronic study (Snellings et al.1984a), B6C3F1mice (30/sex/group) were exposed to ethylene oxide at concentrations of 0, 10, 50, 100 or 250 ppm for 6h/day, 5d/week for 10 or 11weeks. Neurological effects (altered gait, decreased locomotor activity) were observed in 50 ppm females and in both sexes at 100 ppm or higher. At high dose tested, effects on various reflexes (righting, tail pinch and toe pinch) were noted. IPCS (2003) summarizes the neurological findings from several subchronic and chronic studies. Poor coordination of the hindquarters was observed in rats and mice following exposure to ethylene oxide at 450 ppm for 7-8 weeks. Awkward or ataxic gait, paralysis and atrophy of the muscles of the hindlimbs, accompanied in some cases by pathological evidence of axonal degeneration of myelinated fibers in nerves of the hind legs were reported in rats and mice exposed to ethylene oxide to 250-500 ppm. Paralysis of the hind limbs and atrophy of the leg muscles have been reported in rabbits and monkeys following exposure to ≥ 202 ppm (IPCS, 2003). Demyelination of the sciatic nerve was reported in cynomolgus monkeys exposed to 50 and 100 ppm ethylene oxide for 2 years (MRID 42159401). Peripheral neuropathy, impaired hand-eye coordination and memory loss have been reported in case studies of chronically-exposed workers at estimated average exposure levels as low as 3 ppm (with possible short-term peaks as high as 700 ppm) (ATSDR, 1990).

4.2.2.2 Ethylene Chlorohydrin and Ethylene Glycol

No neurotoxicity studies for ethylene chlorohydrin are identified. There was no evidence of neurotoxicity or neuropathology from the available studies with ethylene chlorohydrin. Although data are limited, available toxicity studies conducted in rodents, rabbits and monkeys indicate that neurological effects are not of concern for ethylene glycol (IPCS, 2002).

4.2.3 Developmental and Reproduction Toxicity Studies

4.2.3.1 Ethylene Oxide

Developmental Study - Rat

In a developmental study (MRID 42797702) pregnant CD rats (25/group) were exposed whole body by inhalation to ethylene oxide concentrations of 0, 50, 125 or 225 ppm for 6 hours per day on gestation days 6-15, inclusive. Dose dependent decrease in maternal bodyweight gain was observed during GD 6-15. Dams had a decreased mean body weight gain of 15.4% (statistically not significant), 20.5% ($p \leq 0.05$) and 66.7% ($p \leq 0.01$) in 50, 125 and 225 ppm, respectively, compared to controls. Dams at 125 ppm also had significantly decreased mean body weight gain during entire gestation period whether expressed with (GD 0-21 days: ↓10.3%, $p < 0.01$) or without gravid uterine weight (GD 0-21 days: ↓14.5% $p < 0.05$) compared to controls. Similarly, significantly decreased mean body weight gain during entire gestation period was observed at 225 ppm whether expressed with (GD 0-21 days ↓17.4% $p < 0.01$) or without gravid uterine weight (GD 0-21 days:↓36.4% $p < 0.01$) as compared to controls. Also, significantly decreased mean food consumption was noticed during GD 6-15 in dams at 225 ppm (↓13.6% $p < 0.01$). There were no treatment-related effects on numbers of corpora lutea, pre or post

implantation loss as compared to controls. Based on decreased body weight gain at 125 ppm, the maternal NOAEL and LOAEL were determined as 50 and 125 ppm, respectively.

Developmental toxicity was observed in a concentration related manner at all exposure levels. Statistically significant decreases in mean fetal body weights were reported at 50 ppm (↓4%, $p \leq 0.05$), 125 ppm (↓6%, $p \leq 0.01$), and 225 ppm (↓12%, $p \leq 0.01$) as compared to controls. Due to marginal decreases, the fetal body weight effects in 50 and 125 ppm, were not considered biologically significant. Significantly increased litter incidence ($p < 0.05$ or 0.01) or delayed ossification in skull bones, phalanges, metacarpals, and sternebrae 4 and 6 at 225 ppm and in metatarsals, metacarpals, and sternebrae 5 and 6 at 125 ppm were noticed.

Based on the decreased fetal body weight and increased litter incidence of delayed ossification in metatarsals, metacarpals, and sternebrae at 125 ppm, the developmental NOAEL and LOAEL were determined as 50 and 125 ppm respectively. This rat study is classified as Acceptable/Guideline and meets the guideline requirement (83-3) for developmental toxicity study.

Developmental Study - Rabbit

In a developmental study (MRID 41874102), New Zealand white rabbits were exposed to ethylene oxide via inhalation at 0 and 150 ppm, 7h/day, during GD7-19, or GD1-19. Necropsies were performed on GD30. No evidence of maternal or developmental toxic effects observed at 150 ppm. This study is classified as Unacceptable/Guideline and does not meet the guideline requirement (83-3) for developmental toxicity study. The study tested only single dose and LOAEL for maternal and developmental effects were not determined.

Reproductive Toxicity Study - Rat

In a two generation reproduction study (MRID 42788101), 28 CD rats per sex per group were exposed (whole body) by inhalation to ethylene oxide at concentrations of 0, 10, 33 or 100 ppm for 6 hours /day (5 days/week) during pre-mating and 7 days/week during mating, on gestational days (GDs) 0-20, and on lactational days (LDs 5-28).

Significant decrease in mean body weight gains were noticed at 33 and 100 ppm in F0 males and females and F1 males during premating ($p \leq 0.05$ or $p \leq 0.01$). In addition, decrease in bodyweights were observed in F0 and F1 females during gestation ($p \leq 0.01$) and F1 females alone during early lactation ($p \leq 0.05$ or $p \leq 0.01$) at 100 ppm. Significant decrease ($p \leq 0.01$) in food consumption in lactating F0 and F1 females were observed at 100 ppm. The systemic LOAEL is determined as 33 ppm based on decreased mean body weight gains in F0 males and females and F1 males during premating period. The NOAEL is established as 10 ppm.

Reproductive toxicity was observed at 33 and 100 ppm. It was manifested as a decreased number of live pups per litter in both generations ($p \leq 0.01$) due to significantly increased postimplantation loss at 33 ppm (two-fold increase) and 100 ppm (six-fold increase) in F1 offspring and at 100 ppm in F2 offspring (four-fold increase). In addition at 33 and 100 ppm, mean pup body weight gains were decreased significantly ($p \leq 0.05$ or $p \leq 0.01$) in both F1 and F2

generations during the latter part of lactation, i.e., LD 21. Based on increased postimplantation loss (two-fold) and decreased live pups per litter in F0 generation, the reproductive NOAEL and LOAEL were determined as 10 and 33 ppm, respectively. Based on decreased mean pup body weight gain in both generations, the offspring NOAEL and LOAEL were determined as 10 and 33 ppm, respectively. This study is classified Acceptable/Guideline and meets the requirement set forth under Guideline series 83-4 for a two-generation reproductive toxicity study in rats.

4.2.3.2 Ethylene Chlorohydrin

No developmental toxicity studies in rats are submitted to the Agency. However, two developmental studies in mice are found in the open literature for ethylene chlorohydrin. No reproductive toxicity studies are identified for ethylene chlorohydrin.

Developmental Studies - Mice

In a developmental study (Courtney et al. 1982), pregnant CD-1 mice (10-12/group) were administered with ethylene chlorohydrin by gavage at concentrations of 0, 50, 100 or 150 mg/kg/day, using water as the vehicle, on gestation days 6-16, inclusive. The animals were sacrificed on GD17. At the HDT, 75% of the pregnant mice had mortality after 2-4 treatments and remaining 25% were not pregnant. There was a 61% decrease in the maternal weight gain at 100 mg/kg/day compared to controls (4.9±0.8 versus 1.9±0.6; $p<0.05$). The body weight gain was not affected at 50 mg/kg/day group. There appeared to be an increase in the number of implants per litter (10.1±1.0 versus 12.3 ±0.5; $p<0.05$) as well as the number of fetuses per litter (9.5±1.0 in controls versus 11.4 ±0.6; NS) at MDT. But the fetal weight was decreased significantly in MDT (1.03 ±0.04 versus 0.89 ±0.03g or 1.00 ±0.04 versus 0.88 ±0.03g; $p<0.05$ in both batches). There was also a significant decrease in absolute as well as relative fetal weight at 100 mg/kg/day ($p<0.05$). The incidence of bilateral 14th rib appeared to be higher in the fetuses of 100 mg/kg/day (2 versus 10 fetuses; the ratio not provided). However, the effects were not statistically significant.

Based on the decrease in maternal body weight gain the maternal NOAEL and LOAEL were determined as 100 and 50 mg/kg/day respectively. The developmental LOAEL was determined as 100 mg/kg/day based on decreased fetal weight gain and relative liver weight and possibly increased incidence of the 14th rib. This study is classified as Acceptable/Non-Guideline.

In a developmental study (Courtney et al. 1982), pregnant CD-1 mice (3-13/treatment and 16 for control group) were administered with ethylene chlorohydrin in drinking water at target concentrations of 0, 10, 25, 50 or 200 mg/kg/day on gestation days 6-16, inclusive. The animals were sacrificed on GD17. Based on the water consumption, the actual ethylene chlorohydrin concentrations were 0, 16, 43, 77, or 227 mg/kg/day. There appear to be no weight gain in the 25 mg/kg/day dose level but this effect was not seen at the next two higher dose levels. There were no changes in the maternal or developmental parameters. The study is limited by only 3-4 animals used in all treatment levels except the highest dose tested. Based on the limited findings, the maternal and developmental NOAEL are determined as 227 mg/kg/day. The maternal and

developmental LOAEL are not established. This study is classified as Acceptable/Non-Guideline.

4.2.3.3 Ethylene Glycol

Developmental toxicity studies conducted in rats, mice and rabbits for ethylene glycol are identified from the open literature. The multi-generation reproduction toxicity studies in rats and mice are also identified from the open literature.

Developmental Studies - Rat

In a developmental toxicity study (Price et al. 1985 as cited in NTP-CERHR, 2004), 27-29 CD timed-pregnant rats per treatment were administered by gavage with ethylene glycol (>99% purity) in distilled water at 0, 1250, 2500 or 5000 mg/kg/day daily during GD 6-15. The animals were sacrificed at GD 20. Maternal body weight gains were significantly reduced in all treatment groups. The water consumption was increased in a dose dependent manner and the results were significant in the 2500 and 5000 mg/kg/day groups. The absolute liver weight was significantly decreased at 5000 mg/kg/day, but the relative kidney weights were increased in the 2500 and 5000 mg/kg/day groups. A statistically significant increase in post implantation loss was observed in 5000 mg/kg/day. Live litter size was significantly reduced at the 2500 and 5000 mg/kg/day groups.

The maternal NOAEL is not established in the study and the maternal LOAEL is determined as 1250 mg/kg/day based on decreased maternal body weight gain. There was a significant increase in the percentage of litters with malformed fetuses in all treated groups. There was a significant increase in the litter incidences for fetuses with external malformations (5000 mg/kg/day), visceral malformations (1250 and 5000 mg/kg/day), and skeletal malformations (2500 and 5000 mg/kg/day). The most common malformations were neural tube closure defects, and craniofacial and axial skeletal morphogenesis. The visceral malformations (NTP Expert Panel classified them as variations) included 7 cases of hydroureter, 3 cases of hydronephrosis, and 2 great artery anomalies). The developmental LOAEL is determined as 1250 mg/kg/day based on the visceral malformations. The developmental NOAEL is not established in the study. This study is classified as Acceptable/Non-Guideline.

In a developmental toxicity study (Neeper-Bradley et al. 1990 and 1995, as cited in NTP-CERHR, 2004), 25 Crl:CD (Sprague Dawley) pregnant rats per treatment were administered by gavage with ethylene glycol (99.9% purity) in deionized water at 0, 150, 500, 1000 or 2500 mg/kg/day daily during GD 6-15. The animals were sacrificed at GD 21. Significant decrease in maternal body weight gain ($p<0.01$) and significant increase in water consumption ($p<0.01$) were reported at the HDT. Significant increases in absolute ($p<0.01$) as well as relative ($p<0.01$) kidney weights were found at the HDT. The relative maternal liver weights were reported significantly increased at 1000 ($p<0.01$) and 2500 mg/kg/day ($p<0.001$) groups.

The maternal LOAEL is determined as 1000 mg/kg/day based on significant increase in relative liver weights and the maternal NOAEL is 500 mg/kg/day. It must be noted that NTP did

not consider the increase in relative weights as significant and therefore, concluded the maternal NOAEL as 1000 mg/kg/day.

Significant developmental effects in the 1000 mg/kg/day group included reduced fetal body weight ($p<0.05$) and increased incidences of litters containing fetuses with two skeletal malformations (missing thoracic arch and missing ribs; $p<0.01$). At 2500 mg/kg/day, significantly increased frequencies of litters containing fetuses with visceral, skeletal, external and total malformations (all at $p<0.01$) and decreased fetal body weights ($p<0.01$) were observed. Defects observed in the HDT included gastroschisis, hydrocephaly, lateral ventricle dilation, umbilical hernia, and malformations of the ribs and vertebrae. Skeletal variants in litters from the 1000 and 2500 dose groups primarily involved delayed ossifications. The developmental LOAEL is determined as 1000 mg/kg/day based on decreased fetal weight gain and skeletal malformations. The developmental NOAEL is 500 mg/kg/day. This study is classified as Acceptable/Non-Guideline.

In a developmental toxicity study (Maronpot et al. 1983, as cited in NTP-CERHR, 2004), approximately 20 Fischer 344 pregnant rats per treatment were administered in diet with ethylene glycol (99.9% purity) to the target doses of 0, 40, 200 or 1000 mg/kg/day daily during GD 6-15. The animals were sacrificed at GD 21. The only significant finding in this study was statistically significant increase in incidence of poorly ossified and unossified vertebral centra in fetuses from the 1000 mg/kg/day group.

The maternal NOAEL is determined as 1000 mg/kg/day (HDT) and the maternal LOAEL is not established. The developmental LOAEL is determined as 1000 mg/kg/day based on increased incidence of skeletal variations. The developmental NOAEL is 200 mg/kg/day. It must be noted that NTP did not consider the skeletal variations as significant and concluded the maternal as well as developmental NOAEL as the HDT. This study is classified as Acceptable/Non-Guideline.

Developmental Studies - Mice

In a developmental toxicity study (Price et al. 1984 and 1985, as cited in NTP, 2004), 23-25 COBS Crl:CD-1 pregnant mice per treatment were administered with ethylene glycol (>99% purity) in distilled water at 0, 750, 1500 or 3000 mg/kg/day daily by gavage during GD 6-15. The animals were sacrificed at GD 17. The maternal body weight gain was significantly decreased ($p<0.01$) in 1500 and 3000 mg/kg/day groups. Also, absolute not relative liver weights ($p<0.01$) were decreased significantly in the same dose groups. The maternal LOAEL is identified as 1500 mg/kg/day based on decreased maternal body weight gain and decreased absolute liver weight. The maternal NOAEL is established as 750 mg/kg/day.

A significant reduction in the number of live fetuses per litter was noted at the HDT. Significant decrease in fetal weight ($p<0.01$) was reported in all treatments. The percent of live malformed fetuses per litter ($p<0.01$) and increased incidence of litters with malformed fetuses ($p<0.001$) were significantly increased in all treatment groups. The number of litters with external malformations and the number of litters with visceral malformations were significantly increased ($p<0.01$) at the HDT. The most common malformations involved neural tube closure defects, and craniofacial and axial skeletal dysmorphogenesis. The number of litters with

skeletal malformations were significantly increased ($p<0.001$) in all treatments. The developmental NOAEL is not established in this study. The developmental LOAEL is identified as 750 mg/kg/day (LDT) based on decreased fetal weight and increased percentage of litters with malformed fetuses (mostly skeletal malformations). The developmental NOAEL is not established. This study is classified as Acceptable/Non-Guideline.

In an another developmental toxicity study (Neeper-Bradley et al., 1995 and Tyl and Frank, 1989 as cited in NTP-CERHR, 2004), Crl:CD-1 (ICR) BR pregnant mice (30/group) were administered with ethylene glycol (100% purity) in deionized water at 0, 50, 150, 500 or 1500 mg/kg/day daily by gavage during GD 6-15. The animals were sacrificed on GD18. No chemical-related effects on body weight gain, water consumption, organ weights, number of corpora lutea per dam and number of viable and non-viable implants per litter were observed. Therefore, the maternal NOAEL is determined as 1500 mg/kg/day (HDT) and the LOAEL is not established.

Fetal body weights per litter were significantly reduced at the HDT. The incidences of total malformations in litters were 16%, 35%, 21%, 50% and 81% in control, 50, 150, 500 or 1500 mg/kg/day, respectively and the results were reported as statistically significant in the 500 and 1500 mg/kg/day groups ($p<0.05$). Total skeletal malformations were significantly increased in litters of the 1500 mg/kg/day group. Skeletal malformations included fused or extra ribs, and fused thoracic or lumbar arches. The incidences of extra lumbar rib in litters of the 500 mg/kg/day group and 23 individual skeletal variations (e.g., poorly ossified thoracic and lumbar centra, extra lumbar ribs) in litters of the 1500 mg/kg/day group were significantly increased. The developmental NOAEL is identified as 150 mg/kg/day and the LOAEL is identified as 500 mg/kg/day based on the increased litter incidence of total (appears mainly from skeletal) and skeletal variations (extra lumbar rib). This study is classified as Acceptable/Non-Guideline.

Developmental Study - Rabbit

In a developmental toxicity study (Tyl et al., 1993 as cited in NTP, 2004) New Zealand white rabbits (23-24/group) were administered with ethylene glycol (98% purity) in deionized water at 0, 100, 500, 1000 or 2000 mg/kg/day daily by gavage during GD 6-19. The animals were sacrificed on GD30. At 2000 mg/kg/day, there was a 42% mortality of the does, three delivered early and one aborted. Kidney weights were slightly increased at the HDT, however, the effects were not statistically significant. Necropsy at the HDT revealed renal toxicity including tubule dilatation, and degeneration, epithelial necrosis and intraluminal oxalate crystal deposition. No other maternal effects or developmental effects were reported. Based on mortality effects, early delivery and renal lesions, the maternal LOAEL is determined as 2000 mg/kg/day and the maternal NOAEL is 1000 mg/kg/day. The developmental NOAEL is identified as 2000 mg/kg/day and the developmental LOAEL is not established. This study is classified as Acceptable/Non-Guideline.

Reproduction Study - Rat

In a three-generation reproduction study (DePass et al 1986 and Woodside et al. 1974, as cited in NTP, 2005) Crl: Fischer 344 rats (10 males/treatment and 20 females/treatment for F0 generation; number of rats for F1 and F2 generation not provided) were administered with

ethylene glycol (99.82%) in diet at 0, 40, 200 or 1000 mg/kg/day. Ethylene glycol in diet was adjusted every two weeks to maintain constant dose levels. During the second and third week of lactation, ethylene glycol levels were reduced 2- and 3-fold to adjust for large increases in food consumption that occur during this time. Two groups of control rats were fed diets without ethylene glycol. Exposure of the F0 males and females to ethylene glycol began about 7 weeks of age before mating and was continued for 3 generations. No effects on body weight gain or food consumption were observed at any dose. Ethylene glycol treatment had no effect on fertility index, gestation index, gestation survival index, or days from first mating to litter in the F0-F1, F1-F2, or F2-F3 generation. There was no effect on post natal pup weight gain. No histopathological effects were observed in accessory sex glands, epididymis, testes, uterus, ovaries or kidneys of F2 parents and/or F3 weanlings. Based on the evidence presented, the systemic/reproductive/offspring NOAEL is determined as 1000 mg/kg/day (HDT). The corresponding LOAEL is not established. This study is classified as Acceptable/Non-Guideline.

Reproduction Studies - Mice

In a two-generation reproduction study (Lamb et al , 1985 and Morrissey et al., 1989, as cited in NTP, 2004) COBS Crl:CD-1 (ICR) BR outbred albino mice (20/sex/treatment; 40/sex for controls) were administered with ethylene glycol (99.6%) in drinking water at concentrations of 0, 0.25, 0.5, and 1.0% (w/v). The calculated doses by the study authors were 0, 410, 840 and 1640 mg/kg/day, respectively. Animals had exposure during one-week pre-mating period, a 14-week cohabitation period, a 3-week segregation period, and at least until weaning of the offspring born during the 3-week segregation period. Selected F1 offspring from control and the HDT (20/sex/group) were mated again within the groups for F2 generation. Results from F0 mice indicate no treatment-related effects on body weight, clinical signs, or water consumption at any dose level. There was a slight but statistically significant ($p<0.01$) decrease in number of litters per fertile F0 pair, mean number of F1 live pups/litter ($p<0.05$), mean live pup weight ($p<0.01$) compared to controls in the HDT. In the F1 generation, there were no significant differences in fertility, live litter size, or live pup weight between control and HDT. A number of F1 animals at the HDT had unusual facial features. Skeletal examination in the control and the HDT revealed defects in the skull, sternebrae, ribs and vertebrae in both sexes of the HDT.

Based on the available evidence, the systemic NOAEL is determined as 1640 mg/kg/day (HDT). Systemic LOAEL is not determined. The reproductive LOAEL is determined as 1640 mg/kg/day based on decrease in number of litters per fertile F0 pair and the reproductive NOAEL is 840 mg/kg/day. The offspring LOAEL is determined as 1640 mg/kg/day based on decrease in mean number of F1 pups/litter, mean F1 pup weight and the skeletal effects in F1 pups. The offspring NOAEL is 840 mg/kg/day. Note: This study is limited by lack of histopathological effects either in kidney (target organ) or reproductive organs for F0 or F1 parents. Also data on estrous cycle or sperm measurements were not reported This study is classified as Acceptable/Non-Guideline.

In a two-generation reproduction study (Gulati et al., 1986, as cited in NTP, 2004) COBS Crl:CD-1 (ICR) BR outbred albino mice (20/sex/treatment; 40/sex for controls) were administered with ethylene glycol (99.6%) in drinking water at concentrations of 0, 0.5, 1.0, and 1.5% (w/v). The calculated doses by the study authors were 0, 897, 1798 and 2826 mg/kg/day,

respectively. Animals had exposure during one week pre-mating period, a 14-week cohabitation period, a 3-week segregation period. When F1 litters were weaned, a crossover mating trial was conducted in F0 mice between controls and the HDT (20/sex/group) to determine one or both sexes were affected. Selected F1 offspring from control and the HDT were mated within groups for F2 generation (20/sex/group). The significant systemic effects reported were decreased body weight in F0 males, and absolute liver weights in F0 and F1 parent males at the HDT. Fertility index did not differ between controls and treatment. No treatment related effects on estrous cyclicity was noted. At the HDT, the incidence of abnormal sperm increased in F0 males and motility decreased in F0 and F1 males. The percent sperm motility was also affected mid dose F1 males. The sperm counts were decreased in F1 males at all treatments. The percent sperm motility and incidence of abnormal sperm in low and mid dose F0 males were not determined. The testes, and seminal vescicles weights in F1 males were reduced in all F1 dose males compared to controls. Histopathological examinations of the male reproductive organs in the HDT indicated degeneration of seminiferous tubules, interstitial cell hyperplasia and epididymal lesions in F0 and F1 males of the HDT as compared to controls. Kidney lesions and oxalate crystals were observed in F0 animals but not in F1 animals of the HDT . There were no treatment-related effects on histological findings of ovary, uterus or vagina in either generation. Histopathological effects in low and mid dose for both generations were not examined.

Pup weight adjusted to litter size was significantly reduced at all doses in both F1 and F2 pups. There was a significant decrease in the number of F1 live pups/litter (pup viability) in the HDT. The cross-over mating study indicated that there was no reduction in fertility in the HDT males or females. The only significant effect in the cross-over study was reduced F1 pup weight adjusted to litter size when females were mated with control males. The systemic NOAEL/LOAEL could not be determined due to limited findings reported in low and mid dose F0 parents (i.e., no data on body weight and organ weights for low and mid dose groups in F0 generation). The reproductive LOAEL is determined as 897 mg/kg/day based on decrease in sperm counts, testes and seminal vesicle weights in F1 males. There is no reproductive NOAEL. The offspring LOAEL is determined as 897 mg/kg/day (LDT) based on decrease in F1 and F2 pup weights. There is no offspring NOAEL. This study is classified as Acceptable/Non-Guideline.

4.2.4 Pre-and/or Postnatal Toxicity

4.2.4.1 Ethylene Oxide

Determination of Susceptibility

There is no quantitative susceptibility in fetuses from the rat developmental toxicity study (MRID 42797702) conducted with ethylene oxide. The developmental and the maternal LOAELs are identified at the same dose level (125 ppm). The maternal NOAEL was based on the decrease in body weight gain and the developmental NOAEL was based on decreased fetal weight and skeletal variations. There is evidence of qualitative susceptibility in the rat developmental study due to skeletal variations in rat fetuses (i.e., delayed ossification of phalanges, metatarsals, meta carpals and sternebrae #4-6).

Based on the findings from rat two-generation reproduction study (MRID 42788101), no quantitative susceptibility was evident for pups since the systemic and offspring LOAELs are identified at the same dose level (33 ppm) for the respective body weight effects. However, there is an evidence of qualitative susceptibility in fetuses based on the reproductive LOAEL of 33 ppm for post implantation losses.

Degree of Concern Analysis and Residual Uncertainties for Pre- and/or Post-natal Susceptibility

There is no evidence of increased (quantitative) susceptibility following in utero exposures in rats or after post-natal exposure in the two-generation reproduction study in rats. There is evidence for increased qualitative susceptibility based on delayed ossification in the fetuses in rat developmental study and post implantation loss observed in two-generation reproduction study in rats. There is low concern for the delayed ossification, since the delays were seen in the presence of significant decreases in maternal body weights at the dose that caused the delayed ossification. Also, the post implantation loss is attributed to both maternal and developmental toxic effects. There are no residual uncertainties for pre and/or post-natal toxicity. Based on the available data, there is no need for a Special FQPA Safety Factor (i.e., 1X) for pre and/or post-natal toxicity. Although there is no acceptable rabbit developmental toxicity study submitted for ethylene oxide, the preliminary evidence suggests that no developmental effects were seen up to 150 ppm in rabbit fetuses. Based on the available data, rodents appear to be more sensitive for developmental effects compared to rabbits. Therefore, the dose selected for risk assessment is conservative and protective of effects for children.

4.2.4.2 Ethylene Chlorohydrin

Determination of Susceptibility

Based on the developmental mice study which had ethylene chlorohydrin administered by gavage (Courtney et al. 1982), there is no evidence of quantitative susceptibility for the fetuses. However, there is an indication of qualitative susceptibility based on the presence of increased incidence for 14th rib at 100 mg/kg/day at which dose decrease in maternal body weight was observed. In another developmental study in which ethylene chlorohydrin was administered via drinking water (Courtney et al., 1982), there is no quantitative or qualitative susceptibility up to the doses tested (16-227 mg/kg/day).

Degree of Concern Analysis and Residual Uncertainties for Pre- and or Post-natal Susceptibility

Evidence for qualitative susceptibility manifested as increased incidence of 14th rib in the fetuses of mice. The concern is low for this effect since the increase was seen at the same dose that caused severe maternal toxicity (61% decrease in maternal body weight). Since the toxicology database is incomplete, a 10X database uncertainty factor (UF_{DB}) is applied for risk assessment. The UF_{DB} will address the concerns for residual uncertainties for the incomplete database therefore, the Special FQPA Safety Factor is not needed (i.e., 1X) for pre and/or post natal toxicity.

4.2.4.3 Ethylene Glycol

Determination of Susceptibility

Based on the recent rat developmental toxicity studies using ethylene glycol by gavage (Neeper Bradley et al., 1990 & 1995; Price et al . 1985 as cited in NTP-CERHR, 2004), there is no quantitative susceptibility in rat fetuses as the respective maternal and developmental LOAELs are identical. However, qualitative susceptibility was evident based on increased incidence of skeletal variations. In an another rat developmental study (Maronpot et al., 1983 as cited in NTP-CERHR, 2004), quantitative as well as qualitative susceptibility was evident in rat fetuses. In this study no maternal adverse effects were seen at 1000 mg/kg/day at which dose increased incidence of skeletal variations in rat fetuses was noticed. In three generation reproduction study (Depass, 1986 & Woodside et al 1974 as cited in NTP-CERHR, 2004), no fetal susceptibility (quantitative or qualitative) effects were seen.

Assessment of the maternal and fetal adverse effects reported in CD-1 mice developmental toxicity studies (Price et al., 1985; Neeper-Bradley et al., 1995 & Tyl and Frank, 1989 as reported in NTP-CERHR, 2004), indicate both quantitative and qualitative susceptibility for mouse fetuses. Fetal developmental effects, mostly skeletal variations were observed in mouse fetuses at doses, which produced no significant maternal body weight effects. Similar susceptibility effects (quantitative and qualitative) were also seen in two generation reproduction study using CD-1 mice (Lamb et al., 1985 & Morrissey at al. 1989 as cited in NTP-CERHR, 2004).

No quantitative or qualitative susceptibility was evident in rabbit fetuses as the doses which produced significant effects (mortality and renal lesions) in maternal animals had no adverse effects in fetuses (Tyl et al. 1993 as cited in NTP-CERHR 2004).

Degree of Concern Analysis and Residual Uncertainties for Pre- and/or Post-natal Susceptibility

There is evidence of qualitative susceptibility following in utero exposures to rats and both qualitative and quantitative susceptibility in mice. Developmental effects often characterized as various types of skeletal variations and are not considered as major malformations. There is low concern for these effects since they occurred in at relatively high doses (500 to 1640 mg/kg/day). In the reproduction studies in mice and rats, offspring toxicity was seen in the presence of parental/systemic toxicity, again, at high doses. There are no residual uncertainties for pre and/or post-natal toxicity. Based on the available data, there is no need for a Special FQPA Safety Factor (i.e., 1X) for pre and/or post-natal toxicity.

4.2.5 Recommendation for a Developmental Neurotoxicity Study

4.2.5.1 Ethylene Oxide

Evidence that supports requiring a developmental neurotoxicity study is as follows. The neurotoxic effects for ethylene oxide such as alterations such as drooping eyelids, low arousal and no response to touch, ataxia, decreased hind-limb grip strength, landing foot splay and .

decreased motor activity are identified at doses above 200 ppm in neurotoxicity studies using rats (MRID 44359401; MRID 44256401; MRID 44256402). In one subchronic study using mice, ataxia and decreased motor activity were reported in females at 50 ppm Except for the mice study, the neurological effects occur at doses higher than that produce developmental toxic effects seen at 125 ppm in rat teratogenicity study or offspring toxicity seen at 33 ppm in 2-generation rat reproduction study.

Demyelination of sciatic nerve and axonal dystrophy have been reported in monkeys (n=2) treated with ethylene oxide for two years. These effects are from a small number of animals and are reported at 50 ppm.

Peripheral neuropathy, impaired hand-eye coordination and memory have been reported in workers exposed to ethylene oxide for longer periods. It is reported that these subjects were exposed transiently to very high ethylene concentrations (~700 ppm) .

Since ethylene oxide is not used for dietary risk assessment and the neurological effects occur at high doses in most of the studies and cancer effects are critical endpoint for ethylene oxide, developmental neurotoxicity study is not required for ethylene oxide.

4.2.5.2 Ethylene Chlorohydrin and Ethylene Glycol

Evidence that supports requiring a developmental neurotoxicity study for ethylene chlorohydrin is that the database is inadequate for waiving the developmental neurotoxicity study. The need for the developmental toxicity study would be determined pending the results of the studies listed in the Data Needs section.

There is no evidence that supports requiring a developmental neurotoxicity study for ethylene glycol from the available database.

4.2.6 Data Base Uncertainty Factors

The toxicology database of ethylene chlorohydrin is incomplete for assessing susceptibility to infants and children as required by FQPA. Therefore, 10X database uncertainty factor (UF_{DB}) is applied for risk assessment.

4.3 Special FQPA Safety Factor

Based on the discussion in Section 4.2.4, no Special FQPA Safety Factor (i.e., 1X) is required for any of the chemicals since there are no residual uncertainties for pre and/or post-natal toxicity. It is assumed that the exposure databases are complete and that risk assessment does not underestimate the potential risks for infants and children.

4.4 Hazard Identification and Toxicity Endpoint Selection

4.4.1 Ethylene Chlorohydrin

4.4.1.1 Acute Reference Dose (aRfD) - General Population

The acute RfD for the general population was selected from a developmental toxicity study in mice (Courtney et al. 1982). Pregnant CD-1 mice (10-12/group) were administered with ethylene chlorohydrin by gavage at concentrations of 0, 50, 100 or 150 mg/kg/day, using water as the vehicle, during gestation days 6-16, inclusive. The animals were sacrificed on GD17. At the HDT, 75% of the pregnant mice had mortality after 2-4 treatments and remaining 25% were not pregnant. There was a 61% decrease in the maternal weight gain at 100 mg/kg/day compared to controls (4.9±0.8 versus 1.9±0.6; $p<0.05$). The body weight gain was not affected at 50 mg/kg/day group. There appeared to be an increase in the number of implants per litter (10.1±1.0 versus 12.3 ±0.5; $p<0.05$) as well as the number of fetuses per litter (9.5±1.0 in controls versus 11.4 ±0.6; NS) at the MDT. But the fetal weight was decreased significantly in the MDT (1.03 ±0.04 versus 0.89 ±0.03g or 1.00 ±0.04 versus 0.88 ±0.03g; $p<0.05$ in both batches). There was also a significant decrease in absolute as well as relative fetal weight at 100 mg/kg/day ($p<0.05$). The incidence of bilateral 14^{th} rib appeared to be higher in the fetuses of 100 mg/kg/day (2 versus 10 fetuses; the ratio not provided). However, the effects were not statistically significant.

Dose and Endpoint Selected for Establishing Acute RfD (Gen Population): For the Acute Reference Dose Derivation, LOAEL is determined as 150 mg/kg/day based on the poor survival and the lack of fertility effects. The NOAEL is 100 mg/kg/day. Note: This NOAEL/LOAEL is different from the study NOAEL/LOAEL of 50/100 mg/kg/day.

Uncertainty Factor (UF): 1000X (10X interspecies extrapolation, 10X intraspecies variation and 10X database uncertainty factor for the inadequate toxicity database).

Comments about Study/Endpoint/Uncertainty Factor: Although the study had a maternal NOAEL of 50 mg/kg/day based on decreased body weight gain during the whole gestation period at 100 mg/kg/day, it is difficult to ascertain that the effects are attributed from a single dose. The 61% decrease in body weight gain at 100 mg/kg/day was reported at GD17 after several 11 days of treatment during gestation. Since the survival was very poor (75% mortality compared to controls) at 150 mg/kg/day after 2-4 treatments i.e., after 2-4 days, and no maternal deaths occurred at lower doses, the next lower dose of 100 mg/kg/day was considered appropriate for acute reference dose derivation for all populations. Although the acute oral toxicity in mice (Lawrence et al., 1971a) report the LD_{50} of 81.4 mg/kg/day (95% C.L 66.4-99.7 mg/kg/day), this dose was not considered for deriving acute reference dose derivation because the study selected is recent and the only adverse effects reported were decreased body weight gain at 100 mg/kg/day. Moreover, in another mice developmental study (Courtney et al., 1982) in which ethylene chlorohydrin was administered in drinking water, no adverse effects were reported up to 227 mg/kg/day (HDT).

Acute RfD (General Population) =	**100 mg/kg/day (NOAEL) / 1000 (UF)**	**= 0.1 mg/kg/day**

4.4.1.2 Chronic Reference Dose (aRfD) - All Populations

This endpoint was selected from a subchronic oral toxicity study in rats (Oser et al. 1975). Weanling albino rats (FDRL strain) (25/sex/group) were administered with ethylene chlorohydrin by gavage at concentrations of 0, 30, 45 or 67.5 mg/kg/day for 12 weeks. At weeks 6 and 12, hematological, and clinical parameters were measured. The rats were sacrificed at 12 weeks. Selected organs were weighed and histopathological examinations were made in control and high dose group and a few animals in the mid dose group. Many animals in the high dose group showed signs of labored breathing and became moribund during the first three weeks of the experiment. The survival rate for the HDT was 32% in males and 24% in females as compared to 100% in control males and 96% in control females. The body weight gain in high dose group was significantly lower in males (↓66%) and not affected in females. No alterations in the behavioral abnormalities or blood parameters were noted. Gross examinations at the high dose group of the animals that died during the first three weeks showed dark liver with alternate pale and granular areas, reddened gastro intestinal tissues, hemorrhagic adrenal and pituitary gland, and dark red lungs. The histopathological examinations of the moribund animals at the HDT showed a high incidence of sub acute myocarditis, in males and females, a few cases of colloid depletion in the thyroid (1 male and 4 females), fatty changes in the liver (1 male and 5 females), thyroid congestion (4 males), and a high incidence of congestive pulmonary changes in both sexes.

Based on the findings, the LOAEL is determined as 67.5 mg/kg/day based on decreased body weight gain and survival and gross and histopathological changes. The NOAEL is determined as 45 mg/kg/day.

Dose and Endpoint Selected for Establishing Chronic RfD (Gen Population) For the Chronic Reference Dose Derivation, NOAEL is determined as 45 mg/kg/day based on decreased body weight gain and survival and gross and histopathological changes at 67.5 mg/kg/day

Uncertainty Factor (UF): 1000X (10X interspecies extrapolation, 10X intraspecies variation and 10X database uncertainty factor for the inadequate toxicity database).

Comments about Study/Endpoint/Uncertainty Factor: Since there was no chronic oral toxicity study available, the end point selected from the subchronic toxicity study was used. Although the subchronic study using beagle dogs (also Oser et al., 1975) had lower NOAEL, this study was not preferred due to lack of dose response effects reported in the study. Severe emesis limited the maintenance of dose gradient for the dogs. The additional 3x factor to account for the subchronic effects to chronic effects was not considered since the 10x database uncertainty factor is considered protective of any cumulative toxic effects.

Chronic RfD (General Population) =	**45 mg/kg/day (NOAEL)** / **1000 (UF)**	**=**	**0.045 mg/kg/day**

4.4.2. Ethylene Glycol

4.4.2.1 Acute Reference Dose (cRfD) – All Populations

An appropriate endpoint attributable to a single dose was not available since effects were seen only at high doses (>1000 mg/kg/day) in oral studies including developmental toxicity studies. Therefore, an acute RfD was not established.

4.4.2.2 Chronic Reference Dose (cRfD) – All Populations

This endpoint was select from chronic combined carcinogenicity study (DePass et al., 1986b), Fischer 344 rats (30/sex/group) were administered ethylene glycol at 0, 40, 200, 1000 mg/kg/day in diet for 2 years. The doses were based on the preliminary studies that demonstrated mild renal toxicity in male rats treated for 40 days with a dose similar to the highest dose in this study. Interim sacrifices were made at 6, 12 and 18 months. The endpoints included survival, body weight, organ weight, clinical signs, necropsy, hematology, blood chemistry, and urinalysis. Histopathology was conducted in control and high dose animals only. Calcium oxalate crystals were noticed in urine of both sexes at doses ≥ 200 mg/kg/day. At the HDT, 100% mortality in males was reported by 12 months possibly linked to calcium oxalate mediated nephrosis. The HDT males had decreased body weight gain, increased water intake, blood urea nitrogen, creatinine and neutrophil counts, and decreased erythrocytes count, hematocrit, and hemoglobin levels, and increased urinary volume, and decreased specific gravity and pH. The authors did not consider the changes in hematology and clinical parameters significant in high dose females. Increased kidney weights and calcium oxalate crystals were present in male and female rats of the high dose group. In addition, uric acid crystals in urine were observed in 1000 mg/kg/day females following 18-24 months of treatment. Females in 200 and 100 mg/kg/day groups had fatty changes in liver that reached statistical significance at 1000 mg/kg/day. Significant histopathological changes in 1000 mg/kg/day males include tubular dilation, peritubular nephritis, parathyroid hyperplasia, and generalized soft tissue mineralization. No tumor effects were reported. Since kidney is the target organ and ethylene glycol mediates kidney effects through the metabolites, the presence of oxalate crystals in urine at 200 mg/kg/day is considered as the adverse effect The NOAEL is determined as 40 mg/kg/day. The LOAEL is determined as 200 mg/kg/day based on the presence of calcium oxalate crystals in urine of both sexes and possibly increased fatty changes in liver in females.

Dose and Endpoint Selected for Establishing Chronic RfD (Gen Population) The NOAEL of 40 mg/kg/day based on the increased oxalate excretion in urine of both sexes and mild fatty changes in liver of females at 200 mg/kg/day.

Uncertainty Factor (UF): 100X (10X interspecies extrapolation, 10X intraspecies variation)

Comments about Study/Endpoint/Uncertainty Factor: The study selected is considered appropriate for the route of exposure and duration under consideration. Similar kidney effects were also reported at similar dose level (250 mg/kg/day) in another chronic study (Blood, 1965) and in a subchronic oral toxicity study (Gaunt et al , 1974). The subchronic study was not selected due to inadequate test duration. Although, the NOAEL in the alternate chronic study is higher (100 mg/kg/day), this study was not selected because of a lesser confidence in the number of animals tested and fewer effects measured as compared to the study under consideration.

Chronic RfD (General Population) = $\frac{\text{40 mg/kg/day (NOAEL)}}{\text{100 (UF)}}$ = 0.4 mg/kg/day

4.4.3 Ethylene Oxide

4.4.3.1 Acute Reference Dose (cRfD) – All Populations

The Risk Assessment Team of RRB4 determined the potential exposure from dietary exposure is minimal for the parent compound which exists as a gas Therefore, an acute RfD was not derived for ethylene oxide.

4.4.3.2 Chronic Reference Dose (cRfD) – All Populations

The Risk Assessment Team of RRB4 determined the potential exposure from dietary exposure is minimal for the parent compound, which exists as a gas. Therefore, a chronic RfD was not derived for ethylene oxide.

4.4.3.3 Incidental Oral Exposure (Short-Term, 1-30 days and Intermediate -Term, 1-6 months)

There are no residential uses for ethylene oxide. Therefore, endpoints for incidental oral exposure for the ethylene oxide and/or its reaction products are not derived.

4.4.3.4 Dermal Absorption

Studies on dermal absorption are not identified as the Risk Assessment Team of RRB4 considered the exposure from dermal route to be minimal for ethylene oxide and/or its reaction products

4.4.3.5 Dermal Exposure Short-Term (1-30 days) and Intermediate-Term (1-6 months), Long -Term (>6 months)

The Risk Assessment Team of RRB4 did not consider the exposure for ethylene oxide from dermal exposure significant. Therefore, the endpoints for dermal exposures of different durations were not derived.

4.4.3.6 Inhalation Exposure Short Term (1-30 days) and Intermediate Term (1-6 months)

The inhalation endpoint was selected from subchronic inhalation toxicity in mice (Snellings et al.1984a). B6C3F1mice (30/sex/treatment) were exposed to concentrations of 0, 10, 50, 100 or 250 ppm ethylene oxide for 6h/day, 5d/week for 10 weeks in males and 11 weeks in females. Survival and body weight gain were not affected by the treatment. A dose response effect was observed for neurological effects (altered gait, decreased locomotor activity) and the results were significant at ≥ 50 ppm. Abnormal righting reflex was observed in mice exposed to ≥ 100 ppm. Reduced or absent toe and tail pinch reflexes were observed in mice exposed to 250 ppm. Red blood cell count, hematocrit and hemoglobin concentrations were significantly reduced at the highest concentration. Spleen weights were decreased significantly at ≥ 100 ppm females and 250 ppm males. A significant increase in relative liver weight was noted in 250 ppm females. Male mice had a significant decrease in body weight at 10, 50 and 250 ppm (not at 100 ppm, so no dose response observed for body weight) and a significant decrease in absolute testes weight at ≥ 50 ppm.

Based on neurological effects (altered gait, decreased locomotor activity) and testes weight changes, the LOAEL is identified as 50 ppm. NOAEL is determined as 10 ppm.

Dose and Endpoint Selected: The NOAEL of 7.5 ppm to reflect occupational exposure scenario. Note this is the derived NOAEL and is different from the study NOAEL. Refer to the Comments Section below. The study NOAEL is 10 ppm based on the neurological effects and organ weight changes observed at 50 ppm.

Comments about Study/Endpoint: The study selected is appropriate for the route of exposure and duration. The mice study NOAEL of 10 ppm is converted to 7.5 ppm to reflect the occupational scenario. i.e., the NOAEL of 7.5 ppm was derived after adjusting the 6 hour exposure in the animal study to 8 hours of typical workers (10 ppm x (6h/8h) = 7.5 ppm)

4.4.3.7 Inhalation Long Term (>6 months)

The long term inhalation endpoint was selected from a two generation reproduction study in rats (MRID 42788101). 28 CD rats per sex per group were exposed (whole body) by inhalation to ethylene oxide at concentrations of 0, 10, 33 or 100 ppm for 6 hours /day (5 days/week) during pre-mating and 7 days/week during mating, on gestational days (GDs) 0-20, and on lactational days (LDs 5-28).

Significant decrease in mean body weight gains were noticed at 33 and 100 ppm in F0 males and females and F1 males during premating ($p \leq 0.05$ or $p \leq 0.01$). In addition, decrease in bodyweights were observed in F0 and F1 females during gestation ($p \leq 0.01$) and F1 females alone during early lactation ($p \leq 0.05$ or $p \leq 0.01$) at 100 ppm. Significant decrease ($p \leq 0.01$) in food consumption in lactating F0 and F1 females were observed at 100 ppm.

The systemic LOAEL is determined as 33 ppm based on decreased mean body weight gains in F0 males and females and F1 males during premating period. The NOAEL is established as 10 ppm.

Reproductive toxicity was observed at 33 and 100 ppm. It was manifested as a decreased number of live pups per litter in both generations ($p \leq 0.01$) due to significantly increased postimplantation loss at 33 ppm (two-fold increase) and 100 ppm (six-fold increase) in F1 offspring and at 100 ppm in F2 offspring (four-fold increase). In addition at 33 and 100 ppm, mean pup body weight gains were decreased significantly ($p \leq 0.05$ or $p \leq 0.01$) in both F1 and F2 generations during the latter part of lactation, i.e., LD 21.

Based on increased postimplantation loss (two-fold) and decreased live pups per litter in F0 generation, the reproductive NOAEL and LOAEL were determined as 10 and 33 ppm, respectively. Based on decreased mean pup body weight gain in both generations, the offspring NOAEL and LOAEL were determined as 10 and 33 ppm, respectively. This study is classified Acceptable and meets the requirement set forth under Guideline series 83-4 for a two-generation reproductive toxicity study in rats.

Dose and Endpoint Selected: The NOAEL of 7.5 ppm to reflect occupational exposure scenario. Note this is the derived NOAEL and is different from the study NOAEL. Refer to the Comments Section below. The study systemic NOAEL of 10 ppm is based on decreased mean body weight gains in F0 males and females and F1 males during premating period at the LOAEL of 33 ppm.

Comments about Study/Endpoint: The study selected is appropriate for the route of exposure and duration. The NOAEL selected is similar to the NOAEL (10 ppm) established in a carcinogenicity study in rats. Decreased body weight and survival effects were noted at 33 ppm (Snellings et al. 1984; Garman et al. 1985 and Garman and Snellings,1986). The NOAEL of 10 ppm is adjusted to occupational worker exposure scenarios. The two-generation reproduction study NOAEL of 10 ppm is converted to 7.5 ppm to reflect the occupational scenario. i.e., the NOAEL of 7.5 ppm was derived after adjusting the 6 hour exposure in the animal study to 8 hours (10 ppm x (6h/8h) = 7.5 ppm).

4.4.4 Margins of Exposure

A summary of target Margins of Exposure (MOEs) for risk assessment are provided in Table 9.

Table 9. Margins of Exposure

Route / Duration	Short-Term (1-30 days)	Intermediate-Term 1-6 months	Long-Term >6 months
Occupational Exposure			
Dermal	NA	NA	NA
Inhalation	30	30	30

The occupational MOE is based on the uncertainty factor of 30X (3x interspecies factor and 10x intraspecies factor). The traditional interspecies factor of 10X is reduced to 3X since the

doses are expressed as air concentrations and the pharmacokinetics is assumed similar between animals and humans. The interspecies factor of 3x is considered sufficient to account for only pharmacodynamic differences between animals and humans.

4.4.5. Recommendation for Aggregate Exposure Risk Assessments

As per FQPA, 1996, when there are potential residential exposures to the pesticide, aggregate risk assessment must consider exposures from three major sources: oral, dermal and inhalation exposures. The risk may not be aggregated for the ethylene oxide uses because exposures via the dietary (oral) route are to the reaction products ethylene chlorohydrin and ethylene glycol only, while worker and residential (non-dietary dermal and/or inhalation) exposures are to ethylene oxide only.

4.4.6 Classification of Carcinogenic Potential

4.4.6.1 Ethylene oxide

The overall evidence from human epidemiological studies and carcinogenicity studies in animals and mutagenicity and genotoxicty studies indicates the carcinogenic potential in humans exposed to ethylene oxide. However, the Agency has not yet assigned the classification of carcinogenicity for ethylene oxide.

Animal Studies

In a chronic inhalation toxicity study (Lynch et al., 1984a), male Fischer 344 rats (80/treatment) were exposed to 0, 50 or 100 ppm ethylene oxide for 7h/day, 5d/week for 104 weeks. Significantly decreased body weight gains were reported in both 50 and 100 ppm groups compared to controls ($p<0.05$). Mortality was increased in both dose groups but statistically significant in the high dose animals ($p<0.01$). No treatment related effects on hematological parameters were reported. Absolute weights of kidney and brain were reduced at 50 and 100 ppm groups compared to controls. But, the absolute as well as relative weights of adrenals to body weight were increased in both dose groups. Muscle atrophy was observed in animals exposed to 100 ppm. Inflammatory lesions of the respiratory tract (acute bronchopneumonia, focal chronic pneumonia and edema), degenerative lesions of the adrenal cortex (multifocal cortical hyperplasia and vacuolation) and increased extramedullary hematopoiesis of the spleen were apparent in both dose groups. An increase in the incidence of mononuclear cell leukemia of the spleen was observed in both treatment groups, but was statistically significant ($p<0.05$) only at 50 ppm. The incidences of brain tumors ($p<0.05$) and peritoneal mesotheliomas ($p<0.01$) were each statistically significant at 100 ppm. The reported incidences of tumors for control, 50 and 100 ppm are: 3/78, 9/79, 21/79 for peritoneal mesotheliomas, 0/76, 2/77, 5/79 for mixed cell gliomas of the brain and 24/77, 38/79, 30/76 for mononuclear cell leukemia. The results from this study are complicated by a bacterial infection in the animals that became apparent after the 8^{th} month. This study identifies a systemic LOAEL of 50 ppm based on decreased body weight gain, organ weights and non-neoplastic lesions in adrenal cortex , spleen and respiratory tract. The systemic NOAEL is not determined. This study is classified as Acceptable/Non-Guideline.

In a chronic inhalation carcinogenicity study (Snellings et al., 1984b; Garman and Snellings,1986 and Garman et al., 1985), Fischer 344 rats (120/sex) were exposed to 0 (two groups of controls), 10, 33 or 100 ppm ethylene oxide for 6h/day, 5d/week for up to 2 years. The only non-cancer effects reported were the body weight changes and mortality effects. An increase in mortality was reported in animals exposed to the highest concentration. Body weight gain was significantly reduced in animals exposed to 33 ppm (females) and 100 ppm (males and females). An increased incidence was noted for the mononuclear cell leukemia of the spleen (males and females), peritoneal mesotheliomas (males), brain gliomas, malignant reticuloses and granular cell tumors (males and females) and subcutaneous fibromas. The tumor incidence is provided in the Table 10.

Table 10: Tumor Incidence Data in Fischer 344 rats

Types of tumor	Tumor Incidence			
	0 ppm	10 ppm	33 ppm	100 ppm
Mononuclear cell leukemia (males)	13/97	9/51	12/39	9/30
Mononuclear cell leukemia (females)	11/116	11/54	14/48	15/26
Peritoneal mesothelioma (males)	2/97	2/51	4/39	4/30
#Brain tumors (males)	1/181	1/92	5/85	7/87
#Brain tumors (females)	1/188	1/94	3/92	4/80
Subcutaneous fibromas (males)	3/97	9/51	1/39	11/30

#Includes glioma, malignant reticuloses and granular cell tumors;

The results are complicated by an infection in the animals (sialodacryoadenitis virus) which became apparent during the 15th month. The systemic NOAEL in this study is 10 ppm and the systemic LOAEL is 33 ppm based on reduced body weight gain. This study is classified as Acceptable/Non-Guideline.

In a combined carcinogenicity study (NTP, 1987), B6C3F1 mice (50/sex) were exposed to 0, 50, or 100 ppm ethylene oxide for 6 h/day, 5d/week for 102 weeks. Survival and body weight gain were not affected by treatment. No-treatment related clinical signs or non-neoplastic lesions were reported. However, increased tumor incidence was noted in both dose groups. The reported respective cancer incidences for control, 50, 100 ppm are: 6/50, 10/50, 16/50 in males and 0/49, 1/48, 7/49 in females for alveolar/bronchiolar carcinoma, 1/43, 9/44, 8/42 in males, and 1/46, 6/46, 8/47 in females for harderian gland papillary cystadenoma, 9/49, 6/48, 22/49 in females for malignant lymphoma of hematopoietic system, 0/49, 1/47, 5/49 for uterine adenocarcinoma and 1/49, 8/48, 6/49 for mammary gland adenocarcinoma or adenosquamous carcinoma. The study identifies a systemic NOAEL of 100 ppm (HDT). The systemic LOAEL is not established. The study is classified as Acceptable-Non-Guideline.

Mutagenicity Studies

This report provides only brief summaries of the study conclusions on mutagenicity and genotoxicity of ethylene oxide. For detailed report on mutagenicity and genotoxicity studies of ethylene oxide, the reader is advised to refer to the open literature. Agency received one study on mouse dominant lethal assay (Generoso et al., 1986) for ethylene oxide.

Ethylene oxide has been shown mutagenic in a broad range of test systems including bacteria, fungi, higher plants, Drosophila, mammalian cells both *in vitro* and *in vivo* and in

humans. In fact, ethylene oxide is used as a positive control in several mutagenicity studies for other industrial chemicals.

Ethylene oxide induces point mutations in bacteria (e.g., Salmonella TA100, TA1535, Bacillus subtilis HA101 and TKJ 5211) without addition of exogeneous mammalian metabolic activation system. In fungi, ethylene oxide has been shown to increase ad+ revertants (Neurospora crassa) and induce forward mutations (Schizosaccharomyces pombe). Ethylene oxide is also an effective mutagen in higher plants (e.g., induction of chlorophyll gene mutations in rice and barley). Induction of sex-linked recessive lethal mutations has been demonstrated in Drosophila at doses of ethylene oxide below the LD_{50} levels.

The ability to cause gene mutations *in vitro* has been demonstrated in several studies for ethylene oxide. For example, a dose-dependent increase in mutation frequency was reported at concentrations not causing significant cytotoxicity in Chinese hamster ovary cells, with and without an exogenous metabolic activation system. In male Big Blue (*lacI* transgenic) B6C3F1 mice exposed to 0, 50, 100 or 200 ppm for 6h/day, 5d/week, for 4 weeks, the observed mean frequencies of mutation for *Hprt* locus in splenic T-lymphocytes were $2.2x10^{-6}$, $3.8x10^{-6}$, $6.8x10^{-6}$, and $14.1x10^{-6}$, respectively (Walker et al., 1997a, as cited in IPCS 2003).

Ethylene oxide induces chromosomal aberrations in mammalian cells (e.g., peripheral lymphocytes and bone marrow cells), increased sister-chromatid exchange in rats and rabbits and increased incidence for micronuclei in polychromatic erythrocytes in rats and mice. A dose-dependent increase in unscheduled DNA synthesis has been reported in germinal cells of male mice exposed to ethylene oxide. Ethylene oxide induced dominant lethal mutations in mice and rats and heritable translocations in mice. In one study submitted to the Agency (Generoso et al., 1986), dose dependent increase in dominant lethal mutations, with peak clastogenic activity occurring during the 4.5- to 7.5- day mating intervals following 6-hour exposures for 4 consecutive days to 300, 400 and 500 ppm ethylene oxide.

In human populations, ethylene oxide has been shown to cause chromosomal aberrations consistently in peripheral blood lymphocytes obtained from workers exposed to ethylene oxide at $\geq$ 5 ppm, the effects observed below 5 ppm can be equivocal. At similar doses ($\geq$ 5 ppm), increases in the frequencies of sister chromatid exchanges in peripheral blood lymphocytes have been reported (IPCS, 2003).

Based on the information gathered from several studies, there is an overwhelming evidence that ethylene oxide is a direct acting mutagen and a genotoxic compound and is capable of causing heritable mutations in man.

Human Studies

There are several epidemiological studies reported in the literature investigating the relationship between exposure to ethylene oxide and cancer effects. The summaries of the studies in humans can be found in Section 5.0. The following two studies are recently published in the literature and provide evidence of a positive trend for cancers in males and females and are being considered by ORD for the derivation of cancer slope factors.

Breast cancer incidence was studied in a cohort of 7576 women employed for at least one year in commercial sterilization facilities from 1940s to the 1980s (Steenland et al., 2003). The average duration of exposure was 10.7 years and 18% of the entire cohort (1327) had died. Of the entire cohort, 319 had breast cancer which was ascertained via interview, death certificates, cancer registries, and medical records. Interviews were obtained for 68% of the cohort (5139 women). The standardized incidence ratio (SIR) for incident breast cancer in the whole cohort using external referent rate, SEER (Surveillance, Epidemiology and End Results) was 0.87 with 95% C.I. of 0.77-0.97. Trend analysis in SIRs, using Poisson regression was positive with increasing exposure (p=0.002) and the SIR for those in the top quintile of cumulative exposure with a 15-year lag (>14620 ppm-days) was 1.27 (0.94-1.69) and that for the referent group (0 ppm-day, lagged out) was 0.88 (0.67-1.04). In internal nested case control analyses of those with interviews, thus allowing a complete cancer ascertainment in those subjects, controlling for reproductive risk factors, a positive exposure response was found with the log of cumulative exposures, determined with a 15-year lag (p=0.03) The odds ratios with 15 year lag for cumulative exposure categories, 0 (lagged out), <647, 647-2026, 2026-4919, 4919-14620, >14620 ppm-days were 1.00, 1.06, 0.99, 1.24, 1.42, and 1.87, respectively. In summary, the authors reported an increased risk for breast cancer in workers exposed to ethylene oxide when cumulative exposures are considered.

Mortality analysis was conducted in a 1998 follow-up study of a large cohort of 18235 men and women exposed to ethylene oxide (Steenland et al., 2004). There were 2852 deaths, compared with 1177 in the earlier 1987 follow up. The mortality analysis of the overall cohort indicates no excess risk for hematopoietic cancers combined or of non-Hodgkin's lymphoma. However, internal exposure response analyses conducted using a 15 year lag found positive trends for hematopoietic cancers in males (p=0.02). The odds ratios with 15 year lag for hematopoietic cancer mortality in males were 1.00, 1.23, 2.52, 3.13, and 3.42 for 0 (lagged out), >0-1199, 1200-3679, 3680-13499, >13500 ppm-days, respectively. The trend in hematopoietic cancer was driven by lymphoid tumors (non-Hodgkin's lymphoma, myeloma, lymphocytic leukemia), which also have a positive trend (p= 0.02) with log cumulative exposure for males with a 15 year lag. The odds ratios with 15 year lag for lymphoid cancer mortality in males were 1.00, 0.90, 2.89, 2.74, and 3.76 for 0 (lagged out), >0-1199, 1200-3679, 3680-13499, >13500 ppm-days, respectively. Hematopoietic cancer trends were somewhat weaker in this analysis than trends in the earlier follow-up, and analyses restricted to the post 1987 data did not show any significant positive trends. Although there is no excess overall risk for breast cancer, internal exposure analyses found positive trend for breast cancer using the log of cumulative exposures with a 20 year lag (p=0.01). The odds ratios with 20 year lag for breast cancer mortality correspond to 1.00, 1.76, 1.77, 1.97, and 3.13 for cumulative exposure categories, 0 (lagged out), >0-646, 647-2779, 2780-12321, >12322 ppm-days, respectively. In summary, there is no increased mortality in workers exposed to ethylene oxide from any cancer (except bone cancer from a very small number of subjects). However, there is an association between ethylene oxide exposure and increased risk for hematopoietic cancers in males and breast cancers in females when cumulative exposures were considered.

4.4.6.2 Ethylene Chlorohydrin

Evidence suggests that ethylene chlorohydrin is a weak base pair substitution mutagen in bacteria and the mutagenicity was enhanced in the presence of rat liver S9 extract. Ethylene chlorohydrin tested negative in the mutagenicity tests using mammalian cell cultures (*in vitro*) or rodents (*in vivo*). However, in one test, ethylene chlorohydrin induces DNA repair in human fibroblasts *in vitro*. Ethylene chlorohydrin tested negative for dominant-lethal mutations or heritable translocations in the mouse (NTP, 1985).

There are no chronic combined carcinogenicity studies available in rodents via oral route of exposure. Two chronic studies identified in the literature for rats and mice receiving ethylene chlorohydrin are via the dermal route No evidence of carcinogenicity was found in both the dermal studies. Limited epidemiological studies in male workers exposed to ethylene chlorohydrin provided inconsistent results on increased risk for hematopoietic or lymphopoietic or pancreatic cancers (Olsen et al., 1997 and Benson and Teta, 1993).

4.4.6.3 Ethylene Glycol

In a chronic combined carcinogenicity study (Blood, 1965), Sprague-Dawley rats (16/sex/group) were fed diets containing 0, 0.1, 0.2, 0.5, 1.0 or 4.0% ethylene glycol for 2 years. Assuming the rat consumes food equivalent to 5% of its body weight/day, the estimated doses are 0, 50, 100, 250, 500, 2000 mg/kg/day, respectively. No effects on organ weights or hematological parameters were reported. There was increased incidence of cytoplasmic crystal deposition in renal tubular epithelium at 250 and 500 mg/kg/day groups. Increased mortality, decreased growth, increased water consumption, proteinuria and renal calculi at 500 mg/kg/day males and 2000 mg/kg/day males and females were observed. No tumor effects were reported. The NOAEL is determined as 100 mg/kg/day and LOAEL is determined as 250 mg/kg/day based on increased incidence of cytoplasmic crystal deposition in renal tubular epithelium.

This endpoint was select from chronic combined carcinogenicity study (DePass et al., 1986b), Fischer 344 rats (30/sex/group) were administered ethylene glycol at 0, 40, 200, 1000 mg/kg/day in diet for 2 years. The doses were based on the preliminary studies that demonstrated mild renal toxicity in male rats treated for 40 days with a dose similar to the highest dose in this study. Interim sacrifices were made at 6, 12 and 18 months. The endpoints included survival, body weight, organ weight, clinical signs, necropsy, hematology, blood chemistry, and urinalysis. Histopathology was conducted in control and high dose animals only. Calcium oxalate crystals were noticed in urine of both sexes at doses $\geq$ 200 mg/kg/day. At the HDT, 100% mortality in males was reported by 12 months possibly linked to calcium oxalate mediated nephrosis. The HDT males had decreased body weight gain, increased water intake, blood urea nitrogen, creatinine and neutrophil counts, and decreased erythrocytes count, hematocrit, and hemoglobin levels, and increased urinary volume, and decreased specific gravity and pH. The authors did not consider the changes in hematology and clinical parameters significant in high dose females. Increased kidney weights and calcium oxalate crystals were present in male and female rats of the high dose group. In addition, uric acid crystals in urine were observed in 1000 mg/kg/day females following 18-24 months of treatment. Females in 200 and 100 mg/kg/day groups had fatty changes in liver that reached statistical significance at 1000

mg/kg/day. Significant histopathological changes in 1000 mg/kg/day males include tubular dilation, peritubular nephritis, parathyroid hyperplasia, and generalized soft tissue mineralization. No tumor effects were reported. Since kidney is the target organ and ethylene glycol mediates kidney effects through the metabolites, the presence of oxalate crystals in urine at 200 mg/kg/day is considered as the adverse effect. The NOAEL is determined as 40 mg/kg/day. The LOAEL is determined as 200 mg/kg/day based on the presence of calcium oxalate crystals in urine of both sexes and possibly increased fatty changes in liver in females.

In a chronic carcinogenicity study (NTP, 1993 and IPCS, 2002), B6C3F1 mice were administered with ethylene glycol at 0, 1500, 3000, 6000 mg/kg/day in males and 0, 3000, 6000, 12000 mg/kg/day in females in diet for 2 years. The low dose females had arterial medial hyperplasia in lungs. Mid and high dose mice had transient kidney damage. High dose mice and mid dose males had hyalin degeneration in the liver. No evidence of carcinogenicity at the doses tested. The systemic NOAEL is not established and the LOAEL is identified as 1500 mg/kg/day based on arterial medial hyperplasia in lungs in females.

In a chronic combined carcinogenicity study (DePass et al., 1986b), CD-1 mice (30/sex/group) were administered with ethylene glycol in diet at 0, 40, 200, 1000 mg/kg/day in diet for 2 years. No adverse effects were reported. NOAEL is determined as 1000 mg/kg/day. The LOAEL is not established.

4.4.7 Summary of Endpoints Selected for Risk Assessment

Toxicological dose/endpoints selected for the ethylene oxide risk assessment are provided in Table 11.

Table 11. Summary of Toxicological Doses and Endpoints for Ethylene oxide and the Reaction Products (Ethylene Chlorohydrin and Ethylene Glycol) for Use in Human Risk Assessments

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Ethylene Chlorohydrin			
Acute Dietary (General populations)	Dose for Risk Assessment = **100** mg/kg/day UF = **1000** **Acute RfD** = **0.1** mg/kg/day	FQPA SF = **1X** **aPAD** = acute RfD / FQPA SF = **0.10** mg/kg/day	Developmental Toxicity Study – CD-1 Mice (Courtney et al., 1982) At 150 mg/kg/day, 75% mortality of maternal animals observed after 2-4 treatments (days) of dosing. Note: This study NOAEL/LOAEL is different from the study NOAEL/LOAEL.

Table 11. Summary of Toxicological Doses and Endpoints for Ethylene oxide and the Reaction Products (Ethylene Chlorohydrin and Ethylene Glycol) for Use in Human Risk Assessments

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Chronic Dietary (All populations)	NOAEL= **45** mg/kg/day UF = **1000** **Chronic RfD** = **0.045** mg/kg/day	FQPA SF = **1X** **cPAD** = chronic RfD / FQPA SF = **0.045** mg/kg/day	Subchronic Toxicity Study – Albino Rats (Courtney et al., 1982). LOAEL: 67.5 mg/kg/day Decreased mean body weight in males (↓34%), poor survival, i.e., 32% in males and 24% in females as compared to 100% in control males and 96% in control females, labored breathing and gross effects such as dark liver and lungs and hemorrhagic gastro intestinal tissues and adrenal and pituitary glands . Histopathological effects include subacute myocarditis, colloid depletion in thyroid, thyroid congestion, fatty liver and congestive pulmonary changes.
Ethylene Glycol			
Chronic Dietary (All populations)	NOAEL= **40** mg/kg/day UF = **100** **Chronic RfD = 0.4** mg/kg/day	FQPA SF = **1X** **cPAD** = chronic RfD / FQPA SF = **0.4** mg/kg/day	Chronic Oral Toxicity in Rats (DePass et al., 1986b). Increased oxalate crystals in urine of both sexes and possible fatty liver changes in females at 200 mg/kg/day. At THE HDT, 100% mortality by 12 months, decreased body weight, changes in clinical chemistry and hematological parameters, organ weight changes, and chronic nephritis in males and mild fatty changes in the liver of females.
Ethylene Oxide			
Inhalation Short-Term (1 - 30 days) and Intermediate-Term (1 – 6 months)	¶ NOAEL= **7.5 ppm (13.5 mg/m^3)** Inhalation Absorption Rate = N/A	**Residential MOE =N/A** **Occupational MOE = 30**	Subchronic Inhalation Toxicity Study in Mice (Snellings et al., 1984a) ¶ LOAEL = 37.5 ppm (68 mg/m^3) based on neurological effects (altered gait and decreased motor activity) and absolute and relative organ weight changes
Inhalation Long-Term (> 6 months)	¶ NOAEL= **7.5 ppm (13.5 mg/m^3)** Inhalation Absorption Rate = N/A	**Residential MOE =N/A** **Occupational MOE = 30**	Two Generation Reproduction Study, Inhalation Exposure, Rats (MRID 42788101) ¶ Systemic LOAEL = 25 ppm (45 mg/m^3) based on decreased mean body weight gains in F0 males and females and F1 males during premating period. ¶ Reproductive LOAEL = 25 ppm based on increased postimplantation loss (two-fold) and decreased live pups per litter in F0 generation were observed. ¶ Offspring LOAEL = 25 ppm based on decreased mean pup body weight gain in both F0 and F1 generations.
Cancer (Inhalation)	Positive evidence for carcinogenicity in animals and humans. Agency is currently determining the carcinogenicity classification of ethylene oxide. Unit Risk Factor (CDHS) based on mononuclear leukemia in female rats and analysis by linearized multistage model = 8.8×10^{-5} per µg/m3 or 0.16 per ppm		

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable
CDHS - California Department of Health Services;

¶Note: Study NOAEL and LOAEL are adjusted to human equivalent doses for occupational scenario only. e.g., animal NOAEL of 10 ppm (6h/day, 5d/week) is adjusted to human NOAEL of 7.5 ppm (8 h/day, 5d/week), assuming the regional gas dose ratio (RGDR) is similar between animals and humans (10 ppm x 6h/8h =7.5 ppm); In case of any continuous exposures (e.g. RfC), rat NOAEL of 10 ppm would be converted to human equivalent dose of 1.79 ppm [10 ppm x (6h/24h) x (5days in week/7days in week) =1.79 ppm] assuming similar RGDR between animals and humans (USEPA,1994).
* Refer to Section 4.3

4.5 Endocrine Disruption

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following recommendations of its Endocrine Disruptor and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

In the available toxicity studies on ethylene oxide, there was possible testicular toxic effects (altered sperm counts and motility) in chronic monkey toxicity study using very limited number of animals. When additional appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, ethylene oxide may be subjected to further screening and/or testing to better characterize effects related to endocrine disruption.

5.0 PUBLIC HEALTH DATA

There is considerable public health information available on ethylene oxide. HED relied upon a detailed review of available incident and epidemiological data for the ethylene oxide RED (J. Blondell, D313773, 3/9/05)

5.1 Incident Reports

The following data bases were consulted for poisoning incident data on the active ingredient ferbam; OPP Incident Data System (IDS), Poison Control Centers, California Department of Pesticide Regulation, National Pesticide Telecommunications Network (NPTN), and National Institute of Occupational Safety and Health's (NIOSH) Sentinel Event Notification System for Occupational Risks.

5.2 Epidemiological Data

There is considerable epidemiological literature involving cancer, neurological, and reproductive effects of poisoning for ethylene oxide. Rather than a cumbersome summary of every individual study, HED conducted a high quality review based on human studies published up to August 1999. This review "Concise International Chemical Assessment Document 54: Ethylene Oxide" was published by the World Health Organization in 2003. The main contributors concerning human effects were R. G. Liteplo and M.E. Meek from Health Canada. Earlier studies are covered when they have key pertinent data or where WHO conclusions about the significance of a study differ from this review. Also included in the HED review were any new studies published since August 1999. The review includes acute, cancer, neurological, and reproductive effects. No attempt was made to review all of the cytogenetic effects, which constitute a controversial health endpoint. However, such effects are mentioned in connection with the overall weight-of-evidence determination of ethylene oxide's potential as a carcinogen.

5.3 Conclusions

Ethylene oxide is an irritant to skin, eyes, and mucous membranes. Headache, eye irritation/pain, cough/choke, nausea, throat irritation, and dizziness are among the more common symptoms. Aqueous solutions can cause blistering of the skin. The area of skin may thereafter be sensitized to the fumigant. Inhalation of high concentration is likely to cause pulmonary edema and cardiac arrhythmias. Headache, nausea, vomiting, weakness, and a persistent cough are common early manifestations of acute poisoning. Dermatitis has been reported from exposure to airborne levels of ethylene oxide as well as direct contact to the skin from an aqueous solution. Dermal irritation and systemic effects (e.g., headache, nausea, dizziness) have also occurred as a result of handling contaminated materials (e.g., exposure to artificial lens implants) or from wearing contaminated clothing. Ethylene oxide can cause sensitization, which may be expressed as contact dermatitis or anaphylaxis. However, the anaphylactic reactions have been noted primarily in individuals undergoing dialysis with equipment that had been sterilized by ethylene oxide. Case reports of asthmatic reactions and lens opacities have been reported, associated with occupational exposure.

Three cohort studies have found evidence that exposure to ethylene oxide is a cause of hematopoietic cancers such as leukemia, non-Hodgkin's lymphoma and Hodgkin's disease. Based on earlier reviews by IARC and WHO, ethylene oxide had been classified as having sufficient evidence to be a human carcinogen or "highly likely" to be so. Based on more recent studies the it may be appropriate to downgrade ethylene oxide to a probable carcinogen in humans based upon the relatively low strength of association, inconsistency between males and females, some lack of replication in other studies, and limited evidence of dose-response based on a lag-time that is not biologically justified.

HED agrees with World Health Organization (2003) findings that "neurological effects (primarily sensorimotor polyneuropathy) have been observed in workers exposed to relatively high concentrations" which dissipate with cessation of exposure. Individuals exposed to greater than 1300 mg of ethylene oxide per cubic meter have shown axonal degeneration with mild

changes in the myelin sheath based on sural nerve biopsies. Central nervous system effects, such as seizures, have been observed following exposures around 1000 mg per cubic meter.

There has been suggestive evidence that ethylene oxide was a possible cause of spontaneous abortion based on three studies. Although the evidence was relatively weak in two of the studies which did not adjust for confounders and/or had borderline statistical significance. The evidence was much stronger in a study of Finnish sterilizing workers.

Ethylene oxide is a probable human carcinogen and can cause significant dermal and sensitizing effects from relatively low-level exposure to residue in clothing or on materials. Exposures should only be permitted in settings under strict supervision and very tight engineering and industrial hygiene controls to prevent any exposures.

6.0 DIETARY AND DRINKING WATER EXPOSURE ASSESSMENT

6.1 Residue Profile

Tolerances for residues of ethylene oxide in/on black walnuts, copra, and spices are currently established under 40 CFR §180.151. Registered food uses for ethylene oxide as cited on active labels include whole and ground spices and "other seasoning materials". The American Spice Trade Association (ASTA) defines spices any dried plant product used primarily for seasoning purposes. According to ASTA, this includes tropical aromatics (pepper, cinnamon, cloves, etc.), leafy herbs (basil, oregano, marjoram, etc.), spice seeds (sesame, poppy, mustard, etc.), dehydrated vegetables (onions, garlic, etc.), and blends such as curry, chili powders, poultry seasoning, etc.

The existing 50 ppm ethylene oxide tolerance should be revised to include the commodities spices, herbs, and dried vegetables. The existing 50 ppm tolerance level for ethylene oxide is adequate for all treated commodities. However, additional separate ethylene oxide tolerances are required for treated items such as dried onion, dried garlic, and dehydrated vegetables which are included in the "other crop groups" category as defined by the Agency. The existing tolerance should also be revised to include and the ethylene oxide reaction product, ethylene chlorohydrin. HED has determined that a 2000 ppm tolerance should be established for residues of ethylene chlorohydrin in/on dried spices and herbs (except basil). A 5000 ppm tolerance should be established for ethylene chlorohydrin in/on dried basil. Since residue data are not available for ethylene chlorohydrin residues in/on dried vegetables, tolerances for these residues could be based on the 5000 ppm basil tolerance. A tolerance in/on black walnut for ethylene chlorohydrin at the LOQ (<100 ppm) is optional. No tolerance is required for ethylene glycol because there is no acute toxicity endpoint, chronic dietary risks are well below HED's level of concern, and the tolerance established for ethylene chlorohydrin is adequate to cover potential residues of concern from ethylene oxide sterilization. (J. Stokes, D313744, 3/31/05)

Residues included in the dietary assessment for spices/herbs, dried vegetables and walnuts include the ethylene oxide reaction products ethylene chlorohydrin and ethylene glycol. These reaction products are considered residues of concern for dietary exposure based on sterilization study data that indicate persistent high levels of these residues after treatment.

While the tolerance for ethylene oxide is retained for regulatory compliance purposes, ethylene oxide is not considered a residue of concern for dietary exposure because spice sterilization study data indicate that ethylene oxide residues disappear rapidly after sterilization and are unlikely to be found in spices available for consumption. The spice sterilization study data also indicate that ethylene bromohydrin residues occur post treatment but are minimal relative to ethylene chlorohydrin residues. Therefore, ethylene bromohydrin is not considered a residue of concern for dietary exposure and is not assessed separately.

6.2 Magnitude of the Residue in Plants and Animals

Information on the magnitude of the residue is based primarily on a study entitled, "Persistence Study of Residues of Ethylene Oxide and Reaction Products in Spices and Black Walnuts", conducted by McCormick Technical Resource Center (1994). Study results showed that ethylene glycol and its reaction products ethylene chlorohydrin, ethylene bromohydrin, and ethylene glycol are found in treated commodities on treatment day 0. Levels of ethylene oxide, ethylene chlorohydrin, ethylene bromohydrin, and ethylene glycol are generally higher in ground herbs and spices than those in their whole form, with minor exceptions such as basil. The level of ethylene oxide in whole and ground spices and herbs drop off sharply within the first two weeks after treatment There is no consistent trend of decline of ethylene chlorohydrin from the initial levels among spices and herbs and these levels tend to stabilize after the first two weeks. Most of the treated herbs/ spices contain about 100 ppm or less ethylene bromohydrin throughout the analysis period, with the exception of whole and ground nutmeg which may contain up to 300 ppm ethylene bromohydrin at the 1 month interval. Levels of ethylene glycol in various treated spices and herbs appear to stabilize during the 2 week to 1 month period.

Higher levels of ethylene chlorohydrin, ethylene bromohydrin, and ethylene glycol in treated spices and herbs are to be expected since these three compounds are much less volatile and much less reactive than ethylene oxide. Levels of reaction products in treated spices and herbs obtained in this study are in accord with those high levels reported by spice companies in 1968 and FDA in 1983. The 1994 study corroborates results from previously conducted residue identification (using ^{14}C ethylene oxide) and equivalency studies (using cold ethylene oxide) in which high levels of ethylene oxide, ethylene chlorohydrin, ethylene bromohydrin, and ethylene glycol were found in herbs and spices under very similar treatment parameters.

6.3 Residue Analytical Method

In study entitled, "Analytical Method Validation Study for Determination of Residues in Spices and Black Walnuts: Ethylene Oxide, Ethylene Chlorohydrin, Ethylene Bromohydrin, and Ethylene Glycol" (1993) three separate methods were developed for the determination of residues of ethylene oxide, ethylene chlorohydrin/ethylene bromohydrin, and ethylene glycol: Method No. RA 10.2, "Determination of Ethylene Oxide Residues in Spices by Headspace Gas Chromatography"; Method No. RA 12.1, "Determination of 2-Chloroethanol and 2-Bromoethanol Residues in Spices and Related Products"; and Method No. RA 24.0, "Determination of Ethylene Glycol Residues in Spices and Related Products".

A method validation study was conducted to demonstrate the reliability of these methods for measuring these residues in spices and walnuts. The registrant defined the limit of quantitation (LOQ) of the analytical method of each analyte as the lowest fortification level which yielded reproducible mean recoveries in the range of 60-120% for ethylene oxide, 70-120% for ethylene chlorohydrin and ethylene glycol, and 70-142% for ethylene bromohydrin. LOQ's were initially estimated based upon visual inspection of chromatograms of control versus fortified control samples. The overall recoveries for herbs, spices and black walnuts are considered acceptable in view of the numerous natural components present in herbs and spices. The methodologies are adequate for the current use. However the methods should be tested in the Agency laboratory. Multiresidue methods are needed for ethylene oxide, and ethylene chlorohydrin. The registrant should submit data on these methods.

Based on the post harvest use of ethylene oxide on spices and walnut, there are no expected residues in livestock commodities from their rations Therefore, an enforcement method is not required.

6.4 Acute and Chronic Dietary Exposure and Risk

Refined ethylene oxide acute and chronic dietary exposure assessments were conducted using two peer reviewed software models, the Lifeline™ Model (Version 2.0), and the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, Version 2.03). Both models incorporate consumption data from USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1994-1996 and 1998. The 1994-96, 98 data are based on the reported consumption of more than 20,000 individuals over two non-consecutive survey days.

The Lifeline™ and DEEM™ programs convert raw agricultural commodity (RAC) residues into residues in/on foods as eaten or consumed based on recipes of raw ingredients for each food item. Lifeline™ converts the RAC residues by randomly selecting a RAC residue value from the residue distribution and calculating a net residue for that food based on the ingredients' mass contribution to that food item. Lifeline™ models the individual's dietary exposures over a season by selecting a new CSFII diary each day from a set of similar individuals based on age and season attributes and grouping the dairies based on age and the season. This probabilistic methodology is used to estimate both acute and chronic dietary exposures in Lifeline™.

In DEEM™, consumption data are averaged for the entire U.S. population and within population subgroups for chronic exposure assessment, but are retained as individual consumption events for acute exposure assessment. DEEM™ estimates chronic dietary exposure by estimating the residue level in each treated food/food form, multiplying that estimate by the average daily consumption estimate for that food/food form, and summing residue intake estimates for all food/food forms to arrive at a total average estimated exposure. For acute exposures, DEEM™ uses individual on-day food consumption data on an individual by individual basis. The reported consumption amounts of each food item are matched in multiple random pairings with reside values and them summed in a probabilistic acute dietary exposure assessment.

Data from the 1994 ethylene oxide sterilization study was used to estimate residues of ethylene oxide and its reaction products in spices, herbs, walnuts, and dried vegetables (J. Stokes, D313774, 3/31/05). Spice, herb, and walnut commodities were treated with ethylene oxide in commercial treatment chambers under representative sterilization conditions and subsequently stored under typical conditions representative of actual handling practices in the spice and black walnut industries. Twenty-nine whole and ground spices and herbs were evaluated to represent three major categories of leaves, seeds and classical spices. Six whole and ground spices were also evaluated for residues resulting from repeated (two) treatments with ethylene oxide as representatives of the leaf, seed and classical spice categories. Three commercial sizes of black walnuts were evaluated. Spices were analyzed immediately after the first and second ethylene oxide treatments at post-treatment sampling intervals of zero days, three days, seven days, one week, two weeks, one month, two months and subsequent two month intervals until two consecutive values for ethylene oxide were below the LOQ of the analytical method (which typically occurred at four to six months). Based on information provided by ASTA indicating that the shortest interval between ethylene oxide treatment and the availability of spices for consumption is approximately two months, only residue data measured at 2 to 6 month intervals were used to assess dietary exposures. Because HED has no specific information on the extent to which commodities require multiple treatments with ethylene oxide, dietary exposures have been assessed separately for singly and doubly treated spices/herbs using the residue data provided in the spice sterilization study.

Refined acute and chronic dietary exposure assessments were conducted for all supported ethylene oxide food uses. Only the ethylene oxide reaction products ethylene chlorohydrin and ethylene glycol were included in the dietary assessment for ethylene oxide treated commodities for reasons explained above. Spices, herbs, and dried vegetables (garlic and onion) were treated as non-blended commodities for this assessment because sterilization occurs post-application and therefore blending of treated and non-treated spices, herbs, and dried vegetables is not likely to occur. Therefore, the entire distribution of residue data from the sterilization study was used for the DEEM and Lifeline acute assessments. Average residues were used for the chronic assessment. Percent crop sterilized data provide by BEAD was used for all commodities. The estimated maximum % crop sterilized with ethylene oxide was used for the acute analysis, when available. The estimated average % crop sterilized was used for the chronic analysis. No processing factors have been used because ethylene oxide spice sterilization is conducted post-processing. Available chemical specific data from a 1993 ^{14}C-ethylene cooking study conducted by Agrisearch Inc., were used for cooked commodities. A drinking water exposure assessment was not conducted for this assessment because the Environment Fate and Effects Division expects that uses of ethylene oxide for indoor food and nonfood uses will result in insignificant exposure to drinking water resources. (B. Daiss, D313777, 3/30/05)

6.4.1 Acute Dietary Risk Assessment

A refined probabilistic acute dietary exposure assessment was conducted for all supported ethylene oxide food uses. Dietary risk estimates are provided for the general U.S. population and all population subgroups. This assessment concludes that for all supported commodities, the acute dietary exposure estimates for ethylene chlorohydrin are above HED's level of concern. The DEEM and Lifeline model acute dietary exposure estimates for the highest

exposed population subgroup, children 1-2 years of age, are is 560% and 650% of the aPAD respectively for a single ethylene oxide treatment, and 740% and 820% respectively for commodities treated twice with ethylene oxide. Results of the DEEM and Lifeline chronic dietary exposure analyses are presented in Tables 12 and 13.

Table 12. Ethylene Chlorohydrin Acute Dietary Exposure Estimate – 1 Treatment

Population Subgroup	aPAD (mg/kg/day)	99.9%ile Exposure (mg/kg/day)		99.9%ile %aPAD	
		DEEM-FCID	Lifeline	DEEM-FCID	Lifeline
General U.S. Population	0.1	0.2161	0.2279	216	228
All Infants (< 1 year old)	0.1	0.3047	0.4821	304	482
Children 1-2 years old	0.1	0.5525	0.6497	563	650
Children 3-5 years old	0.1	0.4524	0.5420	452	542
Children 6-12 years old	0.1	0.2403	0.2403	240	240
Youth 13-19 years old	0.1	0.1356	0.1720	136	172
Adults 20-49 years old	0.1	0.1150	0.1320	115	132
Females 13-49 years old	0.1	0.1146	0.1573	115	157
Adults 50+ years old	0.1	0.0712	0.1229	71	123

Table 13. Ethylene Chlorohydrin Acute Dietary Exposure Estimate – 2 Treatment

Population Subgroup	cPAD (mg/kg/day)	99.9%ile Exposure (mg/kg/day)		99.9%ile %aPAD	
		DEEM-FCID	Lifeline	DEEM-FCID	Lifeline
General U.S. Population	0.1	0.2847	0.3048	285	305
All Infants (< 1 year old)	0.1	0.4031	0.4417	403	442
Children 1-2 years old	0.1	0.7412	0.8225	741	823
Children 3-5 years old	0.1	0.5905	0.7662	590	766
Children 6-12 years old	0.1	0.3195	0.3346	320	335
Youth 13-19 years old	0.1	0.1778	0.2225	178	223
Adults 20-49 years old	0.1	0.1430	0.1772	143	177
Females 13-49 years old	0.1	0.1462	0.2093	147	209
Adults 50+ years old	0.1	0.0901	0.1612	90	161

6.4.2 Chronic Dietary Risk Assessment

A refined chronic dietary exposure assessment was conducted for all supported ethylene oxide food uses for the general U.S. population and various population subgroups. This assessment concludes that for all supported commodities, the chronic dietary exposure estimates for both ethylene chlorohydrin and ethylene glycol are below HED's level of concern.

6.4.2.1 Ethylene Chlorohydrin

For ethylene chlorohydrin, the DEEM and Lifeline model chronic dietary exposure estimates for the highest exposed population subgroup, children 1-2 years of age, are both 38% of the cPAD for twice treated commodities. Results of the DEEM and Lifeline chronic dietary exposure analyses for ethylene chlorohydrin are presented in Table 14.

Table 14. Ethylene Chlorohydrin Chronic Dietary Exposure Estimate and Percent of Chronic RfD

Population Subgroup	cPAD (mg/kg/day)	Exposure (mg/kg/day)		%cPAD	
		DEEM-FCID	Lifeline	DEEM-FCID	Lifeline
General U.S. Population	0.045	0.0047	0.0047	10	10
All Infants (< 1 year old)	0.045	0.0031	0.0047	7	10
Children 1-2 years old	0.045	0.0170	0.0169	38	38
Children 3-5 years old	0.045	0.0125	0.0149	28	33
Children 6-12 years old	0.045	0.0072	0.0070	16	15
Youth 13-19 years old	0.045	0.0044	0.0049	10	11
Adults 20-49 years old	0.045	0.0038	0.0038	8	8
Females 13-49 years old	0.045	0.0036	0.0045	8	10
Adults 50+ years old	0.045	0.0024	0.0034	5	8

6.4.2.2 Ethylene Glycol

The results of both the DEEM and Lifeline chronic dietary exposure analyses for ethylene glycol are reported in the Table 15. These assessments conclude that for all supported commodities, the chronic dietary exposure estimates are below HED's level of concern. The DEEM and Lifeline chronic dietary exposure estimates for the highest exposed population subgroup, children 1-2 years of age, are 7% and 4% of the cPAD respectively.

Table 15. Ethylene Glycol Chronic Dietary Exposure Estimate and Percent of Chronic RfD

Population Subgroup	cPAD (mg/kg/day)	Exposure (mg/kg/day)		%cPAD	
		DEEM-FCID	Lifeline	DEEM-FCID	Lifeline
General U S Population	0.4	0.0081	0.0049	2	1
All Infants (< 1 year old)	0.4	0.0052	0.0043	1	1
Children 1-2 years old	0.4	0.0267	0.0171	7	4
Children 3-5 years old	0.4	0.0211	0.0137	5	3
Children 6-12 years old	0.4	0.0129	0.0073	3	2
Youth 13-19 years old	0.4	0.0083	0.0051	2	1
Adults 20-49 years old	0.4	0.0066	0.0040	2	1
Females 13-49 years old	0.4	0.0062	0.0047	2	1
Adults 50+ years old	0.4	0.0042	0.0037	1	1

6.5 Drinking Water Profile

EFED maintains that additional environmental fate and ecological effects data are not necessary for the reregistration of ethylene oxide. Should outdoor uses of ethylene oxide ever be considered for registration, then EFED will require the submission of relevant fate and effects data. Given the unlikelihood that drinking water resources will be exposed to ethylene oxide from the current use pattern, no drinking water assessment will be provided for the Health Effects Division's dietary risk assessment. (E. Odenkirchen, D279672, 12/12/01)

7.0 RESIDENTIAL EXPOSURE/RISK ASSESSMENT

There are no residential handler (applicator) uses for ethylene oxide. However, residential exposure can occur as a result of the use of ethylene oxide as a sterilant for musical wind instruments, and from ambient releases from commercial sterilization sources. Based on a qualitative screening-level risk assessment conducted by OPP's Antimicrobial Division, residues from the use of ethylene oxide for the sterilization of musical wind instrument are not likely to result in adverse health effects to musicians (D. Smegal, D309124, 2/15/05).

7.1 OAR Residual Risk Assessment

EPA's Office of Air and Radiation has conducted a residual risk assessment for the ethylene oxide commercial sterilization source category as part of its residual risk program. HED is using OAR's assessment to address risk for the residential ambient exposure scenario. The residual risk program assesses public health and environmental risk which may remain after implementation of certain air toxics regulations required under the Clean Air Act. The ethylene oxide commercial sterilization source category covers the use of ethylene oxide as a sterilant or fumigant. OAR's assessment covers both major and area sources, i.e., all ethylene oxide emission points were covered in the residual risk assessment. The assessment estimates cancer, and short and long term non-cancer risk to the general population from exposure to ambient concentrations of ethylene oxide.

Continuous emissions monitoring data are not available for these sources. Therefore, OAR estimated emissions using process knowledge of how much ethylene oxide goes through the main vent, rear chamber exhaust, and aeration room vent, and considering the respective Maximum Available Control Technology (MACT) requirements for these emission points. The detailed modeling and risk assessment methodology for OAR's assessment is provided in the document entitled, "Residual Risk Assessment for the Ethylene Oxide Commercial Sterilization Source Category" (Mark Morris, OAR, 2/25/05)

7.2 Toxicological Endpoints

Multiple acute benchmarks were used in the OAR assessment. For the long term non-cancer endpoint, OAR used an inhalation reference exposure level (REL) developed by California EPA. For the cancer assessment, a URF established by the California Department of Health Services (CDHS) was used. Table 16 presents cancer, and chronic and acute non-cancer endpoints used in the OAR assessment.

Table 16. Toxicity Endpoints used in OAR Ethylene Oxide Residual Risk assessment.						
Cancer	**Chronic**	**Acute**				
URE[a] (per $\mu g/m^3$)	RfC[b] ($\mu g/m^3$)	AEGL-2[c] ($\mu g/m^3$)	AEGL-3 ($\mu g/m^3$)	ERPG-2[d] ($\mu g/m^3$)	ERPG-3 ($\mu g/m^3$)	IDLH/10[e] ($\mu g/m^3$)
8.8 E-05[f]	30	81,000	360,000	90,000	900,000	140,000

[a]Unit risk estimate (URE): The upper_bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 $\mu g/m^3$ in air. The interpretation of unit risk would be as follows: if URE = 1.5 x 10_6 $\mu g/m^3$, up to 1.5 additional people are expected to develop cancer in their lifetime per 1 000 000 people exposed continuously for a lifetime to 1 μg of the chemical per m^3 of air.

[b]Rather than an EPA RfC, this value is a Reference Exposure Level (REL) developed by California EPA. Similar to EPA's RfC, the REL is defined by California EPA as "an airborne level that would pose no significant health risk to individuals exposed to that level for an indefinite period of time".

[c]Acute Exposure Guideline Level (AEGL). The AEGLs for a substance take the form of a matrix, with separate ambient levels above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects (AEGL-1), irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape(AEGL-2), and life-threatening health effects or death (AEGL-3).

[d]Emergency Response Planning Guideline (ERPG). The ERPGs represent concentrations for exposure of the general population for up to 1 hour associated with effects expected to be mild or transient (ERPG_1), irreversible or serious (ERPG_2), and potentially life_threatening or lethal (ERPG_3).

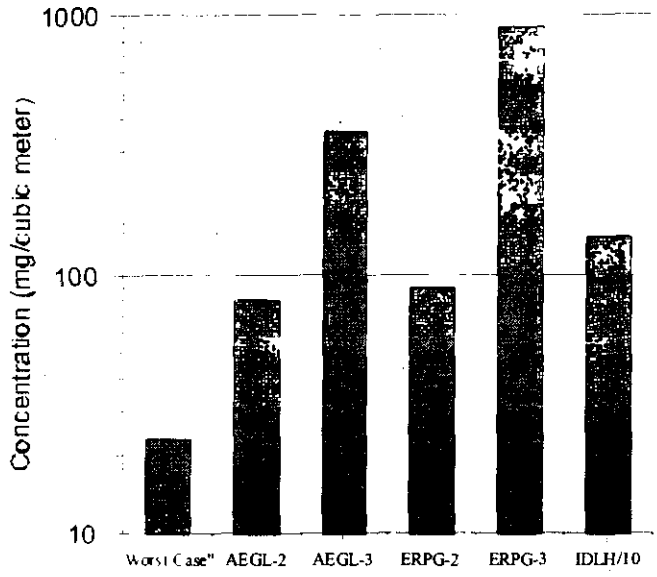
[e]IDLH: Immediately dangerous to life or health.

7.3 Acute Exposure/Risk Assessment

For the acute exposure assessment, OAR conducted a screening assessment of the potential for public health impacts associated with short-term emissions from ethylene oxide commercial sterilization sources. A hypothetical 1-hour exposure scenario was constructed from the available data. A screening Gaussian air dispersion model (SCREEN3) was used to predict maximum 1-hour concentrations from 100-5000 meters immediately downwind from a source. A relatively large degree of conservatism is incorporated in the modeling procedure to provide reasonable assurance that maximum concentrations will not be underestimated.

Results of the acute exposure assessment indicate that estimated acute exposures are not of concern as shown in figure 1. This figure illustrates the relationship of the "worst-case" 1-hour concentration estimate derived for this source category to the available acute reference values. As can be seen from the figure, three types of acute reference values are available: interim AEGLs, ERPGs and the IDLH/10. The worst-case concentration estimate is approximately 27,000 $\mu g/m^3$, one-third of the lowest of these reference values, the 1-hour interim AEGL-2 value of 81,000 $\mu g/m^3$.

Figure 1. Short Term Concentration Comparisons



The interim AEGL-2 value was derived from the exposure resulting in reduced fetal weight in rats. This interim AEGL-2 value reflects consideration of EPA comment on an earlier draft value that was not based on developmental effects. An AEGL-1 value has not been derived because the odor threshold and concentrations causing mild sensory irritation are higher than the AEGL-2.

7.4 Cancer and Chronic Non-Cancer Exposure/Risk Assessment

OAR used the EPA Human Exposure - Screen (HEM-Screen for the chronic portion of the residual risk assessment. The HEM-Screen model contains (1) an atmospheric dispersion model with meteorological data, and (2) U.S. Bureau of Census population data for 2000 and the census block level.

The HEM-Screen's dispersion model is a Gaussian model (based on the Industrial Source Complex Long Term model, ISCLT2) that has been simplified to improve computational efficiency. Necessary source related inputs include map coordinates, release heights, exit velocities, stack diameters, temperatures, and annual emission rates. For simplicity, all of the emissions from a source were assumed to originate from a single point (the centroid of the plant site). For this source category, this assumption is not likely to introduce significant uncertainty because the emission points are typically located in the same building or in adjacent buildings.

OAR estimated ambient concentration at census blocks at varying distances from ethylene oxide commercial sterilization sources. The ambient concentration is presumed representative of the air breathed continuously throughout a lifetime (70 years) by people living in that block. The census block concentration estimates were (1) multiplied by the ethylene oxide URE to obtain an estimate of individual lifetime cancer risk for each block, and (2) divided by the chronic RfC to quantify the non-cancer hazard quotient (HQ) for each block. (The HQ, a ratio of exposure to the toxicity benchmark is commonly used as a surrogate indicator of non-cancer risk; HQ's < 1 indicate that exposures are below the RfC or RfD and not likely to cause adverse effects; HQ >1 indicate that the potential for adverse effects is increased.) Finally,

potential annual population impact was quantified by multiplying the individual lifetime cancer risk estimates for each census block by the number of people living in that block, dividing by 70, and then summing the individual block values across census blocks. These calculations were performed for every census block within 50 kilometers of the source.

Table 17 summarizes the results of the chronic assessment. The cancer risk assessment indicates that no source poses a lifetime cancer risk greater than 100 in a million, while approximately half of the modeled sources pose a lifetime cancer risk greater than 1 in a million. There are 45 sources with census block estimates that exceed 1 in 1 million individual lifetime cancer risk, 19 sources with census block estimates that exceed 10 in 1 million individual lifetime cancer risk, and no sources predicted to exceed 100 in a million individual lifetime cancer risk. Approximately 250,000 people live in areas where the individual lifetime cancer risk estimates are greater than 1 in 1 million, 7,300 people live in areas where the individual lifetime cancer risk estimates exceed 10 in 1 million, and no people live in areas where individual lifetime cancer risk estimates exceed 100 in 1 million. There are no sources with census block estimates that exceed a chronic HQ of 1 (the maximum predicted HQ from any source is 0.03).

The chronic non-cancer assessment indicated that no source emitted ethylene oxide in quantities that resulted in exposures that approached the inhalation reference concentration, indicating that chronic non-cancer effects are unlikely to occur. Use of HED's equivalent inhalation REL of 0.6 mg/ m^3 (based on a NOAEL=18 mg/ m^3 and UF=30) would also result in a maximum HQ well below the level of concern (HQ = 0.02).

OAR notes in its assessment that EPA ORD is conducting but has not yet completed a full evaluation of the data on which it will determine an EPA cancer URE for ethylene oxide. OAR further notes that, when this evaluation is complete, the resulting unit risk estimate for ethylene oxide will likely be higher than the CalEPA value used in the risk assessment for this source category.

Table 17. Summary of Cancer & Chronic Risk Assessment Results for Modeled Sources

Cancer Results	
Highest census block individual lifetime cancer risk	90 in a million
Number of sources with a census block individual lifetime cancer risk at or above 100 in a million	0
Number of sources with a census block individual lifetime cancer risk at or above 10 in a million	19
Number of sources with a census block individual lifetime cancer risk at or above 1 in a million	45
Number of people residing in census blocks for which individual lifetime cancer risk is at or above 100 in a million	0
Number of people residing in census blocks for which individual lifetime cancer risk is at or above 10 in a million	7,200
Number of people residing in census blocks for which individual lifetime cancer risk is at or above 1 in a million	250,000
Potential population impact (cancer cases/year)	0.04
Total population within 50 km of any source	99 million

Table 17. Summary of Cancer & Chronic Risk Assessment Results for Modeled Sources	
Chronic non-cancer results	
Highest census block HQ	0.03

8.0 AGGREGATE RISK ASSESSMENT AND RISK CHARACTERIZATION

Aggregate risk assessment integrates the assessments conducted for dietary, drinking water, and residential exposure. An aggregate assessment of risk is not required because drinking water exposures are not expected and there is not a common chemical exposure for dietary and residential (non-dietary) exposure scenarios (i.e , the reaction products ethylene chlorohydrin and ethylene glycol are the chemicals of concern for dietary (oral) exposure while ethylene oxide is the compound of concern for residential non-dietary (inhalation) exposure.

9.0 CUMULATIVE RISK

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."

EPA does not have, at this time, available data to determine whether ethylene oxide has a common mechanism of toxicity with other substances. 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 ethylene oxide and any other substances and, ethylene oxide does not appear to produce a toxic metabolite produced by other substances which have tolerances in the U. S. For the purposes of this tolerance reassessment action, therefore, EPA has not assumed that ethylene oxide 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 OPP 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/fedrgstr/EPA_PEST/2002/January/Day_16/.

10.0 OCCUPATIONAL EXPOSURE/RISK ASSESSMENT

Occupational exposures and risks are assessed for ethylene oxide sterilization in the spice industry. The assessment addresses exposure to ethylene oxide and its primary reaction products, ethylene chlorohydrin and ethylene glycol. (M. Crowley, D313772, 3/28/05) A target level of concern or margin of exposure (MOE) of 30 is considered adequate for occupational inhalation exposure, the primary exposure route of concern. OPP's cancer risk level of concern for occupational exposure is 1×10^{-4}

10.1 Exposure Scenarios

HED does not currently have a clear understanding of the precise activities to which workers are exposed during and after the ethylene oxide sterilization process or of typical exposure durations associated with these activities. Therefore, for the current assessment, HED used conservative assumptions regarding exposure duration. HED has requested and anticipates receiving detailed information from the registrant regarding the nature and duration of exposures typical of the spice sterilization industry and will revise the assessment accordingly upon receipt of such information. For the purposes of this occupational exposure assessment, "sterilization activities" include loading and unloading the sterilization chambers (opening chamber and chamber re-entry) and worker presence in the process area around the sterilization chamber. "Post-sterilization activities" include transporting boxes/drums/bags and bagging/containerizing treated spices. Further information regarding these activities from the spice industry is needed.

Based on available data, HED anticipates the following spice industry-related activities to result in potential worker exposure to ethylene oxide and its reaction products.

- Inhalation exposure to ethylene oxide during sterilization activities;
- Dermal exposure to ethylene glycol and the halohydrins during post-sterilization activities;
- Inhalation exposure to off-gassed ethylene oxide from treated spices during post-sterilization activities.

10.2 Exposure Data

HED does not have monitoring data on which to base assumptions regarding anticipated levels of exposure. Therefore, HED assessed exposures at existing regulatory and/or recommended levels for exposure to ethylene oxide. Table 18 lists various organizations and their regulatory/or recommended levels for occupational exposure to ethylene oxide.

Table 18: Ethylene Oxide Regulatory Levels

Organization	Concentration (ppm)	Nomenclature
Occupational Safety and Health Administration (OSHA)[4]	1	PEL[1]
	5	STEL[2]
	0.5	Action Level[3]
National Institute for Occupational Safety and Health (NIOSH)	< 0.1	REL[5]
American Conference of Governmental Industrial Hygienists (ACGIH)	1	TLV[6]
California Division of Occupational Safety and Health (Cal/OSHA)	1	PEL
European Union	Under Council Directive 79/117/EEC, the European Union banned the use of ethylene oxide in 1991.[7]	

NA = Not Available

[1] Permissible Exposure Limit (PEL): The employer shall ensure that no employee is exposed to an airborne concentration of EtO in excess of the PEL as an 8-hour time-weighted average (8-hour TWA).

[2] Short-Term Exposure Limit (STEL): The employer shall ensure that no employee is exposed to an airborne concentration of EtO in excess of the STEL as averaged over a sampling period of 15 minutes.

[3] Action Level: Concentration as an 8-hour TWA, above which the employer must initiate certain compliance activities such as periodic employee exposure monitoring and medical surveillance.

[4] OSHA, 1984 and 1988. *Note:* A review of the ethylene oxide OSHA standard in accordance with the Regulatory Flexibility Act and Executive Order 12866 is scheduled to be available to the public in 2005 (OSHA, 2004).

[5] Recommended Exposure Limit (REL): NIOSH-recommended exposure limit for an 8- or 10-h TWA and/or ceiling.
[6] Threshold Limit Value (TLV): Expressed as a TWA; the concentration of a substance to which most workers can be exposed without adverse effects.
[7] Pesticides Safety Directorate.

10.3 Exposure Assumptions

Information regarding daily/weekly/yearly usage of ethylene oxide is unavailable, therefore it is assumed that there is potential for all exposure durations (i.e., short (1-30 days)-/intermediate (1-6 months)-/ and long (> 6 months)-term). For cancer risk calculations it was assumed that exposure frequency (the amount of days per year workers are exposed to ethylene oxide) was 240 days per year, occupational exposure duration was 35 years over a 70 year lifespan; these are standard HED assumptions.

10.4 Cancer and Non-Cancer Exposure and Risk Estimates

10.4.1 Inhalation Exposure and Risk

Table 19 shows cancer and non-cancer risk estimates at regulatory levels and at limits of detection (LOD) for various analytical methods. As previously noted, EPA is currently conducting an assessment of ethylene oxide carcinogenicity. EPA's assessment has not yet completed internal or external peer review. However, based on preliminary findings, the URF derived by ORD will likely be higher than the URF used for this assessment and consequently, will result in increased cancer risk estimates from inhalation exposure to ethylene oxide.

Table 19: Cancer and Non-Cancer Risk Estimates at Regulatory Levels and LODs for Analytical Methods[1]

Organization	Concentration (ppm)	Non-Cancer MOE (LOC/MOE = 30)	Cancer Risk California URF
OSHA/ACGIH/CalOSHA 8-hour TWA (i.e., OSHA PEL)	1	7.5	1.8×10^{-2}
NIOSH REL	< 0.1	75	1.8×10^{-3}
Analytical Method			
OSHA Method 30 LOD [August 1981]	0.0133	560	2.3×10^{-4}
OSHA Method 49 LOD [November 1984]	0.0007	11000	1.2×10^{-5}
OSHA Method 50 LOD [January 1985]	0.003	2500	5.3×10^{-5}
NIOSH Method 1614 [August 1994]	0.00072	10000	1.3×10^{-5}
NIOSH Method 3702 [August 1994]	0.001	7500	1.8×10^{-5}

* provisional URF pending peer review

Table 20 provides the concentrations at which risks are not of concern for cancer and non-cancer effects.

Table 20. Exposure Levels at which Cancer and Non-Cancer Risks are Not of Concern

Cancer Risk					
URF Source	URF (ppm^{-1})	Cancer Risk	Exposure Frequency (days/year)	LADD* (ppm)	Exposure Conc. (ppm)
California OEHHA	0.16	1.0E-04	240	6.25E-04	0.0057031
Non-Cancer Risk					
Target MOE		Exposure Concentration (ppm)			
30		0.25			

* Lifetime Average Daily Dose

10.4.2 Dermal Exposure and Risk

Dermal exposure and risks to ethylene oxide, halohydrins, and ethylene glycol residues following sterilization cannot be determined without further information regarding the nature and extent of post-sterilization activities (e.g., transportation of treated spices and methods for bagging/containerizing treated spices). However, it is reasonable to assume that handling of and exposure to treated spices during post-sterilization activities is limited and dermal exposure is negligible.

11.0 DATA NEEDS

11.1 Residue Chemistry Data Needs

- Directions for use must be clearly defined on all labels that are allowed for fumigation of spices and walnuts. Labels of all ethylene oxide formulations that are used to treat herbs and spices, and black walnut must include postharvest directions stating exposure time, temperature and percent humidity, amount of active ingredient ethylene oxide, aeration time in treatment chamber, additional storage conditions before treated spices and black walnut are released to market for consumption, and any other parameters (i.e., equipment type, capacity, that are necessary to insure consistency in each treatment. These data are needed so the established tolerances will always adequately cover potential residues of concern from ethylene oxide fumigation of spices/herbs and black walnut. Labels must clearly define terms "spices" and "other seasoning materials").

- A 2000 ppm tolerance should be established for residues of ethylene chlorohydrin in/on spices and herbs (dried) (except basil). A 5000 ppm tolerance should be established in/on basil (dried). The existing 50 ppm ETO tolerance for black walnut is adequate.

- According to the registrants, items such as dried onion, dried garlic, and dehydrated vegetables are included in ASTA definition of spices. As these foods are in the "other crops groups" category as defined by the Agency, tolerances should be established on these items. Since residue data is not available for ethylene chlorohydrin residues in/on dried vegetables, tolerances for these residues could be based on the 5000 ppm basil tolerance in lieu of additional residue data.

- The analytical methodology should be tested in an Agency laboratory. The need for independent method trial will be determined by an Agency laboratory.

- The tolerance and/or use in/on coconut copra should be revoked as the registrant is not supporting this use.

- The residue data is adequate to support the fumigant uses on spices and herbs (whole and ground), and black walnuts.

11.2 Toxicity Data Needs

The database for ethylene oxide is found adequate. No additional study is required for the parent. However, the following studies are identified as data gaps for the ethylene oxide reaction product ethylene chlorohydrin.

Ethylene chlorohydrin

870.3700b	Developmental Toxicity (rabbits)
870.3800	Two-generation Reproduction Toxicity (rats)
870.4300	Chronic/Oncogenicity- Oral (rats and mice)
870.4100b	Chronic Toxicity-Oral (nonrodent)

APPENDICES

1.0 GUIDELINE TOXICOLOGY DATA SUMMARY

Data requirements (40 CFR 158.340) for ethylene oxide† are provided in the following table. Use of the new guideline numbers does not imply that new (1998) guideline protocols were used.

Data Requirements for Ethylene Oxide

Test	Technical	
	Required	**Satisfied**
870.1100 Acute Oral Toxicity	no	-
870.1200 Acute Dermal Toxicity	no	-
870.1300 Acute Inhalation Toxicity	yes	yes
870.2400 Primary Eye Irritation	yes	no#
870.2500 Primary Dermal Irritation	no	-
870.2600 Dermal Sensitization	yes	yes
870.3100 Oral Subchronic (rodent)	no	-
870.3150 Oral Subchronic (nonrodent)	no	-
870.3200 21-Day Dermal	yes	no#
870.3250 90-Day Dermal	no	-
870.3465 90-Day Inhalation	yes	yes*
870.3700a Developmental Toxicity (rodent)	yes	yes
870.3700b Developmental Toxicity (nonrodent)	yes	no**
870.3800 Reproduction	yes	yes
870.4100a Chronic Toxicity (rodent	yes	yes*
870.4100b Chronic Toxicity (nonrodent)	yes	yes
870.4200a Oncogenicity (rat)	yes	yes*
870.4200b Oncogenicity (mouse	yes	yes*
870.4300 Chronic/Oncogenicity	yes	yes*
870.5100 Mutagenicity—Gene Mutation - bacterial	yes	yes*
870.5300 Mutagenicity—Gene Mutation - mammalian	yes	yes*
870.5xxx Mutagenicity—Structural Chromosomal Aberrations	yes	yes*
870.5xxx Mutagenicity—Other Genotoxic Effects	yes	yes*
870.6100a Acute Delayed Neurotox. (hen)	no	-
870.6100b 90-Day Neurotoxicity (hen)	no	-
870.6200a Acute Neurotox. Screening Battery (rat)	yes	yes
870.6200b 90 Day Neuro. Screening Battery (rat)	yes	yes
870.6300 Develop. Neuro	no	-
870.7485 General Metabolism	yes	yes*
870.7600 Dermal Penetration	yes	no#
Special Studies for Ocular Effects		
Acute Oral (rat)	no	-
Subchronic Oral (rat)	no	-
Six-month Oral (dog)	no	-

† Data gap exists for the metabolite of ethylene oxide, ethylene chlorohydrin; Refer to the Data Needs Section

#No study required as ethylene oxide is a gas and exposure from this route is minimal for the uses on spices

* No study submitted but information from the open literature is sufficient to satisfy the guideline studies

** No guideline study required as ethylene oxide is a gas and not evaluated for dietary risk assessment. Further, data from the preliminary rabbit developmental study (MRID 41874102) indicate rabbits are not sensitive for developmental effects as compared to rats (MRID 42797702).

2.0 SUPPORTING TOXICOLOGY STUDIES

Acute Neurotoxicity Study (Ethylene Oxide)

In an acute neurotoxicity study (MRID 44256402), groups of ten Sprague-Dawley rats/sex were exposed to 0, 100, 300, or 500 ppm Ethylene Oxide for six hours by whole body inhalation and observed for 14 days. Neurobehavioral assessment (functional observational battery and motor activity testing) was performed on all animals/sex/group immediately following exposure on day 1 and on days 8 and 15. At study termination, five animals/sex/group were euthanized and perfused *in situ* for neuropathological examination. Of the perfused animals, all control and high-concentration animals were subjected to histopathological evaluation of brain and peripheral nervous system tissues.

No treatment-related clinical signs of toxicity were observed in any animal during exposure, or during daily and weekly examinations. All animals survived to scheduled termination. For males and females, absolute body weight was similar between the treated and control groups throughout the study. Body weight gain was slightly decreased for the high-concentration groups during the 2-week observation interval. Overall weight gain by the high-concentration males and females was 88% and 86%, respectively, of the control level. Food consumption was not affected by treatment.

During FOB assessments after exposure, an increased number of high-concentration males and females had drooping eyelids or half-closed eyes (5 and 3, respectively), a low arousal level (9 and 6, respectively), and no response to an approaching object (6 and 4, respectively) compared with 0-1 in the control groups. In the mid-concentration groups, increased incidences were observed for low arousal (5) and no approach response (6) in males and of drooping eyelids (5) in females. Slightly impaired locomotion was observed in two mid-concentration males, and in one and two high-concentration males and females, respectively, on day 1. In mid- and high-concentration males, some evidence of persistent effects were observed on day 8 and 15. On day 8 in the control, low-, mid-, and high-concentration males, slightly impaired locomotion was seen in 1, 2, 5, and 4 animals, respectively, and low arousal was seen in 1, 3, 5, and 4, respectively. On day 15 in the control, low-, mid-, and high-concentration males, slightly impaired locomotion was observed in 1, 3, 5, and 7 animals, respectively, and low arousal was observed in 0, 3, 6, and 6, respectively. No effects were found on fore- and hind-limb grip strengths, landing foot splay, or reflex assessments.

Motor activity was markedly lower for high-concentration males and females compared with controls after exposure on day 1. Total activity on day 1 for high-concentration males and females was 50% and 55%, respectively, of the control group level. Activity by the mid-concentration males was 50% of the control level during the first 5-minute interval resulting in total activity 70% of the controls for the entire session. No other treatment-related effects were noted.

Gross necropsy was unremarkable. No microscopic lesions were described for the brain, spinal column, or peripheral nerves from any control or high-concentration rat.

The acute inhalation neurotoxicity LOAEL for ethylene oxide in Sprague-Dawley rats is 300 ppm based on FOB findings in males and females and impaired locomotion and reduced motor activity in males. The NOAEL is 100 ppm.

This neurotoxicity study is classified as **Acceptable/Guideline** and satisfies the guideline requirement for an acute neurotoxicity study in rats (870.6200; OECD 424).

Subchronic Neurotoxicity Study - Ethylene Oxide

In a range-finding study (MRID 44256401), groups of five Sprague-Dawley rats/sex were exposed to target concentrations of 0, 100, 300, 400, or 500 ppm Ethylene Oxide for six hours/day, five days/week for 4 weeks by whole body inhalation. The study was designed to assess the inhalation toxicity of ethylene oxide and to establish exposure concentrations for longer-term studies. Mean analytical exposure concentrations were 0, 98.4 ± 3.76, 300 ± 15, 397 ± 23, and 501 ±12 ppm. The mean nominal concentrations were 0, 109 ± 10.7, 292 ± 19, 382, ± 24, and 506 ± 11 ppm. Particle size distribution measurements suggested the absence of any aerosol formation.

One 500 ppm female was found dead on day 18. Antemortem clinical signs included irregular gait, labored breathing, paleness, lethargy, emaciation, anogenital stains, black/brown stains on the snout, unthrifty coat, decreased food consumption, and decreased fecal volume/no stool. All other rats survived to terminal sacrifice. Irregular gait and decreased fecal volume were observed in all animals exposed to 500 ppm. Some animals in the 500 ppm group also exhibited lethargy, prostration, emaciation, yellow angenital staining, moist rales, labored breathing, black/brown stains on the snout, paleness, emaciation, and decreased food consumption.

Decreased ($p \leq 0.05$ or 0.01) mean body weight and body weight gain were observed in animals exposed to 300, 400, or 500 ppm. At week 4, mean body weight was decreased 12.1%, 23.8%, and 42.4% in males and 14.4%, 20.1%, and 40.6% in females in the 300, 400, and 500 ppm groups, respectively. Food consumption was decreased ($p \leq 0.01$) in 500 ppm males in weeks 1 (18%) and 3 (12%) and in 500 ppm females in week 1 (15%).

Hindlimb grip strength was decreased ($p \leq 0.05$ or 0.01) at 300, 400, and 500 ppm in both males and females at weeks 3 and 4 in all trials. In the 500 ppm group, decreases averaged 53% and 60% at week 3 and 76% and 86% at week 4 for males and females, respectively. In the 400 ppm group, decreases averaged 31% in males and 38% in females at week 3 and 48% for both sexes at week 4. In the 300 ppm group, decreases averaged 27% in males and 23% in females at week 3 and 36% for males and 22% for females at week 4. Landing foot splay was also decreased ($p \leq 0.05$ or 0.01) in both sexes at weeks 3 and 4 in the 400 and 500 ppm groups. In the 500 ppm group, decreases averaged 65% and 64% at week 3 and 68% and 72% at week 4 for males and females, respectively. In the 400 ppm group, decreases averaged 33% in males and 31% in females at week 3 and 42% for males and 29% for females at week 4.

Decreased absolute brain weight was noted in males exposed to 400 (6.8%; $p \leq 0.05$) or 500 ppm (8.9%; $p \leq 0.01$). No brain weight effects were noted in any females or in males exposed to 100 or 300 ppm. No treatment-related macroscopic lesions were noted at necropsy. Treatment-

related microscopic lesions were noted in all males and females from the 500 ppm group and included minimal to slight vacuolation of the white matter of the thalamus and medulla oblongata. No similar microscopic lesions were noted in the control animals.

Based on the results of this study, the NOAEL for ethylene oxide administered to Sprague-Dawley rats via whole body inhalation for 4-weeks is 100 ppm. The LOAEL is 300 ppm based on decreased body weight and body weight gain and decreased hindlimb grip strength and landing foot splay.

In a subchronic neurotoxicity study (MRID 44359401), groups of fifteen Sprague-Dawley rats/sex were exposed to 0, 25, 50, 100, or 200 ppm Ethylene Oxide for six hours/day, five days/week for 14 weeks (at least 65 exposures) by whole body inhalation. Exposure concentrations were selected based on results of a range-finding study, MRID 44256401. To assess the reversibility of any observed effects, ten rats/sex/dose were observed during an additional 13-week recovery period. Neurobehavioral assessment (functional observational battery and motor activity testing) was performed on ten animals/sex/group pre-test, and during the exposure period (weeks 5, 9, and 14), and after the recovery period (weeks 27/28). Following at least 65 exposures, five animals/sex/group were euthanized and perfused *in situ* for neuropathological examination. Also, after the 13-week recovery period, five animals/sex/group were sacrificed and selected tissues preserved for neuropathological examination. The remaining five animals/sex/group were sacrificed and discarded. Of the perfused animals, all control and high-concentration animals were subjected to histopathological evaluation of brain and peripheral nervous system tissues.

No treatment-related clinical signs of toxicity were observed in any animal during exposure, or during daily and weekly examinations. There were no deaths during the exposure period in any test group. One male exposed to 100 ppm was found dead during the recovery period (4 weeks after termination of exposure). Antemortem observations included lethargy, paleness, labored breathing, ano-genital staining, decreased fecal volume/no stool, and decreased food consumption.

Mean body weight was decreased approximately 8-13% ($p \leq 0.05$ or 0.01) in high-concentration males from week four until cessation of exposure in week 13. Mean body weight gain was decreased ($p \leq 0.05$ or 0.01) in high-concentration males during every week of the exposure period except week three; the decrease over weeks 1-13 was 16%. In high-concentration females, mean body weight was decreased approximately 8-10% ($p \leq 0.05$) from weeks 10 through 13, and mean body weight gain was decreased approximately 9% from weeks 6 through 13. The effects on body weight were reversible. The high-concentration males and females gained more weight than controls during the recovery period, and at week 26 mean body weight of high-concentration males was decreased only 3% compared to controls, and body weight gain of high-concentration females was increased 3.5% compared to controls. There were no treatment-related effects on body weight or body weight gain in either sex in the 25, 50, or 100 ppm groups. The only treatment-related effect on food consumption was an increase ($p \leq 0.05$) in food consumption in high-concentration males and females during the recovery period.

A 25% decrease ($p \leq 0.05$) in hindlimb grip strength in high-concentration females at the end of the exposure period was noted in the FOB assessment. No other treatment-related FOB effects were noted in either sex at any time point at any test concentration. There were no treatment-related effects on motor activity.

A malignant glioma was noted in the cerebral cortex of one high-concentration male following the recovery period. Mononuclear cell leukemia was noted in the male exposed to 100 ppm that died during week 4 of the recovery period. A hemangiosarcoma in the skin/subcutaneous tissue was noted in one 25 ppm male, and basal cell carcinoma of the skin was noted in one 50 ppm female and one 200 ppm female. Although there was no concentration-response relationship or common tumor type, these neoplasms were considered treatment-related because of the atypical presence of neoplasms in animals of this age and the lack of neoplasms in the control group.

Based on the results of this study, the NOAEL for ethylene oxide administered to Sprague-Dawley rats via whole body inhalation for 13-weeks (at least 65 exposures) is 100 ppm. The LOAEL is 200 ppm based on decreased body weight and body weight gain and decreased hindlimb grip strength in females.

Based on the data presented in this study, there is evidence of carcinogenicity in Sprague-Dawley rats exposed to ethylene oxide by inhalation in all treatment groups during the 13 week recovery period .

This neurotoxicity study is classified as **Acceptable/Guideline** and satisfies the guideline requirement for an acute neurotoxicity study in rats (870.6200; OECD 424). A minor deficiency was that the duration of open field observation was not stated.

Chronic Monkey Study (MRID 42159401, Setzer et al., 1996 and IPCS, 2003)

In a chronic monkey study (MRID 42159401, Setzer et al., 1996 and IPCS, 2003), groups of 12 male cynomolgus monkeys were exposed to 0, 50 or 100 ppm for 7 hours/day, 5days/week for 104 weeks. Some animals were followed for seven years after exposure ceased. Bodyweight gain was reduced in animals exposed to the highest concentration. No group differences in red or white cell counts, clinical chemistry or electrocardiographic indices were found. Axonal dystrophy in the nucleus gracilis of the medulla oblongata of the brain, and demyelination of the sciatic nerve were seen in both dose groups. Decreased nerve conduction velocity was observed in only 2 of 12 monkeys exposed to 100 ppm. Sperm count and motility were significantly reduced in animals from both treatment groups. Lens opacities appeared to be elevated in a concentration dependent manner, however, the increase was not significant at the termination of exposure. Following 10 years without exposure, a subsequent eye exam showed that severity of lens injury for 100-ppm exposure was significantly different from controls. The incidence of lens opacities was 0/12, 2/11, and 3/11, respectively, when assessed at the termination of exposure, or 2/4, 2/3, and 4/4, respectively, when assessed 10 years after the cessation of exposure.

The study identifies a systemic LOAEL of 50 ppm based on decreased motility, sperm counts, demyelination of the sciatic nerve and axonal dystrophy and possible lens opacities.

Subchronic Toxicity Studies – Ethylene Chlorohydrin

Study 1

In a subchronic oral toxicity study (Oser et al., 1975), 7-9 month old beagle dogs (~10/sex/group) were administered with ethylene chlorohydrin in wet mash by gavage at concentrations of 0, 600, 900 or 1350 ppm for 15 weeks. Due to emesis, the concentration gradient could not be maintained and the calculated doses correspond to 0, 13.3/16.9, 18.4/20.3, 18.3/19.3 (m/f) mg/kg/day respectively. At weeks 6 and 12, hematological, and clinical parameters were measured. The dogs were sacrificed at 15 weeks. Selected organs were weighed and histopathological examinations were made mainly in the control and high dose groups. For the low dose groups, livers and kidneys alone were examined.

In the middle and high dose groups, there appeared to be some decrease in hemoglobin and hematocrit at week 6 but these levels increased at week 12 and none of these effects are statistically significant from controls. No other blood parameters were affected. No dose related effects in organ weights or histopathological changes were noticed.

Due to emesis, in the high dose groups, there was loss of chemical intake and therefore, no dose response effects could be measured.

The NOAEL is determined as 18.3 mg/kg/day and the LOAEL is not established.

Study 2

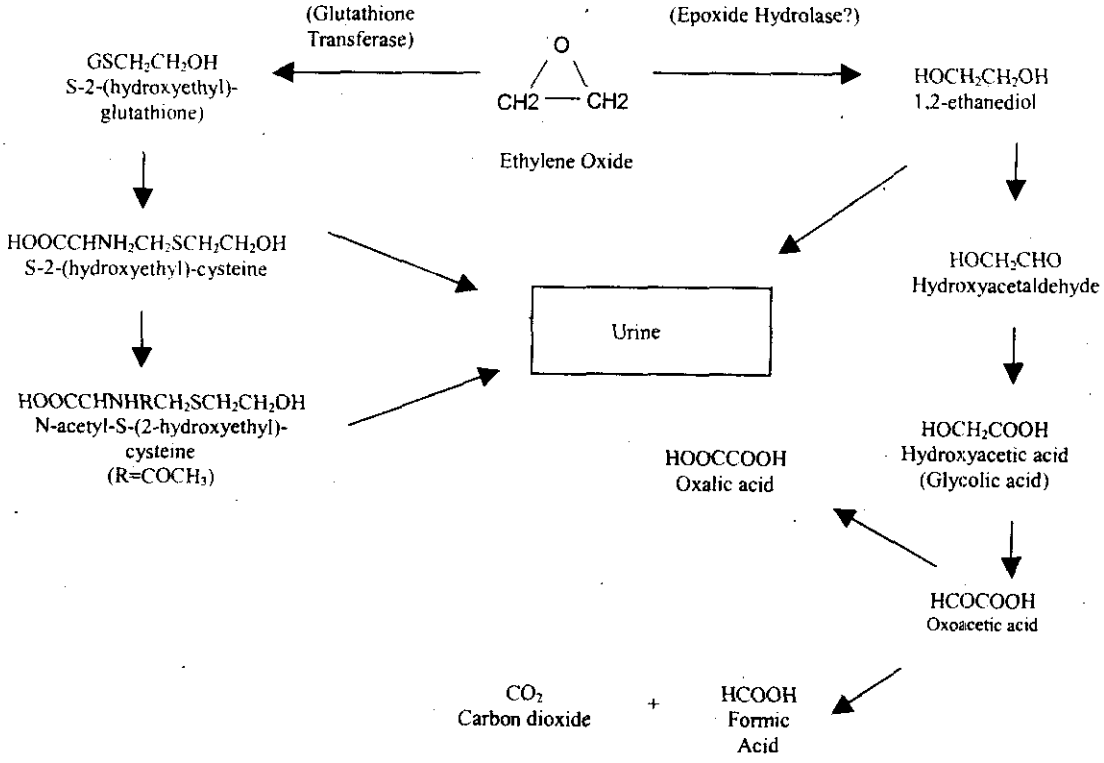
In a subchronic oral toxicity study (Oser et al. 1975), adult monkeys (~2/sex/group) were administered with ethylene chlorohydrin in apple sauce by gavage at concentrations of 0, 30, 45 or 62.5 mg/kg/day for 12 weeks. At weeks 6 and 12, hematological, and clinical parameters were measured. The monkeys were sacrificed at 12 weeks. Selected organs were weighed and histopathological examinations were made mainly in the control and high dose groups. For the low dose groups, livers and kidneys alone were examined.

No dose related effects were seen either in body weight, organ weight or clinical parameters.

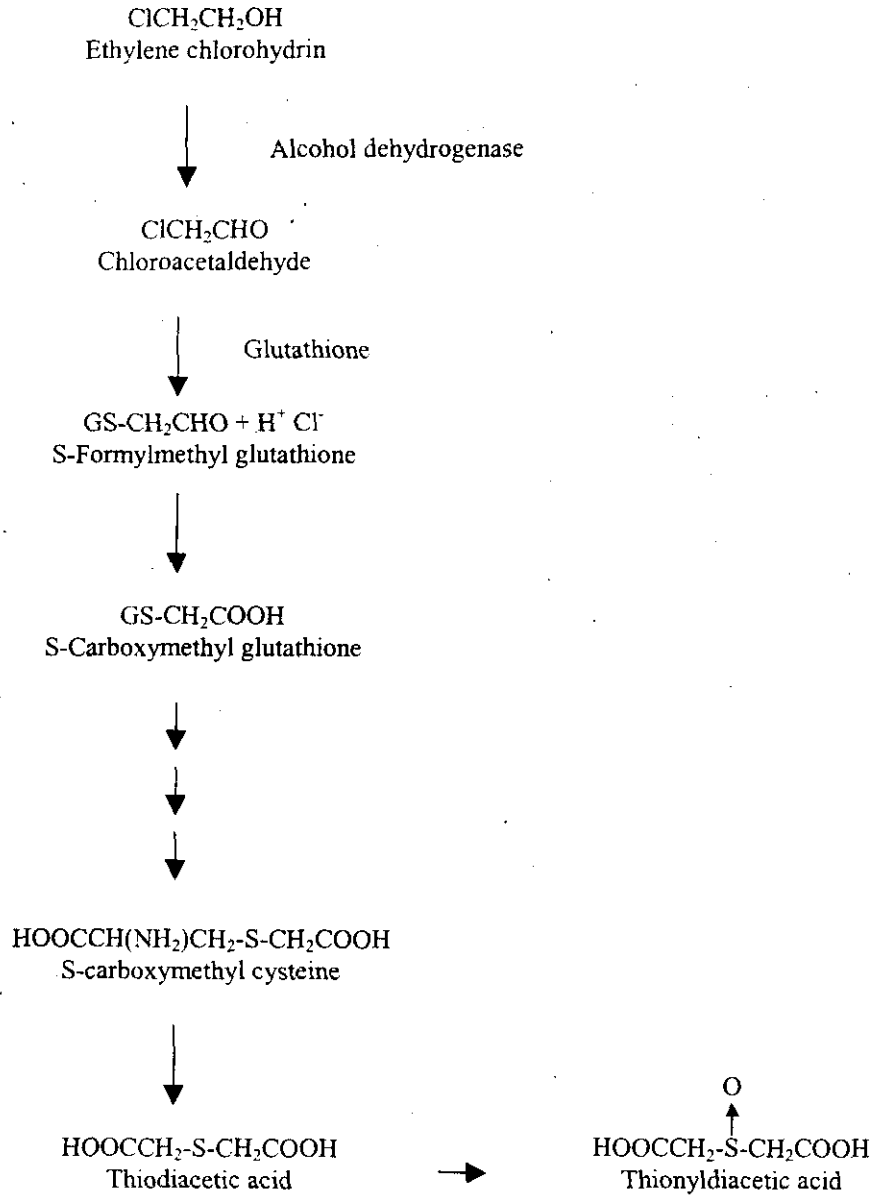
The NOAEL is determined as 62.5 mg/kg/day and the LOAEL is not established.

3.0 Metabolism Diagrams

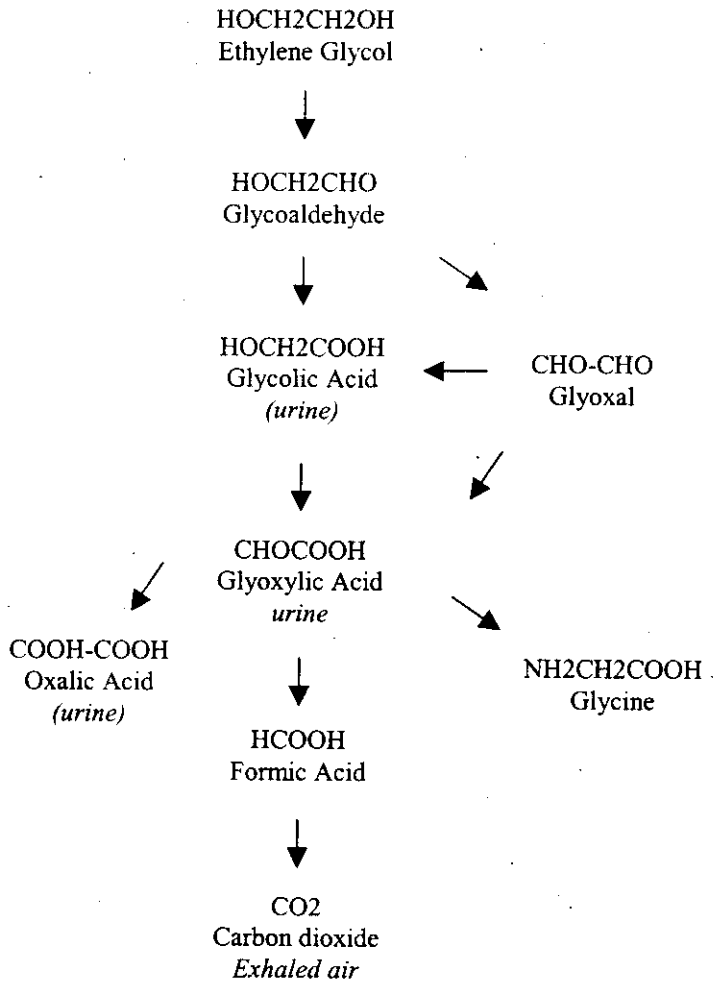
Ethylene Oxide Metabolism (IPCS Report 2003)



Ethylene Chlorohydrin Metabolism (NTP, 1985)



Ethylene Glycol Metabolism (IPCS, 2002)



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