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Reregistration Eligibility Decision for Propylene Oxide

Reregistration Eligibility Decision (RED) Document for Propylene Oxide

List B

Case Number 2560

Approved by: _____ Date: July 31, 2006

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Glossary of Terms and Abbreviations

AGDCI	Agricultural Data Call-In
ai	Active Ingredient
aPAD	Acute Population Adjusted Dose
BCF	Bioconcentration Factor
CFR	Code of Federal Regulations
cPAD	Chronic Population Adjusted Dose
CSF	Confidential Statement of Formulation
CSFII	USDA Continuing Surveys for Food Intake by Individuals
DCI	Data Call-In
DEEM	Dietary Exposure Evaluation Model
DFR	Dislodgeable Foliar Residue
DNT	Developmental Neurotoxicity
EC	Emulsifiable Concentrate Formulation
EDWC	Estimated Drinking Water Concentration
EEC	Estimated Environmental Concentration
EPA	Environmental Protection Agency
EUP	End-Use Product
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FFDCA	Federal Food, Drug, and Cosmetic Act
FQPA	Food Quality Protection Act
GLN	Guideline Number
IR	Index Reservoir
LC_{50}	Median Lethal Concentration. A statistically derived concentration of a substance that can be expected to cause death in 50% of test animals. It is usually expressed as the weight of a substance per weight or volume of water, air, or feed, e.g., mg/l, mg/kg, or ppm.
LD_{50}	Median Lethal Dose. A statistically derived single dose that can be expected to cause death in 50% of the test animals when administered by the route indicated (oral, dermal, inhalation). It is expressed as a weight of substance per unit weight of animal, e.g., mg/kg.
LOC	Level of Concern
LOAEL	Lowest Observed Adverse Effect Level
MATC	Maximum Acceptable Toxicant Concentration
µg/g	Micrograms Per Gram
µg/L	Micrograms Per Liter
mg/kg/day	Milligram Per Kilogram Per Day
mg/L	Milligram Per Liter
MOE	Margin of Exposure
MRID	Master Record Identification Number. EPA's system for recording and tracking studies submitted.
MUP	Manufacturing-Use Product
NOAEL	No Observed Adverse Effect Level
OPP	EPA Office of Pesticide Programs

OPPTS	EPA Office of Prevention, Pesticides, and Toxic Substances
PAD	Population Adjusted Dose
PCA	Percent Crop Area
PDP	USDA Pesticide Data Program
PHED	Pesticide Handler's Exposure Data
PHI	Pre-harvest Interval
ppb	Parts Per Billion
PPE	Personal Protective Equipment
ppm	Parts Per Million
PRZM/EXAMS	Pesticide Root Zone Mode/Exposure Analysis Modeling System, Tier II Surface Water Computer Model
Q*	The Carcinogenic Potential of a Compound, Quantified by the EPA's Cancer Risk Model
RAC	Raw Agriculture Commodity
RED	Reregistration Eligibility Decision
REI	Restricted-Entry Interval
RfD	Reference Dose
RQ	Risk Quotient
SCI-GROW2	Tier I Ground Water Computer Model
SAP	Science Advisory Panel
SF	Safety Factor
SLC	Single Layer Clothing
TGAI	Technical Grade Active Ingredient
USDA	United States Department of Agriculture
USGS	United States Geological Survey
UF	Uncertainty Factor
UV	Ultraviolet
WPS	Worker Protection Standard

Abstract

This document presents the Environmental Protection Agency's (EPA or the Agency's) decision regarding the reregistration eligibility of the registered uses of the active ingredient propylene oxide (PPO). The Agency has conducted human health and environmental fate and effects risk assessments for PPO and has made tolerance reassessment decisions for existing tolerances. The Agency has determined that, with label amendments and changes as specified in this document, there is a reasonable certainty that no harm will result to the general U.S. population, infants, children, or other major identifiable subgroups of consumers, from the use of PPO. The Agency has determined that products containing the active ingredient PPO are eligible for reregistration provided that the risk mitigation measures outlined in this document are adopted and label amendments are made to reflect these measures.

EPA has identified potential human health risks of concern associated with the current registered uses of PPO from residential bystander exposure and occupational exposure. To reduce these exposures and to address current risks of concern, EPA is requiring that all vacuum-sealed pressurized chambers (also referred to as commercial sterilization chambers) used in PPO fumigation be equipped with emission reduction technology, that a buffer zone of 180 feet be maintained around fumigation facilities that are not vacuum-sealed pressurized chambers, and that an 8-hour time weighted average concentration limit of 2 parts per million for occupational exposure be satisfied. Additionally, EPA has determined that products containing the active ingredient PPO meet the criteria for restricted use classification and is requiring that all labels include language identifying end-use products as restricted use. The Agency is also requiring appropriate data to confirm the decisions presented in this Reregistration Eligibility Decision.

I. Introduction

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) was amended in 1988 to accelerate the reregistration of products with active ingredients registered prior to November 1, 1984. The amended Act calls for the development and submission of data to support the reregistration of an active ingredient, as well as a review of all data submitted to the Environmental Protection Agency (hereafter referred to as EPA or the Agency). Reregistration involves a thorough review of the scientific database underlying a pesticide's registration. The purpose of the Agency's review is to reassess the potential hazards arising from the currently registered uses of a pesticide, to determine the need for additional data on health and environmental effects, and to determine whether or not the pesticide meets the "no unreasonable adverse effects" criteria of FIFRA.

On August 3, 1996, the Food Quality Protection Act (FQPA) was signed into law. This Act amended FIFRA and the Federal Food, Drug, and Cosmetic Act (FFDCA) to require reassessment of all existing tolerances for pesticides in food by August 3, 2006. EPA decided that, for those chemicals that have tolerances and are undergoing reregistration, tolerance reassessment would be accomplished through the reregistration process. Under FQPA, in reassessing these tolerances, the Agency must consider, among other things, aggregate risks from non-occupational sources of pesticide exposure, whether there is increased susceptibility among infants and children, and the cumulative effects of pesticides that have a common mechanism of toxicity. When the Agency determines that aggregate risks are not of concern and concludes that there is a reasonable certainty of no harm from aggregate exposure, the tolerances are considered reassessed.

Risks summarized in this document are for propylene oxide (PPO) only. FQPA requires EPA to consider available information concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity" when considering whether to establish, modify, or revoke a tolerance. 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 PPO, and PPO does not appear to produce a toxic metabolite produced by other substances. Therefore, for the purposes of this reregistration decision, EPA has not assumed that PPO shares a common mechanism of toxicity with other compounds. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs (OPP) concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://epa.gov/pesticides/cumulative/.

This document presents EPA's revised human health and environmental fate and effects risk assessments (see Appendices J and K), its progress toward tolerance reassessment, and the reregistration eligibility decision for PPO. The document consists of six sections. Section I contains the regulatory framework for reregistration and tolerance reassessment. Section II provides a description of the chemical and a profile of the use and usage of the chemical. Section III references the revised human health and environmental fate and effects risk assessments attached as Appendices to this document. Section IV presents the Agency's risk

management, reregistration eligibility, and tolerance reassessment decisions. Section V summarizes the data requirements necessary to confirm the reregistration eligibility decision as well as specific label changes and language necessary to implement the risk mitigation measures outlined in Section IV. Section VI, the Appendices, provides related information and supporting documents. The preliminary and revised risk assessments for PPO are available in the public docket EPA-HQ-OPP-2005-0253 located on-line in the Federal Docket Management System (FDMS) at http://www.regulations.gov.

II. Chemical Overview

A. Chemical Identity

Chemical Structure:

Empirical Formula:	C_3H_6O
Common Name:	Propylene oxide
CAS Name:	Propylene oxide; 1,2-epoxypropane
CAS Registry Number:	75-76-9
OPP Chemical Code:	042501
Case Number:	2560
Technical Registrant:	Aberco, Inc.
Reaction Products:	Propylene chlorohydrin (C_3H_7ClO) and Propylene bromohydrin (C_3H_7BrO)

PPO is a colorless liquid that is highly volatile and flammable at room temperature and normal atmospheric pressure. There are two reaction products formed during the PPO sterilization process – propylene chlorohydrin (PCH) and propylene bromohydrin (PBH). In addition to PPO, PCH is considered to be a residue of concern for dietary risk assessment and tolerance reassessment purposes because residues persist at high levels and are likely to be present in treated commodities at the time of consumption. PBH residues are minimal relative to PCH residues; therefore, PBH is not considered to be a residue of concern.

PPO has been used to treat food products since 1958. PPO was classified as List B through the FIFRA amendments of 1988. A FIFRA '88 Data Call-In (DCI) was issued for PPO in October 1989. Subsequent DCIs were issued in 1990, 1991, and 1993.

B. Use and Usage Profile

The following is information on the currently registered uses of PPO. Sections IV and V include information on those currently registered uses which are not eligible for reregistration and Appendix A provides a detailed table of those uses which are eligible for reregistration.

Type of Pesticide:	PPO is an insecticidal fumigant and sterilant used both to control bacteria contamination, mold contamination, insect infestations, and microbial spoilage of food products as well as to control insects in nonfood products.
Formulations:	PPO is formulated as a pressurized liquid and/or gas.
Methods of Application:	End-use products containing PPO can be applied indoors or outdoors as a gas in vacuum-sealed pressurized chambers (also referred to as commercial sterilization chambers). PPO can also be applied outdoors as a gas in other types of chambers and in/under loose-fitting structures such as trailers, rail cars, tents or tarps where gas is confined and entry is restricted during fumigation.
Use Sites:	PPO is registered for use on several food items such as dried herbs and spices, dried onions, dried garlic, cacao beans, cocoa powder and in-shell and processed nutmeats (except peanuts). There are proposed new uses on figs, prunes, and raisins. PPO also has nonfood uses for cosmetic articles, gums, ores, packaging, pigments, pharmaceutical materials, and discarded nutshells prior to disposal. There is an additional proposed new nonfood use on books.
Application Rates:	The maximum application rate (in vapor form) is 2.4 ounces (oz) active ingredient (ai) per ft^3 in vacuum-sealed pressurized chambers (also referred to as commercial sterilization chambers). The maximum application rate (in vapor form) is 0.0448 oz ai/ft^3 in other types of chambers and in/under loose-fitting structures such as trailers, rail cars, tents or tarps that are used in outdoor commodity fumigation.
Estimated Usage:	Approximately 64.8 million pounds of commodities are treated with PPO annually. PPO is used mostly on nutmeats (approximately 1.8% crop treated) and spices (approximately 1% crop treated).

C. Tolerances

Currently there are four tolerances listed in 40 CFR 180.491 for PPO on raw agricultural commodities. Tolerances for PPO residues are expressed in terms of the parent compound (PPO) only. Tolerances for PPO currently exist for spices (processed), nutmeat (processed,

except peanuts), gum (edible), and cocoa bean (bean). Section IV includes a summary of the tolerance reassessment decision for PPO and lists those tolerances the Agency will propose to revoke, decrease, increase, maintain, reassign, and establish.

III. Propylene Oxide Risk Assessments

Please refer to Appendices J and K for the human health and environmental fate and effects risk assessments for PPO, dated July 31, 2006 and May 16, 2006, respectively, for details on the risks associated with the use of PPO. These documents are also available in the public docket EPA-HQ-OPP-2005-0253 located on-line at http://www.regulations.gov.

IV. Risk Management, Reregistration, and Tolerance Reassessment Decisions

A. Determination of Reregistration Eligibility

Section 4(g)(2)(A) of FIFRA calls for the Agency to determine, after submission of relevant data concerning an active ingredient, whether or not products containing the active ingredient are eligible for reregistration. The Agency has previously identified and required the submission of the generic (technical grade) data required to support reregistration of products containing PPO as an active ingredient. The Agency has completed its review of these generic data, and has determined that the data are sufficient to support reregistration of all products containing PPO provided the registrations are amended in a manner consistent with this document.

The Agency has completed its review of submitted data and its assessment of the dietary (both food and drinking water), residential, occupational, and ecological risks associated with the use of pesticide products containing the active ingredient PPO. Based on these data and public comments received on the Agency's assessments for the active ingredient PPO, the Agency has sufficient information on the human health and ecological effects of PPO to make decisions as part of the tolerance reassessment process under FFDCA and reregistration process under FIFRA, as amended by FQPA. The Agency has determined that products containing the active ingredient PPO are eligible for reregistration provided that the risk mitigation measures outlined in this document are adopted and label amendments are made to reflect these measures. Specific label changes and language are presented in Section V. Appendix A provides a detailed table of those uses eligible for reregistration. Appendix B identifies generic data requirements that the Agency reviewed as part of its determination of reregistration eligibility of PPO, and lists the submitted studies the Agency found acceptable. Data gaps are identified as either outstanding generic data requirements that have not been satisfied with acceptable data or additional data requirements necessary to confirm the decision presented here.

Based on its evaluation of PPO, the Agency has determined that products containing the active ingredient PPO, unless labeled and used as specified in this document, would present risks inconsistent with FIFRA and FFDCA. Accordingly, should a registrant fail to implement any of the risk mitigation measures identified in this document, the Agency may take appropriate

regulatory action to address the risk concerns from the use of PPO. If all changes outlined in this document are incorporated into the product labels, then all current risks for PPO will be adequately addressed for the purposes of this determination under FIFRA. Once a comprehensive endangered species assessment is completed, further changes to these registrations may be necessary as explained in Section IV.D.4 of this document below.

B. Public Comments and Responses

Through the Agency's public participation process, EPA worked with stakeholders and the public to reach these regulatory decisions for PPO. During the public comment period on the risk assessments, which closed on January 9, 2006, the Agency received comments from Aberco, Inc. (the technical registrant), the American Chemistry Council, a number of nut growers (Navarro Pecan Company, Carriere Family Farms, Frazier Nut Farms, Green Valley Pecan Company, Blue Diamond Growers, Sun Valley Pecan Company), the Almond Board of California, and the California Walnut Commission. These comments expressed disagreement with the Agency's use and interpretation of a number of carcinogenicity studies, contended that PPO is a threshold carcinogen via the inhalation route with an identifiable threshold or dose below which the risk of developing cancer is negligible, refuted the Agency's preliminary list of data requirements, described the process of nutmeat fumigation and supplied usage statistics for nutmeats, supplied residue data for nutmeats, supplied worker exposure data for the fumigation of nutmeats, indicated why PPO is important to the nut industry, and suggested potential mitigation measures.

These comments were reviewed and taken into consideration when the revised risk assessments and their supporting documents, in addition to this PPO RED, were completed. The comments are available in their entirety in the public docket EPA-HQ-OPP-2005-0253 located on-line at http://www.regulations.gov. The Agency's responses to substantive comments are available in memoranda in the public docket and the revised assessments available in the public docket reflect these responses.

C. Regulatory Position

1. Food Quality Protection Act Findings

a. "Risk Cup" Determination

As part of the FQPA tolerance reassessment process, EPA assessed the risks associated with PPO. The Agency has concluded that, with the risk mitigation measures outlined in this document, the aggregate risk from food, drinking water, and residential exposures to PPO is within its own "risk cup." The Agency has determined that the human health risks from these combined exposures are within acceptable levels and that the established tolerances for PPO, with label amendments and changes as specified in this document, meet the safety standards under the FQPA amendments to Section 408(b)(2)(C) and 408(b)(2)(D) of the FFDCA. In reaching these determinations, EPA has considered the available information on the special sensitivity of infants and children.

b. Determination of Safety to U.S. Population (Including Infants and Children)

The Agency has determined that there is a reasonable certainty that no harm will result to the general U.S. population, infants, children, or other major identifiable subgroups of consumers, from the use of PPO. The safety determination considers factors such as the toxicity, use practices and exposure scenarios, and environmental behavior of PPO. In determining whether or not infants and children are particularly susceptible to toxic effects from PPO residues, the Agency considered the completeness of the hazard database for developmental and reproductive effects, the nature of the effects observed, and other information.

The Agency determined it was necessary to retain a 10X FQPA database uncertainty factor for PPO and PCH (its reaction product) in the dietary human health risk assessment because of the lack of acceptable developmental toxicity studies for PPO and PCH. This lack of acceptable studies limits the ability to assess the fetal susceptibility effects under FQPA. However, there are no residual uncertainties for pre- and/or post-natal toxicity if the 10X database uncertainty factor is retained. The endpoints and corresponding doses selected for regulatory purposes are considered protective for infants and children and the human health risk assessment does not underestimate the potential risks for infants and children.

c. Endocrine Disruptor Effects

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 endocrine effects as the Administrator may designate." Following recommendations of its Endocrine Disruptor Screening 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 EPA include evaluations of potential effects in wildlife. For pesticides, 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 for additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

In the available subchronic and reproduction toxicity studies on PCH (a reaction product of PPO), there was an observed increase in the percentage of abnormal sperm. This effect was observed in the same study from which the endpoint and corresponding dose ("lowest observed adverse effect level" or LOAEL) were selected for regulatory purposes for PCH. The human health risk assessment is therefore protective of this observed potential endocrine effect. When the appropriate screening and/or testing protocols being considered under the EDSP have been developed, PPO may be subject to additional screening and/or testing to better characterize effects related to endocrine disruption.

d. Cumulative Risks

FQPA stipulates that when determining the safety of a pesticide chemical EPA shall base its assessment of the risk posed by the chemical on, among other things, available information concerning the cumulative effects to human health that may result from dietary (both food and drinking water), residential, or other non-occupational exposure to other substances that have a common mechanism of toxicity. The reason for consideration of other substances is due to the possibility that low-level exposures to multiple chemical substances that cause a common toxic effect by a common mechanism could lead to the same adverse health effect as would a higher level of exposure to any of the other substances individually. A person exposed to a pesticide at a level that is considered safe may in fact experience harm if that person is also exposed to other substances that cause a common toxic effect by a mechanism common with that of the subject pesticide, even if the individual exposure levels to the other substances are also considered safe.

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 PPO, and PPO does not appear to produce a toxic metabolite produced by other substances. Therefore, for the purposes of this reregistration decision, EPA has not assumed that PPO shares a common mechanism of toxicity with other compounds. 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 OPP concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://epa.gov/pesticides/cumulative/.

2. Tolerance Summary

The tolerance summary and tolerance reassessment decision is presented for PPO in Table 1 below. Currently there are four tolerances listed in 40 CFR 180.491 for residues of PPO on raw agricultural commodities.

Available residue data support maintaining the existing tolerance for spices (processed), although the tolerance needs to be clearly defined as herbs and spices (group 19, dried). This tolerance covers only those commodities in crop group 19 as listed in 40 CRF 180.41(b)(19). Available residue data for cacao bean (cocoa powder) support establishing a tolerance for PPO for this commodity and lowering the existing tolerance for cacao bean (bean). Although newly submitted preliminary residue data from industry representatives show that PPO residues are lower on nutmeat (processed, except peanuts) than the existing tolerance when typical application rates are considered, the existing and reassessed tolerance reflects the labeled maximum application rate allowable for these commodities. Therefore, no change to the current tolerance is required for nutmeat (processed, except peanuts).

The Agency will propose establishing tolerances for PPO for grape (raisin), fig, and plum (prune, dried), which are all proposed new uses for PPO for which the Agency has received a tolerance petition, based on the available residue data. Available residue data also support establishing tolerances for PPO for the dehydrated vegetables onion (dried), and garlic (dried). Although the technical registrant considers these commodities to be spices under the existing

tolerance for spices (processed), EPA defines these two commodities in a separate crop group (crop group 3) so separate tolerances must be established in order to support PPO use on these commodities. Additional corrections need to be made to some of the existing commodity definitions as indicated below in Table 1.

Additionally, the Agency will propose to revoke the existing tolerance for gum (edible) based on the registrant's request for termination of PPO use on all edible gums pursuant to FIFRA Section 6(f)(1)(A), as announced in a *Federal Register* Notice published on May 24, 2005, 71 *FR* 29957.

Since the Agency has determined that residues of concern in/on raw agricultural commodities are not only PPO but also its reaction product, PCH, the Agency will propose that tolerances for PCH also be established for the following raw agricultural commodities: cacao bean (dried bean), cacao bean (cocoa powder), nut (tree, group 14), herbs and spices, (group 19, dried, except basil), onion (dried), garlic (dried), grape (raisin), fig, and plum (prune, dried). The Agency will propose establishing a separate tolerance for PCH for basil (dried) as available residue data supports establishing a tolerance for basil at a higher level than for other commodities in crop group 19. The proposed tolerance levels listed below in Table 1 for these raw agricultural commodities are based on available residue data.

Additionally, in 40 CFR 180.491(a)(2), (a)(4), and (a)(5) application directions for PPO are listed, including time and temperature conditions. The Agency will propose that Sections (a)(2), (a)(4), and (a)(5) be removed so that treatment parameters are not defined in the tolerance expression. Additionally, the Agency will propose that Sections (a)(3) and (a)(1) be combined into one Section (a)(1) and revised as indicated in Appendix 8 of the human health risk assessment (Appendix J). The Agency will propose that a new Section (a)(2) be added as indicated in the human health risk assessment and that it include tolerances for PCH. Where labeling revisions are warranted for treatment parameters, label changes and language are specified in Section V.

In terms of confirmatory data requirements, analytical reference standards for PPO and PCH need to be supplied to the EPA National Pesticide Standards Repository, as indicated below in Table 2.

CODEX maximum residue limits (MRLs) and Canadian MRLs do not exist for PPO or PCH.

Table 1. Tolerance reassessment summary for PPO

Cocoa bean, bean	300	200	Available residue data supports lowering tolerance. [*Cacao bean, dried bean*]
Gum, edible	300	Revoke	Registrant has requested termination of use.
Nutmeat, processed, except peanuts	300	300	[*Nut, tree, group 14*]
Spices, processed	300	300	[*Herbs and spices, group 19, dried*]

Existing Commodity	Existing Tolerance (ppm)	Tolerance Reassessment Decision (ppm)	Comments [*Correct Commodity Definition*]
Cacao bean, cocoa powder	None	200	Available residue data supports establishing a tolerance.
Onion, dried	None	300	Available residue data supports establishing a tolerance.
Garlic, dried	None	300	Available residue data supports establishing a tolerance.
Grape, raisin	None	1	Proposed new use.
Fig	None	3	Proposed new use.
Plum, prune, dried	None	2	Proposed new use.
Cacao bean, dried bean	None	20	Available residue data supports establishing a tolerance.
Cacao bean, cocoa powder	None	20	Available residue data supports establishing a tolerance.
Nut, tree, group 14	None	10	Available residue data supports establishing a tolerance.
Herbs and spices, group 19, dried, except basil	None	1500	Available residue data supports establishing a tolerance.
Basil, dried	None	6000	Available residue data supports establishing a separate tolerance.
Onion, dried	None	6000	Available residue data supports establishing a tolerance.
Garlic, dried	None	6000	Available residue data supports establishing a tolerance.
Grape, raisin	None	4	Proposed new use.
Fig	None	3	Proposed new use.
Plum, prune, dried	None	2	Proposed new use.

D. Regulatory Rationale

The Agency has determined that products containing the active ingredient PPO are eligible for reregistration provided that the risk mitigation measures outlined in this document are adopted and label amendments are made to reflect these measures. The following is a summary of the risk mitigation measures and EPA's rationale for the decision for managing risks associated with the use of PPO. Where labeling revisions are warranted, label changes and language are specified in Section V.

1. Human Health Risk Management and Mitigation

a. Dietary Risk Mitigation (Food and Drinking Water)

As discussed in Section 6.2 of the human health risk assessment (Appendix J), there are no risk estimates that exceed EPA's level of concern from dietary exposure (from both food and drinking water) to PPO or PCH. Therefore, no dietary risk mitigation is necessary. Although there are no risks of concern at the current labeled maximum application rate for PPO, Aberco, Inc., the technical registrant, proposed lowering the maximum application rate from 2.4 to 2.0 oz ai/ft^3 for tree nuts, herbs, spices, dried onion, dried garlic, cacao beans, and cocoa powder. This rate reduction will further reduce potential dietary exposure. Label changes and language necessary to incorporate this rate reduction are specified in Table 3 in Section V.

b. Residential Risk Mitigation

As discussed in Section 7 of the human health risk assessment (Appendix J), there are no residential uses for PPO but there is the potential for residential bystander exposure through the inhalation route to emissions from nearby PPO fumigation facilities. In the case of PPO, residential bystanders are considered to be any person in the vicinity of a fumigation facility unless he or she is a worker supervising or performing fumigation activities. This includes other workers, nearby residents, and other bystanders. Residential risks were assessed separately for exposure to emissions resulting from three methods of fumigation: fumigation with vacuum-sealed pressurized chambers (also referred to as commercial sterilization chambers) equipped with emission reduction technology, fumigation with vacuum-sealed pressurized chambers not equipped with emission reduction technology, and all other commodity fumigation (which occurs outdoors in chambers and in/under loose-fitting structures such as trailers, rail cars, tents, or tarps). Maximum application rates vary depending on the type of fumigation facility. The end-use product labeled for use only in vacuum-sealed pressurized chambers has a maximum application rate of 2.4 oz ai/ft^3 while the end-use product labeled to provide for use in facilities that are not vacuum-sealed pressurized chambers has a maximum application rate of 0.0448 oz ai/ft^3.

For vacuum-sealed pressurized chambers equipped with emission reduction technology that achieves a 99% reduction in PPO emissions, potential non-cancer (acute and chronic) risks, as well as cancer risks, for residential bystanders are not of concern. Therefore, no residential risk mitigation is needed for vacuum-sealed pressurized chambers equipped with emission reduction technology.

For fumigation in vacuum-sealed pressurized chambers not equipped with emission reduction technology, there are potential acute risks of concern to residential bystanders at the higher rate used in these chambers. The Probabilistic Exposure and Risk Model for FUMigants, or PERFUM, (V2.1.2) was used to determine distances from these facilities where residential bystanders would not be exposed to concentrations of PPO that exceed the acute level of concern during fumigation treatment and aeration. PERFUM is available at http://www.sciences.com/perfum/index.html and will eventually be placed on the Agency's website at http://www.epa.gov/opphed01/models/fumigant/. The PERFUM modeling framework was subjected to a Scientific Advisory Panel (SAP) review in 2004. Please refer to the SAP background documents and the SAP report at http://www.epa.gov/scipoly/sap/2004/index.htm. Characterization of the Agency's use of PERFUM in estimating acute bystander exposure to PPO is included in Section 7.2 of the human health risk assessment (Appendix J).

The distances identified by PERFUM for vacuum-sealed pressurized chambers not equipped with emissions technology range up to 1440 meters (or 4724 feet), as indicated in Section 7.2 of the human health risk assessment (Appendix J). EPA understands that the vast majority of these facilities currently use emission reduction technology, often to comply with air pollution standards. Therefore, to reduce residential bystander exposure to PPO and address acute risks of concern associated with fumigations in vacuum-sealed pressurized chambers, the Agency is requiring that all of these facilities utilize emission reduction technology, such as scrubbers and acid bubblers, that achieve a performance standard of 99% emission reduction.

EPA has concluded that use of emission reduction technology is protective, practical, and feasible. As noted above, all risks for residential bystanders are below EPA's level of concern for vacuum-sealed pressurized chambers equipped with such emission reduction technology. Therefore, potential risks resulting from exposure from the use of PPO in vacuum-sealed pressurized chambers will be addressed with addition of this technology requirement. Please refer to Table 3 in Section V for the specific label changes and language needed.

For all other commodity fumigation (i.e., those with a much lower maximum application rate), potential acute risks of concern were also identified for residential bystanders. Longer durations of exposure to bystanders are not expected because these methods of fumigation occur infrequently and intermittently in non-permanent sources (e.g., temporary or mobile structures such as rail cars, tents, and tarps as indicated above). Risks were assessed for residential bystanders during fumigation treatment and aeration at various distances from the fumigation facility using PERFUM, although the distances needed to mitigate risks of concern were much smaller than for vacuum-sealed pressurized chambers using the higher application rate. To reduce residential bystander exposure to PPO and address acute risks of concern associated with fumigations in facilities other than vacuum-sealed pressurized chambers equipped with emission reduction technology, EPA is requiring facilities that are not vacuum-sealed pressurized chambers to maintain a buffer zone of 55 meters (or 180 feet), within which bystanders must be excluded during fumigation treatment and aeration. This buffer zone must be established and maintained until PPO concentrations being exhausted from the treated enclosure are less than 10 ppm (although aeration may continue after this concentration threshold is met).

The buffer zone of 180 feet is based on the application rate and size of the fumigation facility and was calculated for a 5000 ft^3 facility to which a maximum of 0.0448 oz ai/ft^3 is applied. Language on the product label that provides for use in facilities that are not vacuum-sealed pressurized chambers restricts use to small-scale structures, as described above. A higher application rate or larger fumigation facility would result in a larger buffer zone being necessary to ensure that risks to residential bystanders are not of concern. Therefore, EPA is requiring that labels for products that can be used in facilities other than vacuum-sealed pressurized chambers equipped with emission reduction technology, clearly limit fumigation to a maximum application rate of 0.0448 oz ai/ft^3 in a facility that is at maximum 5000 ft^3. The Agency believes that these restrictions are reasonable and sufficient to allow for all existing and proposed new uses. Please refer to Table 3 in Section V for the specific label changes and language needed.

c. Aggregate Risk Mitigation

As discussed in Section 8 of the human health risk assessment (Appendix J), a quantitative aggregate risk assessment was not completed for PPO because the endpoints and corresponding doses or concentrations selected for dietary and residential (in this case, residential bystander) exposures are not based on a common effect. As such, mitigation for specific routes and pathways of exposure will be protective of aggregate risks, including cancer risks, and no additional risk mitigation is necessary based on aggregate exposure.

d. Occupational Risk Mitigation

As discussed in Section 10 of the human health risk assessment (Appendix J) there are potential cancer and non-cancer chronic risks of concern to workers, including workers who are supervising or performing fumigation activities and other on-site personnel who are not involved in fumigation activities (such as fork-lift drivers), from the use of PPO in vacuum-sealed pressurized chambers and all other commodity fumigation.

There are no occupational risks of concern from the dermal route of exposure to PPO if the following personal protective equipment (PPE) is worn, which the Agency has determined adequately reduces the potential for dermal exposure: chemical-resistant gloves, chemical-resistant apron, chemical-resistant footwear, face-sealing (vapor-proof) goggles, and a full-face shield (unless a respirator that covers the entire face is worn). EPA has determined that this PPE must be worn when there is the potential for contact with liquid PPO due to PPO's classification as a severe eye and skin irritant. Please refer to Table 3 in Section V for the specific label language needed.

Potential risks of concern do exist, however, from the inhalation route of exposure to PPO at the current labeled exposure concentration limit of 20 parts per million (ppm). As discussed in Section 10 of the human health risk assessment (Appendix J), at an exposure concentration greater than 2 ppm as an 8-hour time weighted average (TWA), potential non-cancer risks to workers exceed EPA's level of concern. To reduce occupational exposure to PPO and address risks of concern for workers, the daily or 8-hour TWA concentration must be limited to 2 ppm and specified as an 8-hour TWA on PPO labels. Additionally, the Agency is requiring that respiratory protection, as described below, must be worn when concentrations of PPO are measured at or above 20 ppm as a direct-read sample in any area a worker may be in.

The Agency has concluded that mitigation for non-cancer risks of concern at an 8-hour TWA concentration of 2 ppm, which is the recommended worker exposure concentration by the American Conference of Governmental Industrial Hygienists, is protective of all potential exposure durations (including acute, short-term, intermediate-term, and chronic). Additionally, data supporting a threshold carcinogenic mode of action (MOA) for PPO have been provided to EPA. Initial analysis by the Agency indicates that the proposed MOA is highly plausible. Therefore, EPA has also concluded that potential cancer risks to workers from inhalation exposure to PPO should be regulated at this same concentration limit because the non-cancer chronic endpoint is based on nasal lesions that are considered precursors to the development of tumors. The Agency has concluded that potential cancer risks will not exceed EPA's level of concern using the 8-hour TWA concentration limit of 2 ppm.

To ensure that occupational exposure to PPO is below 2 ppm as an 8-hour TWA concentration, the responsible party supervising the fumigation must determine when appropriate respiratory PPE, aeration/ventilation, and other mitigation techniques (such as changing work schedules or fumigation processes) are necessary. Responsible parties supervising fumigations may use a variety of air monitoring devices to determine when mitigation is needed. These devices include direct-read instrumentation, passive air monitoring (i.e., badges with activated carbon adsorbent), and active air monitoring (i.e., calibrated air collection pumps with standard

charcoal filter tubing). Workers who are supervising or performing fumigation activities are the only workers who may be within the buffer zone described above for bystanders, provided their exposure to PPO does not exceed an 8-hour TWA of 2 ppm.

If the responsible party determines that respiratory PPE is needed to ensure that PPO concentrations are not greater than 2 ppm as a TWA for an individual worker, or, concentrations of PPO are measured at or above 20 ppm as a direct-read sample in any area a worker may be in, either a supplied air (SA) respirator or self-contained breathing apparatus (SCBA) must be worn. The Agency has determined that the use of air purifying respirators (APRs) for protection against PPO exposure is not permissible at this time due to several factors. The National Institute for Occupational Safety and Health (NIOSH) has not given certification to any cartridge used with APRs that is specifically for protection against PPO, and NIOSH does not recommend use of APRs for PPO. In addition, no manufacturer has identified a cartridge for use as protection against PPO in APRs. If, in the future, a cartridge is certified for protection against PPO, the Agency may approve use of APRs with the certified cartridge for protection against PPO. Please refer to Table 3 in Section V for the specific label changes and language needed.

EPA has determined that for PPO a performance standard approach is appropriate for protecting workers because strict label requirements would not consider site-specific circumstances. By specifying a performance standard on product labels, the Agency is providing responsible parties supervising fumigations with the flexibility to identify the best mitigation practices for each fumigation facility and to adjust the periods during which appropriate respiratory PPE, aeration/ventilation, and/or other mitigation techniques are necessary for that facility. By monitoring to determine whether and when respiratory PPE is needed to meet the performance standard, responsible parties supervising fumigations can ensure workers are protected without burdening them with unnecessary protective equipment.

2. Ecological Risk Management and Mitigation

As discussed in the environmental fate and effects risk assessment (Appendix K), ecological risks (direct adverse acute and chronic effects) to non-target aquatic and terrestrial organisms are not of concern from the use of PPO in indoor vacuum-sealed pressurized chambers. For all outdoor commodity fumigation with PPO, ecological risks (direct adverse acute and chronic effects) to non-target aquatic and terrestrial organisms are also not of concern. Quantitative determinations regarding the potential for acute risks of concern, or direct adverse acute effects, to non-target aquatic plants from PPO dissolved in surface water, and to non-target terrestrial plants from contact with PPO in its vapor form, cannot be made due to the lack of available effects data with which to define suitable toxicity endpoints. However, EPA has concluded that none of the uses or use patterns of PPO are expected to result in significant exposure in surface water and that the short durations for which plants can be exposed to PPO in its vapor form may be insufficient to cause demonstrable adverse effects. The Agency intends to require confirmatory acute toxicity data for these taxa, and the specific data requirement is listed below in Table 2 in Section V.

3. Other Labeling Requirements

In order to be eligible for reregistration, additional PPO use and user safety information also needs to be included in the labeling of all end-use products containing PPO. Uses and use patterns need to be clarified as indicated in Table 3 below to reflect and better describe actual use patterns for PPO. EPA has determined that products containing the active ingredient PPO meet the criteria for restricted use classification due to PPO's toxicity (see 40 CFR 152.170). Further, individuals handling and applying such products need specialized training and equipment and must perform complex operations or procedures to ensure safe use. As such, all labels must include language identifying end-use products as restricted use. For the specific label statements and a list of additional data requirements necessary to confirm this decision, refer to Section V of this RED document.

4. Threatened and Endangered Species Considerations

The Agency's screening level risk assessment for endangered and threatened species concluded that use of PPO has no direct adverse effects on listed species in the following taxonomic groups: terrestrial invertebrates, birds, terrestrial phase amphibians, reptiles, mammals, freshwater fish, aquatic phase amphibians, freshwater crustaceans, marine/estuarine fish, and marine/estuarine invertebrates. The Agency's level of concern for direct adverse effects was exceeded, however, for listed species in the following taxonomic groups: monocot terrestrial and semi-aquatic plants, dicot terrestrial and semi-aquatic plants, aquatic vascular plants, and mollusks. There is also the potential for indirect adverse effects for listed species in multiple taxonomic groups that are dependent upon species that do experience direct adverse effects. These findings are based solely on EPA's screening level assessment and do not constitute "may affect" findings under the Endangered Species Act.

The Agency has developed the Endangered Species Protection Program to identify pesticides whose use may cause adverse impacts on threatened and endangered species and to implement mitigation measures that address these impacts. The Endangered Species Act requires federal agencies to ensure that their actions are not likely to jeopardize listed species or adversely modify designated critical habitat. To analyze the potential of registered pesticide uses that may affect any particular species, EPA uses basic toxicity and exposure data developed for REDs and considers it in relation to individual species by evaluating important ecological parameters, pesticide use information, the geographic relationship between specific pesticide uses and species locations, and biological requirements and behavioral aspects of the particular species. When conducted, this species-specific analysis will take into consideration any risk mitigation measures that are being implemented at the time as a result of this RED.

Following this future species-specific analysis, a determination that there is a likelihood of potential effects to a listed species or its critical habitat may result in limitations on use of PPO, other measures to mitigate any potential effects, or consultations with the Fish and Wildlife Service and/or the National Marine Fisheries as appropriate. If the Agency determines use of PPO "may affect" listed species or their designated critical habitat, EPA will employ the provisions in the Services regulations (50 CFR Part 402). Until a species-specific analysis is completed, the risk mitigation measures being implemented through this RED (e.g., the

requirement for use of 99% emission reduction technology for vacuum-sealed pressurized chambers) will reduce the likelihood that endangered and threatened species may be exposed to PPO at levels of concern. EPA is not requiring specific PPO label language at the present time relative to threatened and endangered species. If, in the future, specific measures are necessary for the protection of listed species, the Agency will implement them through the Endangered Species Protection Program.

V. What Registrants Need to Do

The Agency has determined that products containing the active ingredient PPO are eligible for reregistration provided that the risk mitigation measures outlined in this document are adopted and label amendments are made to reflect these measures. The Agency intends to issue DCIs for generic (technical grade) data and product-specific data. Generally, registrants will have 90 days from receipt of a generic DCI to complete and submit response forms or request time extension and/or waiver requests with a full written justification. The DCIs will include specific requirements and instructions on how to do so. Table 2 below presents the additional generic data the Agency intends to require for PPO to confirm the decision that products containing the active ingredient PPO are eligible for reregistration. For product-specific DCIs, registrants will have eight months from receipt of the DCI to submit data and to submit amended labels. In order for products containing the active ingredient PPO to be eligible for reregistration, all product labels must be amended to incorporate the specific changes and language presented in Table 3 below. Table 3 also describes how the required language should be incorporated.

A. Manufacturing-Use Products

1. Additional Generic Data Requirements

The generic database supporting the reregistration of PPO has been reviewed and determined to be substantially complete. However, EPA is requiring the following additional data to confirm the decisions presented in this RED. The Agency intends to issue a generic DCI for this data.

Table 2. Data requirements for the reregistration of PPO

Submittal of Analytical Reference Standards Analytical references standards for PPO and PCH are not currently available in the EPA National Pesticide Standards Repository. Analytical reference standards of PPO and PCH must be supplied and supplies replenished as requested by the Repository.	860.1650	171-13
Chronic Toxicity (nonrodent) (in reserve) Pending results of further review of the proposed cancer threshold or MOA for PPO.	870.4100b	83-1
Modified Aquatic Plant Toxicity Study	Special Study	N/A
Modified Terrestrial Plant Toxicity Study	Special Study	N/A

2. Labeling for Manufacturing-Use Products

To ensure compliance with FIFRA, labeling for all manufacturing-use products (MUPs) should be revised to comply with all current EPA regulations, PR Notices, and applicable policies. The MUP labeling should bear the specific language presented in Table 3 below.

B. End-Use Products

1. Additional Product-Specific Data Requirements

Section 4(g)(2)(B) of FIFRA calls for the Agency to obtain any needed product-specific data regarding the pesticide after a determination of eligibility has been made. The registrant must review previous data submissions to ensure they meet current EPA acceptance criteria and if not, commit to conduct new studies. If a registrant believes that previously submitted data meet current testing standards, then the study MRID numbers can be cited according to the instructions in the Requirement Status and Registrations Response Form provided for each product. The Agency intends to issue a separate product-specific DCI outlining specific data requirements.

2. Labeling for End-Use Products

To be eligible for reregistration, labeling changes are necessary to implement measures outlined in Section IV above. The specific changes and language are presented in Table 3 below. Generally, conditions for the distribution and sale of products bearing old labels/labeling will be established when the label changes are approved. However, specific existing stocks time frames will be established case-by-case, depending on the number of products involved, the number of label changes, and other factors.

Table 3. Summary of required labeling changes for PPO products

For all Manufacturing-Use Products	"Propylene oxide only can be formulated into end-use products containing directions for use that include acceptable air concentration levels of 2 ppm as an 8-hour time weighted average and other measures for ensuring that workers and other persons are not exposed to concentrations of propylene oxide that exceed this level unless appropriate respiratory protection is used." "Propylene oxide cannot be formulated into end-use products labeled for use on edible gums or birdseed. End-use product labels must be revised to delete all references to and use directions for edible gums or birdseed." "Propylene oxide only can be formulated into end-use products that are classified as and identified as Restricted Use."	Directions for Use
One of these statements may be added to a label to allow reformulation of the product for a specific use or use-pattern or all additional uses supported by a formulator or user group	"This product may be used to formulate products for specific use(s) not listed on the MP label if the formulator, user group, or grower has complied with U.S. EPA submission requirements regarding support of such use(s)." "This product may be used to formulate products for any additional use(s) not listed on the MP label if the formulator, user group, or grower has complied with U.S. EPA submission requirements regarding support of such use(s)."	Directions for Use
Environmental Hazards Statements Required by the RED and Agency Label Policies	**"ENVIRONMENTAL HAZARDS** This pesticide is toxic to birds and mammals. Do not discharge effluent containing this product into lakes, streams, ponds, estuaries, oceans, or other waters unless in accordance with the requirements of a National Pollution Discharge Elimination System (NPDES) permit and the permitting authority has been notified in writing prior to discharge. Do not discharge effluent containing this product to sewer systems without previously notifying the local sewage treatment plant authority. For guidance contact your State Water Board or Regional Office of the EPA."	Precautionary Statements

End-Use Products Intended for Occupational Use		
Restricted Use Pesticide	"RESTRICTED USE PESTICIDE DUE TO INHALATION TOXICITY For retail sale to and use only by Certified Applicators or persons under their direct supervision and only for those uses covered by the Certified Applicator's certification."	Top of Front Panel
Identify as a fumigant all propylene oxide end-use products	Prominently identify the end-use product as a "**Fumigant"**	Insert the word "fumigant" as part of the product name or close to the product name, either as part of the product-type identification or as a separate word or sentence
Add precautionary language in Spanish on propylene oxide end-use products	Add the following Spanish signal word and statement: "**PELIGRO** Si Usted no entiende la etiqueta, busque a alquien para que se la explique a Usted en detalle. (If you do not understand the label, find someone to explain it to you in detail.)"	On front panel of the label near the signal word DANGER.
Add acceptable air concentration language to propylene oxide end-use products	"**AIR CONCENTRATION LEVEL** The acceptable air concentration level for persons exposed to propylene oxide is 2 ppm (8 mg/m^3) as a time weighted average."	In the Hazards to Humans and Domestic Animals section of the labeling immediately following the precautionary statements.

PPE Requirements Established by the RED for propylene oxide end-use products	"**PERSONAL PROTECTIVE EQUIPMENT** Some materials that are chemical-resistant to this product are (*registrant inserts correct chemical-resistant material*). If you want more options, follow the instructions for category [*registrant inserts* *A,B,C,D,E,F,G,orH*] on an EPA chemical-resistance category selection chart. All handlers opening propylene oxide drums or tanks, cleaning up leaks or spills, or who otherwise may potentially contact liquid propylene oxide, must wear: > long-sleeved shirt and long pants, > chemical-resistant gloves, > chemical-resistant footwear plus socks, > chemical-resistant apron. > face-sealing goggles, and > full-face shield, unless a respirator that covers the entire face is worn. **Respirator Requirements:** Once propylene oxide has been introduced into an enclosure, the certified applicator supervising the fumigation must make sure that all persons in the exposure area (the treatment area and the buffer zone, if applicable) have appropriate respiratory protection or are removed from the exposure area. **Air Concentrations 20 PPM or Greater from a Direct-Read Device or Air Concentrations Greater than 2 ppm as an 8-Hour Time Weighted Average:** If propylene oxide air concentration level is measured to be 20 ppm or greater at anytime when measured using a direct read device *or* if propylene air concentration exceeds 2 ppm as an 8-hour time weighted average, each person in the exposure area must wear either -- a supplied-air respirator (MSHA/NIOSH approval number prefix TC-19C), or -- a self-contained breathing apparatus (SCBA) (MSHA/NIOSH approval number prefix TC-13F). **Air Concentrations at or below 2 PPM as an 8-hour Time Weighted Average:** No respirator is required if the air concentration level of propylene oxide in the exposure area is measured to be at or below 2 ppm as an 8-hour time weighted average *and* the air concentration is lower than 20 ppm using a direct-read device."	Immediately following/below Precautionary Statements: Hazards to Humans and Domestic Animals

User Safety Requirements for all propylene oxide end-use products	"**WORK SAFETY REQUIREMENTS** Respirator Requirements: When a respirator is required for use with this product, the certified applicator supervising the fumigation must make sure that: a) Respirators must be fit tested and fit checked using a program that conforms with OSHA's requirements (described in 29 CFR Part 1910.134; b) Respirator users must be trained using a program that conforms with OSHA's requirements (described in 29 CFR Part 1910.134; c) Respirator users must be examined by a qualified medical practitioner to ensure the physical ability to safely wear the style of respirator to be worn; d) Respirators must be maintained according to a program that conforms with OSHA's requirements (described in 29 CFR Part 1910.134. -- If liquid fumigant splashes or spills on clothing, remove them at once, and place them outdoors in an isolated place to aerate, because fumes will be an intolerable source of irritation. -- Immediately after application remove personal protective equipment. Do not reuse the personal protective equipment until cleaned. Keep and wash the work clothing and personal protective equipment separately from other laundry. -- Discard clothing and other absorbent materials that have been drenched or heavily contaminated with this product. Do not reuse them. -- Follow manufacturer's instructions for cleaning/maintaining personal protective equipment."	Precautionary Statements: Hazards to Humans and Domestic Animals immediately following Personal Protective Equipment Requirements
User Safety Recommendations	"User Safety Recommendations Users should wash hands before eating, drinking, chewing gum, using tobacco, or using the toilet. Users should remove clothing/PPE immediately if pesticide gets inside. Then wash thoroughly and put on clean clothing. Users should remove PPE immediately after handling this product. Wash the outside of gloves before removing. As soon as possible, wash thoroughly and change into clean clothing."	Precautionary Statements under: Hazards to Humans and Domestic Animals immediately following User Safety Requirements (Must be placed in a box.)

Restrictions for Vacuum-Sealed Pressurized Chambers	**"Fumigation in Vacuum-Sealed Pressurized Chambers** All vacuum-sealed pressurized chambers must be fitted with equipment specifically designed to reduce propylene oxide emissions by 99 percent."	In the Directions for Use under "Fumigation in Vacuum-Sealed Pressurized Chambers"
Restrictions for Fumigation Not Contained within a Vacuum-Sealed Pressurized Chamber	**"Fumigation Not Contained Within a Vacuum-Sealed Pressurized Chamber** For any fumigation that does not take place in a vacuum-sealed pressurized chamber, a 180-foot buffer zone must be established around the treated enclosure from the time propylene oxide is introduced into the enclosure and must remain in effect until the air concentration of propylene oxide being exhausted from the treated enclosure is measured to be 10 ppm or less. Fumigation that does not take place in a vacuum-sealed pressurized chamber is limited to a maximum concentration of 0.0448 ounces of propylene oxide per cubic foot of fumigation enclosure and the enclosure where fumigation is taking place can be no more than 5000 cubic feet. **Buffer Zone Entry Restrictions** Entry by the certified applicator supervising the fumigation, or persons under his/her direct supervision, is permitted in the 180-foot buffer zone, provided either: -- the appropriate respirator is worn (see PPE requirements elsewhere in this labeling); *OR* -- the air concentration level for propylene oxide is at or below 2 ppm for an 8-hour time weighted average. The certified applicator supervising the fumigation must ensure that any person, except the certified applicator or persons under his/her direct supervision, is kept outside the 180-foot buffer zone surrounding the treated enclosure from the time propylene oxide is introduced into the enclosure until the air concentration of propylene oxide being exhausted from the treated enclosure is measured to be 10 ppm or less.**"**	In the Directions for Use under the heading: Fumigation Not Contained Within a Vacuum-Sealed Pressurized Chamber" immediately following "Fumigation in Vacuum-Sealed Pressurized Chambers"

Onsite Notification for all propylene oxide end-use products	"**PLACARDING OF FUMIGATED ENCLOSURES** The certified applicator supervising the fumigation (or person under his/her direct supervision) must placard all entrances to the fumigation enclosure with signs bearing: -- skull and crossbones symbol -- "DANGER/PELIGRO," -- "Area under fumigation, DO NOT ENTER/NO ENTRE," -- "Propylene Oxide Fumigant in use," -- the date and time of fumigation, and -- name, address, and telephone number of the certified applicator supervising the fumigation." "The certified applicator supervising the fumigation must ensure that no person, except the certified applicator or persons under his/her direct supervision who are wearing appropriate respiratory protection, enters into the treated enclosure until the signs are removed. Such signs must only be removed when aeration has occurred and when the air concentration level of propylene oxide is monitored as described in this labeling and the monitoring indicates that workers can enter without respiratory protection. Signs must remain legible during entire posting period. The warning signs at entrances to fumigation enclosure may only be removed by the certified applicator supervising the fumigation or person under his/her direct supervision. Vehicles must be placarded with applicable U.S. Department of Transportation warning signs."	In the Directions for Use under the heading "PLACARDING OF FUMIGATED ENCLOSURES"
Environmental Hazards Statements	"**ENVIRONMENTAL HAZARDS** This pesticide is toxic to birds and mammals. Do not discharge effluent containing this product into lakes, streams, ponds, estuaries, oceans or other waters unless in accordance with the requirements of a National Pollutant Discharge Elimination System (NDPES) permit and the permitting authority has been notified in writing prior to discharge. Do not discharge effluent containing this product to sewer systems without previously notifying the local sewage treatment plants authority. For guidance contact your State Water Board or Regional Office of the EPA."	Precautionary Statements under Environmental Hazards
Storage and Disposal language of for all propylene oxide end-use products	"Persons moving, handling, or opening containers must wear the personal protective equipment (including prescribed respirators when necessary) specified in the Human Hazards section of this labeling. Store containers in a well-ventilated area."	Storage and Disposal section of the label

Spill and Leak Procedures of for propylene oxide end-use products	"**SPILL AND LEAK PROCEDURES** Evacuate everyone from the immediate area of the spill or leak. For entry into affected area to correct problem, wear the personal protective equipment (including prescribed respirators) specified in the Hazards to Humans section of this labeling. Move leaking or damaged containers outdoors or to an isolated location. Observe strict safety precautions. Work upwind, if possible. Allow spilled fumigant to evaporate. Only correctly trained and PPE-equipped handlers are permitted to perform such cleanup. Do not permit entry into the spill or leak area by any other person until the air concentration level of propylene oxide is measured to be at or below 2 ppm as an 8-hour time weighted average. Contaminated soil, water, and other cleanup debris is a toxic hazardous waste. Report spill to the National Response Center (800-424-8802) if the reportable quantity of 1000 lbs. is exceeded."	In the labeling section titled "Storage and Disposal" **or** by themselves under the heading "Spill and Leak Procedures"
General Application Restrictions	"**DIRECTIONS FOR USE** It is a violation of Federal Law to use this product in a manner inconsistent with its labeling. Do not apply this product in a way that will contact workers or other persons, either directly or through drift. Only protected handlers may be in the area during application. For any requirements specific to your State or Tribe, consult the agency responsible for pesticide regulation."	Place in the Direction for Use directly below the heading "Directions for Use"

Use-Specific Application Restrictions (The product label must list the specified application rates in ounces or pounds of formulated product in place of ounces of active ingredient.)	For products with the following uses and use patterns please amend labels to include specified language and to reflect the following application rates: **If labels refer to "gums",** the label language must be changed to **"**non-edible gums". **If labels refer to "cocoa beans" or "cocoa",** the label language must be changed to **"**cacao beans" and "cocoa powder". Do not apply more than 2.0 oz ai/ft^3 per application when used in vacuum-sealed pressurized chambers. For all other fumigation methods, do not apply more than 0.0448 oz ai/ft^3. **If labels refer to "processed spices",** the label language must be changed to "dried or processed herbs and spices", "dried onions", and "dried garlic". Do not apply more than 2.0 oz ai/ft^3 per application when used in vacuum-sealed pressurized chambers. For all other fumigation methods, do not apply more than 0.0448 oz ai/ft^3. **If labels refer to "in-shell and processed nutmeats (except peanuts)",** the label language must be changed to "raw or processed tree nuts". Do not apply more than 2.0 oz ai/ft^3 per application when used in vacuum-sealed pressurized chambers. For all other fumigation methods, do not apply more than 0.0448 oz ai/ft^3.	Directions for Use Associated with the Specific Use Pattern

[a] PPE that is established on the basis of Acute Toxicity of the end-use product must be compared to the active ingredient PPE in this document. The more protective PPE must be placed in the product labeling. For guidance on which PPE is considered more protective, see PR Notice 93-7.

VI. Appendices

Appendix A. Propylene Oxide Uses and Use-Patterns Eligible for Reregistration

Cosmetic articles and ingredients	0.0448	N/A	N/A	N/A	
	2.4	N/A	N/A	N/A	Rate allowable only for use in vacuum-sealed pressurized chambers.
Non-edible gums	0.0448	N/A	N/A	N/A	
	2.4	N/A	N/A	N/A	Rate allowable only for use in vacuum-sealed pressurized chambers.
Ores	0.0448	N/A	N/A	N/A	
	2.4	N/A	N/A	N/A	Rate allowable only for use in vacuum-sealed pressurized chambers.
Packaging	0.0448	N/A	N/A	N/A	
	2.4	N/A	N/A	N/A	Rate allowable only for use in vacuum-sealed pressurized chambers.
Pigments	0.0448	N/A	N/A	N/A	
	2.4	N/A	N/A	N/A	Rate allowable only for use in vacuum-sealed pressurized chambers.
Pharmaceutical materials	0.0448	N/A	N/A	N/A	
	2.4	N/A	N/A	N/A	Rate allowable only for use in vacuum-sealed pressurized chambers.
Discarded nut shells prior to disposal	0.0448	N/A	N/A	N/A	
	2.4	N/A	N/A	N/A	Rate allowable only for use in vacuum-sealed pressurized chambers.
Dried or processed herbs and spices	0.0448	N/A	N/A	N/A	
	2.0	N/A	N/A	N/A	Rate allowable only for use in vacuum-sealed pressurized chambers.
Dried onion	0.0448	N/A	N/A	N/A	
	2.0	N/A	N/A	N/A	Rate allowable only for use in vacuum-sealed pressurized chambers.
Dried garlic	0.0448	N/A	N/A	N/A	
	2.0	N/A	N/A	N/A	Rate allowable only for use in vacuum-sealed pressurized chambers.

Cacao bean	0.0448	N/A	N/A	N/A	
	2.0	N/A	N/A	N/A	Rate allowable only for use in vacuum-sealed pressurized chambers.
Cocoa powder	0.0448	N/A	N/A	N/A	
	2.0	N/A	N/A	N/A	Rate allowable only for use in vacuum-sealed pressurized chambers.
Raw or processed tree nuts	0.0448	N/A	N/A	N/A	
	2.0	N/A	N/A	N/A	Rate allowable only for use in vacuum-sealed pressurized chambers.

Appendix B. Table of Generic Data Requirements and Studies Used to Make the Reregistration Decision

Guide to Appendix B

Appendix B contains listing of data requirements which support the reregistration for active ingredients within case #2560 (propylene oxide) covered by this RED. It contains generic data requirements that apply to simazine in all products, including data requirements for which a "typical formulation" is the test substance.

The data table is organized in the following formats:

1. Data Requirement (Column 1). The data requirements are listed in the order in which they appear in 40 CFR part 158. The reference numbers accompanying each test refer to the test protocols set in the Pesticide Assessment Guidance, which are available from the National technical Information Service, 5285 Port Royal Road, Springfield, VA 22161 (703) 487-4650.

2. Use Pattern (Column 2). This column indicates the use patterns for which the data requirements apply. The following letter designations are used for the given use patterns.

    A. Terrestrial food
    B. Terrestrial feed
    C. Terrestrial non-food
    D. Aquatic food
    E. Aquatic non-food outdoor
    F. Aquatic non-food industrial
    G. Aquatic non-food residential
    H. Greenhouse food
    I. Greenhouse non-food
    J. Forestry
    K. Residential
    L. Indoor food
    M. Indoor non-food
    N. Indoor medical
    O. Indoor residential

3. Bibliographic Citation (Column 3). If the Agency has acceptable data in its files, this column list the identify number of each study. This normally is the Master Record Identification (MIRD) number, but may be a "GS" number if no MRID number has been assigned. Refer to the Bibliography appendix (Appendix D) for a complete citation of the study.

830.1550	61-1	Product Identity and Composition	All	41011301
830.1600	61-2A	Description of materials used to produce the product	All	43139701
830.1620	61-2B	Description of production process	Al	43139701
830.1670	61-2B	Formation of Impurities	All	43139701
830.1700	62-1	Preliminary Analysis	All	43139702
830.1750	62-0	Certification of Limits	All	41874103
830.1800	62-3	Analytical Method	All	41874103
830.6302	63-2	Color	All	41874103
830.6303	63-3	Physical State	All	41874103
830.6304	63-4	Odor	All	41874103
830.6313	63-13	Stability to normal and elevated temperatures, metals, and metal ions	All	44799201
830.7000	63-12	pH	All	41011301
830.7050	None	UV/Visible Absorption	All	
830.7220	63-6	Boiling Point	All	41011301
830.7300	63-7	Density	All	41011301
830.7550	63-11	Partition coefficient, shake flask method	All	41011301
830.7840	63-8	Solubility	All	41011301
830.7950	63-9	Vapor Pressure	All	41011301
850.4150 (modified)	122-1	Special Study: Modified Terrestrial Plant Toxicity	All	**Data Gap**
850.4400 or 850.4500 (modified)	122-2 123-2 124-2	Special Study: Modified Aquatic Plant Toxicity	All	**Data Gap**
860.1300	171-4A	Nature of Residue - Plants	A	45301901 45301902
860.1340	171-4C	Residue Analytical Method - Plants	A	45499101
860.1360	171-4M	Multiresidue Method	A	44692802
860.1650	171-13	Analytical Reference Standards	A	**Data Gap**
860.1500	171-4K	Crop Field Trials - Crop group 19A: Herbs		
		Basil, Dried Leaves	A	45301901
		Basil, dried leaves - babyfood		
		Chive		
		Coriander, leaves		
		Coriander, leaves - babyfood		
		Dillweed		
		Herbs, other		
		Lemongrass		
		Marjoram		
		Marjoram - babyfood		
		Parsley, dried leaves		
		Parsley, dried leaves - babyfood		
		Savory		

860.1500	171-4K	Crop Field Trials - Crop group 19B: Spices		
		Cinnamon	A	45301901
		Cinnamon - babyfood		
		Spices, other		
		Spices, other - babyfood		
		Coriander, seed		
		Coriander, seed - babyfood		
		Dill, seed		
		Pepper, black and white		
		Pepper, black white - babyfood		
860.1500	171-4K	Crop Field Trials - Crop group 3: Bulb Vegetables		
		Garlic, dried	A,B	45301901
		Garlic, dried - babyfood		
		Onion, dry bulb, dried		
		Onion, dry bulb, dried - babyfood		
860.1500	171-4K	Crop Field Trials - Crop group 14: Tree Nuts		
		Almond	A,B	46867701
		Almond, babyfood		
		Almond oil		
		Almond oil, babyfood		
		Brazil nut		
		Butternut		
		Cashew		
		Chestnut		
		Flibert		
		Filbert oil		
		Hickory nut		
		Macadamia nut		
		Pecan		
		Walnut	A,B	44692801
860.1500	171-4K	Crop Field Trials - Crop group O: Other		
		Cocoa bean, chocolate	A,B	45138501
		Cocoa bean, powder		
		Fig	A,B	45813601
		Fig, dried		
		Grape, raison		
		Plum prune, fresh		
		Plum prune, fresh, babyfood		
		Plum prune, dried		
		Plum prune, dried, babyfood		
		Plum prune, juice		
		Plum prune, juice, babyfood		
870.1100	81-1	Acute Oral Toxicity - Rat	All	Smyth et al., 1941 and Antonova et al., 1981 as cited in USEPA, 1987
870.1300	81-3	Acute Inhalation Toxicity - Rat	All	NTP, 1985
870.2400	81-4	Primary Eye Irritation - Rabbit	All	Weil et al., 1963 as cited in WHO, 1985
870.2500	81-5	Primary Skin Irritation	All	Rowe et al., 1956 as cited in USEPA, 1987
870.3700	83-3A	Developmental Toxicity - Rat	All	41750801
870.3800	83-4	2-Generation Reproduction - Rat	All	45292701

870.4100	83-1A	Chronic Feeding Toxicity Study - Rat	All	Dunkelberg, 1982
870.4100	83-1B	Chronic Feeding Toxicity Study - Non-rodent	All	Sprinz et al., 1982 as cited in USEPA, 1994 Setzer at al., 1996 **Data Gap**
870.4200	83-2B	Carcinogenicity Mice	All	NTP, 1985
870.4300	83-5	Combined Chronic Toxicity/Carcinogenicity - Rats	All	41874102 42039901 Kuper et al., 1988 Lynch et al., 1984 NTP, 1985
870.5100	84-2	Bacterial Reverse Gene Mutation	All	Multiple references as cited in IARC, 1994
870.5375	84-2B	Cytogenetics	All	
870.5550	84-2	Unscheduled DNA Synthesis in Mammalian Cells in Culture	All	
870.7485	85-1	General Metabolism	All	WHO, 1985
N/A	N/A	24-week Rat Subchronic Inhalation	All	45292801
N/A	N/A	Subchronic Rat Oral (12- 14 days)	All	NTP, 1998
N/A	N/A	Subchronic Mouse Oral (12- 14 days)	All	NTP, 1998
N/A	N/A	Subchronic Inhalation Toxicity - Rat 13 weeks	All	NTP, 1985
N/A	N/A	Subchronic Inhalation Toxicity - Mouse 13 weeks	All	NTP, 1985
870.1100	81-1	Acute Oral Toxicity - Rat	All	Smyth et al., 1941 and USFDA, 1969 and Weisbrod, 1981 and Smyth et al., 1941 and USFDA, 1969 as cited in TNO BIBRA International, 1994
870.1200	81-2	Acute Dermal Toxicity - Rabbit/Rat	All	Smyth et al., 1969 and Weisbrod, 1981 as cited in TNO BIBRA International, 1994
870.1300	81-3	Acute Inhalation Toxicity - Rat	Al	Smyth and Carpenter, 1969 as cited in NTP, 1998
870.2400	81-4	Primary Eye Irritation - Rabbit	All	Carpenter and Smyth et al., 1946 as cited in NTP, 1998
870.2500	81-5	Primary Skin Irritation	All	Smyth et al., 1969 as cited in TNO BIBRA International, 1994
870.3100	82-1A	Subchronic Oral Toxicity: 90-Day Study Rodent	All	NTP, 1998
870.3150	82-1B	Subchronic Oral Toxicity: 90-Day Study Non-rodent	All	NTP, 1998
870.3700	83-3A	Developmental Toxicity - Rat	All	Exxon Chemical Company, 1980 as cited in NTP, 1998
870.3800	83-4	2-Generation Reproduction - Rat	All	NTP, 1998
870.4300	83-5	Combined Chronic Toxicity/Carcinogenicity: Rats	All	NTP, 1998
870.4300	83-5	Combined Chronic Toxicity/Carcinogenicity: Mice	All	NTP, 1998
870.5100	84-2	Bacterial Reverse Gene Mutation	All	NTP, 1998
870.5375	84-2B	Cytogenetics	All	NTP, 1998
870.5550	84-2	Unscheduled DNA Synthesis in Mammalian Cells in Culture	Al	NTP, 1998
870.7485	85-1	General Metabolism	All	NTP, 1998
N/A	N/A	Subchronic Rat Oral (14 days)	All	NTP, 1998

N/A	N/A	Subchronic Mouse Oral (14 days)	All	NTP, 1998

Appendix C. Technical Support Documents

Additional documentation in support of this RED is maintained in the OPP docket EPA-HQ-OPP-2005-0253. This docket may be accessed in the OPP docket room located at Room S-4900, One Potomac Yard, 2777 S. Crystal Drive, Arlington, VA. It is open Monday through Friday, excluding Federal holidays, from 8:30 a.m. to 4:00 p.m. All documents may be viewed in the OPP docket room or downloaded or viewed via the Internet at the following site: http://www.regulations.gov.

The docket initially contained preliminary risk assessments, supporting documents, and technical (or manufacturing-use) registrant error comments for PPO as of November 9, 2005. After a sixty-day public comment period, EPA considered the public comments that were submitted to the docket and revised the risk assessments as necessary. The revised risk assessments, any supporting documents that needed to be revised, an impact assessment, and memos describing the Health Effects Division (HED) and the Biological and Economic Assessment Division (BEAD) response to public comments will be added to the docket on August 9, 2006.

The Agency documents in the docket include:

1. Federal Register Notice: Propylene Oxide Risk Assessment, Notice of Availability, and Risk Reduction Options
2. PPO Revised Risk Assessment
3. PPO Response to Phase 1 Comments
4. Revised Residue Chemistry Chapter for Propylene Oxide Reregistration Eligibility Decision (RED) Document
5. PPO Dietary Chapter
6. Aberco Phase 1 Comments
7. PPO Incident Report
8. PPO MARC Memo
9. EFED PPO Chapter
10. PPO ORE Chapter
11. PPO MARC Memo dated 8/16/00
12. PPO CARC Memo 3/20/00
13. Federal Register Notice: Propylene Oxide Risk Assessment; Notice of Availability and Risk Reduction Options; Extension of Comment Period

14. Request for Additional Information and Risk Management Suggestions for the Reregistration of PPO Phase 3 Public Comment Period

15. Federal Register Notice: Propylene Oxide (PPO) Reregistration Eligibility Decision; Notice of Availability

16. Reader's Guide to the Propylene Oxide Docket EPA-HQ-OPP-2005-0253

17. Reregistration Eligibility Decision for Propylene Oxide

18. Propylene Oxide – Revised HED Risk Assessment for Reregistration Eligibility Decision (RED) Document, PC Code: 042501, DP Barcode: D316547

19. Propylene Oxide Acute, Chronic and Revised Cancer Dietary Exposure Assessments for the Reregistration Eligibility Decision PC Code: 042501, DP Barcode: D329648

20. Addendum to Revised PPO RED Chemistry Chapter Dated 09/19/05: Additional Residue Chemistry Data For Fumigation Use of Propylene Oxide In/on Almond and Walnut Nutmeats and Inshell Almonds. (MRID 46867701)

21. Propylene Oxide: Revised Phase IV Occupational and Residential Exposure Assessment and Recommendations for the Reregistration Eligibility Decision (RED) Document (RED Case 2560)

22. Propylene Oxide: Revised Non-Occupational/Residential Risk Assessment for Commodity Fumigations (RED Case 2560)

23. Appendix I. A.Ventura.4hr 2.8lb MSFEV

24. Appendix I. A.Ventura.4hr 2.8lb NS

25. Appendix I. A.Ventura.4hr 150lb MSFEV

26. Appendix I. A.Ventura.4hr 75lb MSFEV

27. Appendix I. A.Ventura.4hr 43.75lb MSFEV

28. Appendix I. A.Venturya.4hr 31.25lb MSFEV

29. Impact Assessment of Propylene Oxide and Alternatives on Almonds, Pecans, Walnuts and Spices (DP# 316567)

30. Propylene Oxide: Response to Public Comments on the HED Risk Assessment for Propylene Oxide; PC Code 042501; DP Barcode; 329650

31. BEAD Response to Phase 3 Public Comments Concerning the Reregistration of Propylene Oxide (PPO) for Uses on Almonds, Pecans, and Walnuts

32. EFED RED Chapter for Propylene Oxide (042501) DP Barcode D263366

Appendix D. Citations Considered to be Part of the Database Supporting the Reregistration Decision (Bibliography)

Guide to Appendix D

1. Contents of Bibliography. This bibliography contains citations of all studies considered relevant by EPA in arriving at the positions and conclusions stated elsewhere in the Reregistration Eligibility Document. Primary sources for studies in this bibliography have been the body of data submitted to EPA and its predecessor agencies in support of past regulatory decisions. Selections from other sources including the published literature, in those instances where they have been considered, are included.

2. Units of Entry. The unit of entry in this bibliography is called a "study." In the case of published materials, this corresponds closely to an article. In the case of unpublished materials submitted to the Agency, the Agency has sought to identify documents at a level parallel to the published article from within the typically larger volumes in which they were submitted. The resulting "studies" generally have a distinct title (or at least a single subject), can stand alone for purposes of review and can be described with a conventional bibliographic citation. The Agency has also attempted to unite basic documents and commentaries upon them, treating them as a single study.

3. Identification of Entry. The entries in this bibliography are sorted numerically by Master Record Identifier, or "MRID" number. This number is unique to the citation, and should be used whenever a specific reference is required. It is not related to the six-digit "Accession Number" which has been used to identify volumes of submitted studies (see paragraph 4(d)(4) below for further explanation). In a few cases, entries added to the bibliography late in the review may be preceded by a nine character temporary identifier. These entries are listed after all MRID entries. This temporary identifying number is also to be used whenever specific reference is needed.

4. Form of Entry. In addition to the Master Record Identifier (MRID), each entry consists of a citation containing standard elements followed, in the case of material submitted to EPA, by a description of the earliest known submission. Bibliographic conventions used reflect the standard of the American National Standards Institute (ANSI), expanded to provide for certain special needs.

    a. Author. Whenever the author could confidently be identified, the Agency has chosen to show a personal author. When no individual was identified, the Agency has shown an identifiable laboratory or testing facility as the author. When no author or laboratory could be identified, the Agency has shown the first submitter as the author.

    b. Document date. The date of the study is taken directly from the document. When the date is followed by a question mark, the bibliographer has deduced the date from the evidence contained in the

document. When the date appears as (1999), the Agency was unable to determine or estimate the date of the document.

c. Title. In some cases, it has been necessary for the Agency bibliographers to create or enhance a document title. Any such editorial insertions are contained between square brackets.

d. Trailing parentheses. For studies submitted to the Agency in the past, the trailing parentheses include (in addition to any self-explanatory text) the following elements describing the earliest known submission:

(1) Submission date. The date of the earliest known submission appears immediately following the word "received."

(2) Administrative number. The next element immediately following the word "under" is the registration number, experimental use permit number, petition number, or other administrative number associated with the earliest known submission.

(3) Submitter. The third element is the submitter. When authorship is defaulted to the submitter, this element is omitted.

(4) Volume Identification (Accession Numbers). The final element in the trailing parentheses identifies the EPA accession number of the volume in which the original submission of the study appears. The six-digit accession number follows the symbol "CDL," which stands for "Company Data Library." This accession number is in turn followed by an alphabetic suffix which shows the relative position of the study within the volume.

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41011301	Warren, M. (1988) Chemical Identity: 100% Propylene Oxide: Volume #1. Unpublished compilation prepared by Aberco Inc. 102 p.
41874103	Meyland, W.; Papa, L.; DeRossa, C.; et al. (1986) Chemicals of Current Interest - Propylene Oxide Health and Environmental Effects Profile. Unpublished study prepared by Syracuse Research Corp. and Environmental Criteria and Assessment. 45 p.
43139701	Mandava, N. (1994) Propylene Oxide Product Chemistry Data. Unpublished study prepared by Science Regulatory Services Int'l. 27 p.
43139702	Ellison, F. (1994) Propylene Oxide Product Chemistry Data: Lab Project Number: 780-01. Unpublished study prepared by Case Consulting Laboratories, Inc. 16 p.
44799201	Patil, S. (1999) Determination of Propylene Oxide Stability in USP Synthetic Human Gastric Juice and in USP Synthetic Gastric Juice Mixture Modified to the Conditions of the Rat Forestomach, Using (carbon-14)-Propylene Oxide: Pilot Study: Final Report: Lab Project Number: 0533-AC-02. Unpublished study prepared by SISTEK Research Laboratories. 49 p.
N/A	Conway, R.A., G.T. Waggy, M.H. Spiegel, R.L. Berglund. 18983. Environmental fate and effects of ethylene oxide. Environ.Sci.& Technol. 17:107-112.
N/A	Crews, R.C. 1974. Effects of propylene Oxide on Selected Species of Fishes. Technical Report AFATL-TR-74-183. Air Force Armament Laboratory, Eglin Air Force Base, FL, 13pp.
N/A	Hazardous Substances Data Bank (HSDB). 2005. 1,2 Propylene Oxide. Monograph is available on-line through the National Library of Medicine, http://toxnet.nlm.nih.gov.
N/A	Isikber A.A., S. Navarro, S. Finkelman, M. Rindner, A. Azrieli, R. Dias. 2004. Toxicity of propylene oxide at low pressure against life stages of four species of stored product insects. Journal of Economic Entomology, 97:281-295.
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44692801	"Residues of Propylene Oxide, Propylene Chlorohydrin, and Propylene Bromohydrin in Nutmeats Following Fumigation with Propylene Oxide (PPO)." Authored by L. C. Schrier and D. A. Koch. (Dated October 9, 1998).
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45138501	"Magnitude of the Residue in Cocoa Powder Following Fumigation with Propylene Oxide." Authored by J. E. Blinne. (Dated May 18, 2000).
45301901	Blinne, J.; Koch, D. (2001) Magnitude of the Residue in Herbs/Spices Following Fumigation with Propylene Oxide (PPO): Lab Project Number: 45125. Unpublished study prepared by ABC Laboratories, Inc. 1862 p. {OPPTS 860.1500}
45301902	"Analysis of Propylene Oxide (PPO) and Propylene Chlorohydrin (PCH, including 1-chloro-2-propanol and 2-chloro-1-propanol) and Propylene Bromohydrin (PBH, including 1-bromo-2-propanol and 2-bromo-1-propanol) in Fumigated Commodities." Authored by J. E. Blinne and D. A. Koch. (Dated December 19, 2000)

45499101	Simons, C.; Lake, R. (2001) Independent Laboratory Validation of Analytical Method "The Determination of Propylene Oxide (PPO) and Propylene Chlorohydrins (PCH, including 1-chloro-2-propanol and 2-chloro-1-propanol), and Propylene Bromohydrins (PBH, including 1-bromo-2-propanol and 2-bromo-1-propanol) in Fumigated Commodities: Lab Project Number: 042-001: 01P-042-001. Unpublished study prepared by Centre Analytical Laboratories, Inc. 152 p. {OPPTS 860.1340}
45813601	"Magnitude of the Residue in Dried Fruits Following Fumigation with Propylene Oxide (PPO)." Authored by J. E. Blinne. (Dated September 20, 2002).
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41750801	Drummond, J.G., and Keller, K.A. 1988. Inhalation developmental toxicity study in rats. International Research and Development Corporation, Mattawan, MI 49071. Unpublished.
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42039901	Reuzel, P. and C. Kuper 1983. 1,2-Propylene Oxide: Chronic (28-month) Inhalation Toxicity/Carcinogenicity Study of 1,2-Propylene Oxide. TNO Netherlands Organization for Applied Scientific Research, P.O. Box 360, 3700 AJ Zeist, Netherlands. Laboratory project study identification V 82.215/280853, March 2, 1983. Unpublished.
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45292801	Young, J.T., Mattsson, J.L., Albee, R.R., and Schuetz, D.J. 1985. Propylene oxide: assessment of neurotoxic potential in male rats. Mammalian and Environmental Toxicology Research Laboratory, Health & Environmental Sciences, U.S.A., Dow Chemical U.S.A., Midland, MI 48640. Study No. D1831, October 24, 1985. Unpublished.
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N/A	Morris, Mark. USEPA/OAQPS/ESD. Memorandum to Dave Guinnup, USEPA/OAQPS/ESD: Residual Risk Assessment for the Ethylene Oxide Commercial Sterilization Source Category. February 25, 2005.
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N/A	Kuper, C.F., P.G.J. Reuzel, V.J. Feron et al. 1988. Chronic inhalation toxicity and carcinogenicity study of propylene oxide in Wistar rats. Food Chem. Toxicol. 26: 159-167.

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Appendix E. Generic Data Call-In (GDCI)

Note that a complete generic DCI, with all pertinent instructions, will be sent to registrants under separate cover.

Appendix F. Product-Specific Data Call-In (PDCI)

Note that a complete product-specific DCI, with all pertinent instructions, will be sent to registrants under separate cover.

Appendix G. EPA's Batching of Propylene Oxide Products for Meeting Acute Data Requirements for Reregistration

Often products containing an active ingredient are batched in an effort to reduce the time, resources and number of animals needed to fulfill the acute toxicity data requirements for reregistration of the products. Because of the type and small number of products containing the active ingredient PPO, the Agency has determined that batching products which can be considered similar for purposes of acute toxicity is not necessary.

Appendix H. Registrant Sent this Data Call-In Notice

Aberco, Inc.
9430 Lanham Severn Road
Seabrook, MD 20706

Appendix I. List of Available Related Documents and Electronically Available Forms

Pesticide Registration Forms are available at the following EPA internet site: http://www.epa.gov/opprd001/forms/.

Pesticide Registration Forms (These forms are in PDF format and require the Acrobat reader)

Instructions:

1. Print out and complete the forms. (Note: Form numbers that are bolded can be filled out on your computer then printed.)

2. The completed form(s) should be submitted in hardcopy in accord with the existing policy.

3. Mail the forms, along with any additional documents necessary to comply with EPA regulations covering your request, to the following address for the Document Processing Desk.:

    Document Processing Desk (distribution code)*
    Office of Pesticide Programs (7504P)
    Environmental Protection Agency
    1200 Pennsylvania Ave, NW
    Washington, DC 20460-0001

    * Distribution Codes are as follows:
    (APPL) Application for product registration
    (AMEND) Amendment to existing registration
    (CAN) Voluntary Cancellation
    (EUP) Experimental Use Permit
    (DIST) Supplemental Distributor Registration
    (SLN) Special Local Need
    (NEWCO) Request for new company number
    (NOTIF) Notification
    (PETN) Petition for Tolerance
    (XFER) Product Transfer

DO NOT fax or e-mail any form containing "Confidential Business Information" or "Sensitive Information."

If you have any problems accessing these forms, please contact Nicole Williams at (703) 308-5551 or by e-mail at *williams.nicole@epamail.epa.gov*. If you want these forms mailed or faxed to you, please contact Lois White, *white.lois@epa.gov* or Floyd Gayles, *gayles.floyd@epa.gov*.

If you have any questions concerning how to complete these forms, please contact OPP's ombudsperson for conventional pesticide products: Linda Arrington, (703) 305-5446

The following Agency Pesticide Registration Forms are currently available via the Internet at the following locations:

8570-1	Application for Pesticide Registration/Amendment	http://www.epa.gov/opprd001/forms/8570-1.pdf
8570-4	Confidential Statement of Formula	http://www.epa.gov/opprd001/forms/8570-4.pdf
8570-5	Notice of Supplemental Registration of Distribution of a Registered Pesticide Product	http://www.epa.gov/opprd001/forms/8570-5.pdf
8570-17	Application for an Experimental Use Permit	http://www.epa.gov/opprd001/forms/8570-17.pdf
8570-25	Application for/Notification of State Registration of a Pesticide To Meet a Special Local Need	http://www.epa.gov/opprd001/forms/8570-25.pdf
8570-27	Formulator's Exemption Statement	http://www.epa.gov/opprd001/forms/8570-27.pdf
8570-28	Certification of Compliance with Data Gap Procedures	http://www.epa.gov/opprd001/forms/8570-28.pdf
8570-30	Pesticide Registration Maintenance Fee Filing	http://www.epa.gov/opprd001/forms/8570-30.pdf
8570-32	Certification of Attempt to Enter into an Agreement with other Registrants for Development of Data	http://www.epa.gov/opprd001/forms/8570-32.pdf
8570-34	Certification with Respect to Citations of Data (in PR Notice 98-5)	http://www.epa.gov/opppmsd1/PR_Notices/pr98-5.pdf
8570-35	Data Matrix (in PR Notice 98-5)	http://www.epa.gov/opppmsd1/PR_Notices/pr98-5.pdf
8570-36	Summary of the Physical/Chemical Properties (in PR Notice 98-1)	http://www.epa.gov/opppmsd1/PR_Notices/pr98-1.pdf
8570-37	Self-Certification Statement for the Physical/Chemical Properties (in PR Notice 98-1)	http://www.epa.gov/opppmsd1/PR_Notices/pr98-1.pdf

Pesticide Registration Kit http://www.epa.gov/pesticides/registrationkit/

Dear Registrant:

For your convenience, we have assembled an on-line registration kit which contains the following pertinent forms and information needed to register a pesticide product with the U.S. Environmental Protection Agency's Office of Pesticide Programs (OPP):

1. The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug and Cosmetic Act (FFDCA) as Amended by the Food Quality Protection Act (FQPA) of 1996.

2. Pesticide Registration (PR) Notices

    a. 83-3 Label Improvement Program-Storage and Disposal Statements
    b. 84-1 Clarification of Label Improvement Program
    c. 86-5 Standard Format for Data Submitted under FIFRA
    d. 87-1 Label Improvement Program for Pesticides Applied through Irrigation Systems (Chemigation)
    e. 87-6 Inert Ingredients in Pesticide Products Policy Statement
    f. 90-1 Inert Ingredients in Pesticide Products; Revised Policy Statement
    g. 95-2 Notifications, Non-notifications, and Minor Formulation Amendments
    h. 98-1 Self Certification of Product Chemistry Data with Attachments (This document is in PDF format and requires the Acrobat reader.)

Other PR Notices can be found at http://www.epa.gov/opppmsd1/PR_Notices.

3. Pesticide Product Registration Application Forms (These forms are in PDF format and will require the Acrobat reader.)

    a. EPA Form No. 8570-1, Application for Pesticide Registration/Amendment
    b. EPA Form No. 8570-4, Confidential Statement of Formula
    c. EPA Form No. 8570-27, Formulator's Exemption Statement
    d. EPA Form No. 8570-34, Certification with Respect to Citations of Data
    e. EPA Form No. 8570-35, Data Matrix

4. General Pesticide Information (Some of these forms are in PDF format and will require the Acrobat reader.)

    a. Registration Division Personnel Contact List
    b. Biopesticides and Pollution Prevention Division (BPPD) Contacts
    c. Antimicrobials Division Organizational Structure/Contact List
    d. 53 F.R. 15952, Pesticide Registration Procedures; Pesticide Data Requirements (PDF format)
    e. 40 CFR Part 156, Labeling Requirements for Pesticides and Devices (PDF format)
    f. 40 CFR Part 158, Data Requirements for Registration (PDF format)
    g. 50 F.R. 48833, Disclosure of Reviews of Pesticide Data (November 27, 1985)

Before submitting your application for registration, you may wish to consult some additional sources of information. These include:

1. The Office of Pesticide Programs' Web Site

2. The booklet "General Information on Applying for Registration of Pesticides in the United States", PB92-221811, available through the National Technical Information Service (NTIS) at the following address:

    National Technical Information Service (NTIS)
    5285 Port Royal Road

Springfield, VA 22161

The telephone number for NTIS is (703) 605-6000. Please note that EPA is currently in the process of updating this booklet to reflect the changes in the registration program resulting from the passage of the FQPA and the reorganization of the Office of Pesticide Programs. We anticipate that this publication will become available during the Fall of 1998.

3. The National Pesticide Information Retrieval System (NPIRS) of Purdue University's Center for Environmental and Regulatory Information Systems. This service does charge a fee for subscriptions and custom searches. You can contact NPIRS by telephone at (765) 494-6614 or through their website.

4. The National Pesticide Telecommunications Network (NPTN) can provide information on active ingredients, uses, toxicology, and chemistry of pesticides. You can contact NPTN by telephone at (800) 858-7378 or through their website: http://npic.orst.edu

The Agency will return a notice of receipt of an application for registration or amended registration, experimental use permit, or amendment to a petition if the applicant or petitioner encloses with his submission a stamped, self-addressed postcard. The postcard must contain the following entries to be completed by OPP:

- Date of receipt
- EPA identifying number
- Product Manager assignment

Other identifying information may be included by the applicant to link the acknowledgment of receipt to the specific application submitted. EPA will stamp the date of receipt and provide the EPA identifying File Symbol or petition number for the new submission. The identifying number should be used whenever you contact the Agency concerning an application for registration, experimental use permit, or tolerance petition.

To assist us in ensuring that all data you have submitted for the chemical are properly coded and assigned to your company, please include a list of all synonyms, common and trade names, company experimental codes, and other names which identify the chemical (including "blind" codes used when a sample was submitted for testing by commercial or academic facilities). Please provide a CAS number if one has been assigned.

Appendix J. Human Health Risk Assessment

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

July 31, 2006

SUBJECT: Propylene Oxide – Revised HED Risk Assessment for Reregistration Eligibility Decision (RED) Document, PC Code: 042501, DP Barcode: D316547

FROM: Becky Daiss
Biologist
Reregistration Branch 4
Health Effects Division (7509C)

THROUGH: Susan Hummel
Branch Senior Scientist
Reregistration Branch 4
Health Effects Division (7509C)

TO: Susan Bartow
Chemical Review Manager
Special Review Branch
Special Review and Reregistration Division (7509C)

Attached is the revised Health Effect Division's risk assessment of the insecticidal fumigant/sterilant, propylene oxide (PPO). This document revises the September 26, 2005 Revised Propylene Oxide HED Risk Assessment to address public comments. The disciplinary science chapters have also been revised to address public comments. These and other supporting documentation are incorporated into the risk assessment and/or included as appendices as follows:

Hazard Identification Assessment; William Dykstra - Section 4 and Appendices 1-6
Residue Chemistry Assessment; Jerry Stokes (D316571, 9/22/05; D316573, 6/22/06)
Occupational and Residential Exposure Assessment; Matthew Crowley (D316545, 7/31/06; D331131, 7/31/06)
Dietary Exposure and Risk Assessment; Becky Daiss (D329648, 6/30/06)
Incident Report; Jerry Blondell (D316407, 5/17/05)
Drinking Water Assessment; Kevin Costello (D263366, 3/15/00)

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1.0 EXECUTIVE SUMMARY

Use Profile

PPO is used as an insecticidal fumigant on several food items such as processed spices, cocoa (beans and powder), in-shell and processed nutmeats (except peanuts). PPO also has nonfood uses for cosmetic articles, gums, ores, packaging, pigments, pharmaceutical materials, and discarded nut shells prior to disposal.

Currently, there are three registered products for PPO. Both technical and an end-use product contain 100% a.i.. An additional end-use registration product, Propoxide 892 which contains 8% PPO and 92% carbon dioxide (CO_2) is being proposed for uses on dried fruits such as figs, raisins, and prunes.

Regulatory History

Propylene oxide is a FIFRA 88 List B reregistration pesticide. A FIFRA 88 Phase VI Data Call-In (DCI) was issued by the Agency in October 1989 which cited numerous deficiencies in the product and residue chemistry databases. Additional product and residue chemistry data received since 1989 have been reviewed by the Agency. PPO has a tolerance of 300 ppm for processed spices, cocoa (beans or powder), edible gums, and processed nutmeats (except peanuts) under 40 CFR 180.491.

The requirements for the series of acute toxicity studies have been waived in the past based on available information in the literature, consideration of PPO as a low volume, minor use chemical and/or irritant properties of the compound. The requirements for subchronic and chronic oral toxicity studies in rodents and non rodents have been reserved pending dissipation and residue studies (D165449, 9/4/92).

A data call-in for dermal and inhalation exposure monitoring data was requested in 1990 (Morris, 1990). However, a waiver request was granted in 1993 based on labeling restrictions and risk mitigation measures such as site air monitoring and placarding.

OSHA (Occupational Safety and Health Administration) has established the 8-hour time-weighted average (8-hour TWA), permissible exposure limit (PEL) for PPO as 100 ppm. NIOSH (National Institute for Occupational Safety and Health) recommends the Lowest Feasible Concentration (LFC) for occupational carcinogens a group which includes PPO. The ACGIH (American Conference of Governmental Industrial Hygienists) recommends a TLV-TWA (Threshold Limit Value – Time Weighted Average) of 2 ppm for PPO. The exposure limits from NIOSH and ACGIH are recommended levels and are not enforceable. The California Division of Occupational Safety and Health (Cal/OSHA) has established an exposure limit value for PPO as 20 ppm. The current EPA label for PPO requires respiratory protection if PPO concentrations exceed 20 ppm.

Hazard Characterization

Propylene oxide: The database for PPO is incomplete. Based on information available from the literature, PPO is classified as Category III by the oral route and Category IV by the inhalation route. PPO has severe irritant properties to eyes and skin and is classified as Category I for both tissues.

Evidence suggests that PPO, similar to ethylene oxide, is most probably completely absorbed, distributed throughout the body and rapidly metabolized following inhalation. The metabolism occurs predominantly by conjugation with glutathione and hydrolysis to 1, 2-propanediol by epoxide hydrolase.

PPO has been shown to cause awkward gait/ataxia and axonal degeneration of the hindleg nerve in rats at a high dose level (1500 ppm or 3.6 mg/L). At a similar dose level, PPO also caused decreased survival and produced clinical symptoms like dyspnea, hypoactivity, and gasping in rats.

PPO causes nasal cavity lesions (e.g., hyperplasia of the respiratory epithelium) in both rats and mice. Tumors such as hemangiomas and hemangiosarcomas of the nasal cavity were produced in mice exposed to PPO for a long term. Nasal tumor incidences in rats were not statistically significant. Forestomach tumors in rats were reported in one chronic oral toxicity study available in the literature. PPO is mutagenic and forms adducts with proteins and DNA. PPO has been classified by the Agency as a B2 carcinogen (probable human carcinogen).

The PPO database lacks an acceptable rabbit developmental study and a chronic oral toxicity study in non rodents. There is no evidence of increased quantitative or qualitative susceptibility following *in utero* exposures in rats. Also, there are no residual uncertainties found in existing studies for pre- and post natal toxicity in rats.

Propylene Chlorohydrin: PCH exists in two isomers, 1-chloro 2-propanol and 2-chloro-1-propanol. Most of the toxicity studies are done with a mixture of isomers containing predominantly 1-chloro-2-propanol.

There are no guideline studies (acute, subchronic, developmental, reproduction or chronic toxicity studies) submitted to the Agency and the database for PCH is inadequate. The available data from the open literature indicate PCH is Category II or III by the oral route and Category II by the dermal route and the Category is undetermined for the inhalation route.

One rat developmental toxicity study was identified in the literature as a secondary source of information and is unacceptable. There is no rabbit developmental study available for PCH. In a rat two generation reproductive toxicity study identified in the literature, decreased body weight gain in dams during gestation and lactation, increased percentage of abnormal sperm and decreased pup weights were reported. No neurotoxic effects are evident in the available database for PCH.

PCH appears to be widely distributed in tissues, metabolized and excreted following inhalation. Most of the administered radioactivity appears to be excreted in urine as glutathione conjugates. Also, biliary excretion is reported in rats exposed to PCH by inhalation. Following oral exposure, PCH is eliminated as glucuronic acid conjugate in addition to glutathione conjugate.

In subchronic studies conducted using rats and mice cytoplasmic alterations and/or degeneration of acinar cells in the pancreas are reported. In addition, atrophy of the bone marrow and/or spleen and hepatocellular vacuolization were reported and these effects were not reported in the rodent chronic studies.

Inductions of mutations in bacteria and chromosomal aberrations as well as sister chromatid exchange in mammalian cells were reported for PCH.

Dose Response Assessment

For PPO, the acute dietary endpoint for females of 13-49 years is derived from a rat developmental toxicity study. No endpoint of concern is found suitable for the acute dietary endpoint for the general population. The chronic dietary endpoint for PPO is selected from the chronic oral carcinogenicity study. BMD (Bench Mark Dose) modeling was done to derive the chronic reference dose (cRfD) since the study did not establish a clear NOAEL. the chronic cancer risk from the oral route was derived using a revised concentration based cancer slope factor. Since the toxicology database is incomplete, a database uncertainty factor of 10X was applied in addition to the traditional 100X uncertainty factor for the dietary risk assessment to address residual uncertainties. The short-term and long-term inhalation endpoints for workers potentially exposed to PPO were derived using the rat two-generation reproduction study and two-year combined chronic carcinogenicity study in rats, respectively. The chronic cancer risk from the inhalation route for workers was derived using a cancer slope factor of $3.5x10^{-6}$ $(\mu g/m^3)^{-1}$ for nasal tumors. This revised assessment also provides a discussion of use of a margin of exposure (MOE) approach for assessing inhalation risks based on mode of action (MOA) information submitted by and on behalf of the registrant. After an initial analysis, EPA concludes that the proposed MOA is highly plausible, and will review the proposed MOA in more depth, both within OPP and in conjunction other Agency offices. If the proposed MOA is accepted by the Agency, propylene oxide will not be regulated using a q* approach for inhalation exposures. Rather, an MOE analysis will be conducted.

For PCH, no acute dietary endpoint was selected. The chronic reference dose for PCH was derived from the two-generation reproduction study in rats. A database uncertainty factor of 10X is applied for dietary assessment to address any residual uncertainties.

Exposure/Risk Assessment and Risk Characterization

The potential exposures and risk from dietary sources were determined for PPO as well as for the reactive metabolite, PCH found in significant amounts in fumigated spices, nuts and other commodities. Occupational exposure and risk via inhalation for all durations were determined for the parent only. Potential occupational exposures via the dermal route from changing/installing PPO drums and handling treated commodities are considered negligible. There are no residential uses for PPO and therefore, no risk for incidental oral exposures or residential exposures via inhalation was determined; however, a qualitative assessment for background exposures to subjects near PPO commercial fumigation facilities was performed based on the risk estimated by Office of Air for ethylene oxide. HED also conducted a quantitative assessment of potential exposure/risk to bystanders from outdoor commodity fumigation with Propoxide 892 containers such as railcars, tents and tarps.

Dietary Exposure and Risk Characterization

Refined acute and chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID™, Version 2.03), and the Lifeline Model Version 3.0 which use food consumption data from the USDA's Continuing Surveys of Food Intake by Individuals (CSFII) from 1994-1996 and 1998. Residue data obtained from studies on propylene oxide sterilization of nutmeats, cocoa powder, herbs and spices, figs, prunes and raisins were used for the acute and chronic assessments. Residue distribution data from PPO sterilization studies were used for the acute dietary analysis of propylene oxide. Average residues from the sterilization study were used for the chronic and cancer assessments of propylene oxide. Tolerance level residues were used for the chronic dietary analysis of propylene chlorohydrin. Percent crop treated data provided by BEAD were used for the acute and chronic analyses. A drinking water exposure assessment was not conducted for this assessment because the Environmental Fate and Effects Division (EFED) expects that uses of propylene oxide for indoor and outdoor food and nonfood uses will result in insignificant exposure to drinking water resources.

This assessment has been updated to include a revised propylene oxide cancer assessment that incorporates new data on residue levels in treated nutmeats based on actual maximum application rates, incorporates refined estimates of percent of nutmeats treated with propylene oxide, and excludes edible gums from the assessment based on the registrants submission of a voluntary cancellation notice requesting deletion of edible gums from product labels. Only the cancer dietary exposure assessment has been revised for this assessment because only that scenario produced risk estimates above EPA's level of concern. Conservative estimates of acute and chronic dietary risks for PPO are well below HED's level of concern and incorporation of new data would result in risks $\leq$ previously estimated risks.

A refined probabilistic acute dietary exposure assessment for the population subgroup females 13-49 concludes that for all supported commodities, the acute dietary exposure estimates for PPO are below HED's level of concern. This assessment also concludes

that for all supported commodities, the chronic dietary exposure estimates for PPO are below HED's level of concern. The revised cancer dietary risk estimates for propylene oxide are below HED's level of concern; the revised cancer dietary excess lifetime risk estimate for the U.S. general population is $4x10^{-7}$. An acute RfD was not established for propylene chlorohydrin because an endpoint attributable to a single (or few) day exposure was not identified from the available database. This assessment concludes that for all supported commodities, the chronic dietary exposure estimates for propylene chlorohydrin are below HED's level of concern.

Residential Exposure and Risk Characterization

There are no residential uses for PPO. However, exposure to PPO is expected to occur to the subjects residing near PPO fumigation facilities. PPO emissions monitoring data necessary to quantitatively estimate exposures and risks from sterilization/fumigation facilities are unavailable. Therefore, a qualitative assessment was conducted comparing the risks associated with fugitive emissions from the use of a similar chemical, ethylene oxide, in similar commercial fumigation scenarios. Risks to bystanders from comparably controlled commercial sterilization sources are not expected to be of concern based on HED's qualitative risk analysis. Additionally, HED conducted a quantitative assessment of residential bystander risk associated with emissions from outdoor commodity fumigation with the recently registered product Propoxide 892 and from stationary sources that do not have emission controls comparable to those required for ethylene oxide. There is potential for exposure and risk to PPO for non-occupational/residential bystanders as a result of commodity fumigations conducted with the registered product Propoxide 892 and those conducted in non-emission controlled commercial sterilization chambers. However, potential bystander risks may be mitigated by requiring buffer areas at designated distances.

Occupational Exposure and Risk Characterization

The cancer and non-cancer risks from exposure to PPO were determined based on currently recommended or regulatory concentration levels. The short- (1-30 days), intermediate- (1-6 months), and long-term (greater than 6 months) inhalation non-cancer and cancer risks from the use of PPO in commodity sterilization/fumigation are of concern at 20 ppm the exposure limit value established by Cal/OSHA and is included in current EPA PPO label. The acute, short-, intermediate- and long-term non-cancer risks are not of concern at the ACGIH recommended worker exposure concentration of 2 ppm. As previously noted, EPA has concluded that an MOA is highly plausible, and will review the proposed MOA in more depth, both within OPP and in conjunction other Agency offices. If the Agency concurs with the proposed MOA, then cancer and long-term non-cancer risks would be regulated at the same level, since the long-term non-cancer endpoint is based on nasal lesions that are considered precursors to the development of tumors.

The registrant and industry representatives have submitted inhalation monitoring data and descriptive information on typical workday exposure patterns for outdoor fumigation

facilities. The exposure monitoring data was reviewed and incorporated into the revised occupational exposure assessment. Potential risk reduction from respiratory protection has not been quantitatively factored into the risk assessment, however, due to insufficient data on the daily PPO exposure profile. However, a qualitative discussion of potential risk reduction provided by use of respirators is included in this assessment i.e., respiratory protection during peak PPO exposures could reduce the daily average exposure to levels that would not be of concern. Additional monitoring data and information on exposure patterns that may be used to develop effective risk mitigation measures for both indoor and outdoor facilities is expected from the registrant and industry representatives.

2.0 INGREDIENT PROFILE

2.1. Summary of Registered/Proposed Uses

Products and Formulations

The two registered products (one technical and one end-use registration) contain 100% a.i.. An additional end-use registration (8% a.i) is being proposed for use on figs, raisins, and prunes. PPO is used as a post harvest fumigant in the food commodities. Table 1 provides the summary of current and new uses for PPO.

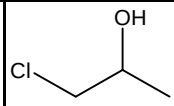
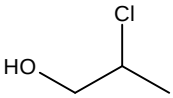
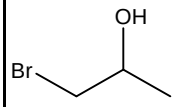
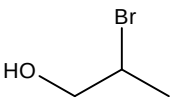
Table 1. Registered Uses of Propylene Oxide

EPA Reg. No.	*Product Name	% AI	Formulation	Application Rate (oz PPO/ft^3)	Uses
47870-1	Propylene Oxide	100	NA	2.4	Spices, nutmeats (except peanuts), cocoa beans, cocoa powder and non food uses
47870-2	Propylene Oxide Technical	100	NA	2.4	Spices, nutmeats (except peanuts), cocoa beans, cocoa powder and non food uses
47870-3	PROPOXIDE 892	8	92% CO_2	0.05	Figs, prunes and raisins and other commodities

*Aberco Inc. is the registrant for all the products.

2.2 Structure, Nomenclature and Physical/Chemical Properties

Product Chemistry data for PPO and its reaction products, i.e., chlorohydrins and bromohydrins are provided in Table 2.

Table 2. Nomenclatures and Physical/Chemical Properties of Propylene Oxide and Reaction Products					
Common name	**Propylene Oxide**	**Propylene chlorohydrins (75% 1-Chloro-2-propanol, 25% 2-Chloro-1-propanol)**		**Propylene bromohydrins (80% 1-Bromo-2-propanol, 20% 2-Bromo-1-propanol)**	
Chemical Structure					
Molecular Formula	C_3H_6O	C_3H_7ClO		C_3H_7BrO	
Molecular Weight	58.080	94.541		138.992	
IUPAC Name	-	-	-	-	-
CAS Name	Propylene oxide; 1,2-epoxypropane	1-chloro-2-propanol	2-chloro-1-propanol	1-bromo-2-propanol	2-bromo-1-propanol
CAS #	75-76-9	127-00-4	37493-14-4	19686-73-8	NA
PC Code	042501	NA	NA	NA	NA
Melting Point/range ºC	-	-	-	-	-
Boiling Point ºC	34.2 ºC	126-127 ºC	130 ºC	145-148 ºC	NA
Density or Specific Gravity at 20 ºC (g/cm3)	0.829- 0.831	1.115	1.09	1.53	NA
Water Solubility (20 ºC)	39.5 g/100 mL	NA	NA	NA	NA
Solvent Solubility at 25 ºC	Miscible with acetone, benzene. carbon tetrachloride, diethyl ether, and methanol.	NA	NA	NA	NA
Vapor Pressure at 20 ºC	440 mm Hg	NA	NA	NA	NA
Dissociation Constant, pKa	NA	NA	NA	NA	NA
Octanol/Water Partition Coefficient (K_{ow}) 25 ºC	K_{ow} 0.03	NA	NA	NA	NA
UV/vis Absorption Spectrum	NA	NA	NA	NA	NA

NA = not available

3.0 METABOLISM ASSESSMENT

3.1 Comparative Metabolic Profile

The available evidence from the open literature suggests that PPO like ethylene oxide is most probably completely absorbed, distributed throughout the body and rapidly metabolized following inhalation. The half-life for the elimination from rat tissues was

reported as 40 minutes following inhalation exposure. PPO is metabolized via conjugation with glutathione and hydrolysis by epoxide hydrolase to 1, 2-propanediol (propylene glycol), which is subsequently metabolized to lactic and pyruvic acids.

The available evidence from the open literature suggests that PCH is widely distributed to tissues, metabolized and excreted following inhalation in animals. Most of the administered radioactivity appears to be excreted in urine as glutathione conjugates. Also, biliary excretion is reported in rats exposed to PCH by inhalation. Following oral exposure, PCH is eliminated as glucuronic acid and glutathione conjugates.

3.2 Nature of the Residue in Foods

3.2.1. Description of Primary Crop Metabolism

The qualitative nature of PPO residues in plants is adequately understood. The residues of propylene glycol, PCHs and PBHs (propylene bromohydrins) are formed upon postharvest fumigation of cocoa bean, nutmeats (except peanut), and spices. Spices that contain salt that are treated with PPO react with chloride ion to form PCH. Similarly, any bromide ion present in the material to be fumigated reacts with PPO to form PBH. In addition, reaction with water in samples can produce small amounts of propylene glycol (PPG).

3.2.2 Description of Livestock Metabolism

Based on the post harvest fumigant uses of PPO on commodities of spices and herbs, nutmeats (except peanut), cocoa bean, fig, prune and raisin, livestock are not exposed to PPO or PCH residues in any feedstuffs, or from dermal treatments. Data on livestock metabolism are not collected and are not required.

3.3 Environmental Degradation

EFED expects that exposure to water resources from the exclusive registration of PPO for indoor food and non food uses will be negligible. EFED has neither required nor received environmental fate data for propylene oxide. In the November 28, 1990 'List B Review for Propylene Oxide', EFED wrote of environmental data that there are no significant issues at this time. EFED maintains that additional environmental data are not necessary for the reregistration of this sterilant. EFED would require this data when PPO would ever be considered for registration for outdoor uses. EFED determined that there would be negligible risk for any contamination of surface and ground water for the current uses of PPO. Therefore, no drinking water assessment was found necessary (K. Costello, D263366, 3/15/2000).

3.4 Summary of Residues for Tolerance Expression and Risk Assessment

PPO and PCH are considered separately as residues of concern for risk assessment and tolerance assessment. The commodity sterilization study residue data indicate that these

compounds are consistently present at high levels. The spice sterilization study data indicate that PBH is also a reaction product of the propylene oxide sterilization process. However, PBH residues are minimal relative to propylene chlorohydrin residues. Therefore, PBH is not considered a residue of concern for risk assessment and is not assessed separately.

Based on current information from the spice industry trade practices, HED concludes that residues measured at 2 days (in transit) after treatment should be used for setting the tolerance level, and the residue data at approximately 2 weeks (and after) should be used in estimating dietary exposure to PPO and PCH only. Because the propylene oxide label requires that treated nutmeats must be allowed to off-gas for at least 28 days, only residue data from $\geq$ 28 days post-fumigation are used in estimating dietary exposure. Based on the differences in physical chemical properties and toxicological effects, PPO and PCH are assessed separately and the residues are not combined in this risk assessment. Table 3 provides the residues included in risk assessment and tolerance expression.

Table 3. Compounds to be included in the Risk Assessment and Tolerance Expression

Commodities		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plant	Primary Crop	Propylene oxide Propylene chlorohydrin	Propylene oxide Propylene chlorohydrin
	Rotational Crop	Not Applicable	Not Applicable
Livestock	Ruminant	Not Applicable	Not Applicable
	Poultry	Not Applicable	Not Applicable
Drinking Water		Not Applicable	Not Applicable

3.4.1 Rationale for Inclusion of Metabolites and Degradates

HED Metabolism Committee concluded that both halohydrins (PCH and PBH) are residues of concern and risk assessment and tolerance expression should include both the parent and the halohydrins pending additional data on residue chemistry and toxicity for these compounds. (D264138, 8/16/00). Based on the available toxicity data and the commodity sterilization study residue data, PPO Risk Assessment Team concludes that propylene oxide and propylene chlorohydrin are residues of concern for dietary exposure since these residues persist at high levels and are likely to be present in treated commodities at time of consumption. The spice sterilization study data indicate that propylene bromohydrin is also a reaction product of the propylene oxide sterilization process. However, PBH residues are minimal relative to propylene chlorohydrin residues. Therefore, PBH is not considered a residue of concern for dietary exposure and is not included in the tolerance expression.

4.0 HAZARD CHARACTERIZATION/ASSESSMENT

4.1 Hazard Characterization

Propylene Oxide

This assessment includes the toxicity assessment of propylene oxide and its reaction product, PCH (1-chloro-2-propanol and its isomer, 2-chloro-1-propanol) found in significant quantities in treated spices and nutmeats. For dietary assessment, endpoints were selected for both parent and the reaction product. For occupational risk assessment the endpoints were selected for the parent only.

The toxicology database for PPO is not complete. The database includes acceptable developmental toxicity, reproduction toxicity, subchronic neurotoxicity (non-guideline), and chronic carcinogenicity studies in rats, all conducted via inhalation. There is one developmental study in rabbits conducted via inhalation which is not acceptable because only one dose was used. Also, the database includes one rat chronic carcinogenicity study conducted via the oral route which provides limited information as the study was conducted in one sex (females only) and lacked measurements on systemic toxicity (body weights, food consumption, clinical measurements, organ weight changes etc.) or carcinogenicity effects in major tissues. Therefore, the PPO database lacks a developmental toxicity study in rabbits, and subchronic and chronic oral toxicity studies in non rodents.

Waivers were issued in the past for acute oral (§81-1, 870.1100), dermal (§81-2, 870.1200), eye irritation (§81-4, 870.2400), skin irritation (§81-5, 870.2500) and dermal sensitization (§81-6, 870.2600) studies based on the corrosive nature of the compound and the acceptance of the chemical as a low volume minor-use chemical. The requirement for an acute inhalation study was satisfied based on available information from the open literature (D165449, dated 9/4/92). PPO is classified as Category III by the oral route and Category IV by the inhalation route. PPO is a severe eye and skin irritant and is classified as Category I for both routes of exposure.

Based on the available toxicity data, an additional 10X data base uncertainty factor is deemed necessary for the dietary assessment to address the inadequate subchronic and chronic data for the oral route of exposure and the lack of an acceptable rabbit developmental study. There is no evidence of increased quantitative or qualitative susceptibility following *in utero* exposures in rats. Also, there are no susceptibility effects in pups in the two-generation reproductive toxicity study.

No data on absorption and metabolism of PPO have been submitted. Evidence suggests that PPO like ethylene oxide is most probably completely absorbed, distributed throughout the body and rapidly metabolized following inhalation. The half-life for the elimination from rat tissues was reported as 40 minutes for inhalation exposure. Metabolism occurs predominantly by conjugation with glutathione and hydrolysis by

epoxide hydrolase to 1,2-propanediol, which is subsequently metabolized to lactic and pyruvic acids.

PPO has been shown to cause awkward gait/ataxia and axonal degeneration of the hindleg nerve in rats at a very high dose (3.6 mg/L) in one subchronic toxicity study. Axonal dystrophy was reported in monkeys exposed to PPO for 2 years, but there was no dose response effect and the study was conducted with a limited number of animals per group (n=2). PPO produces nasal cavity lesions in rats and mice in chronic studies. The lesions include atrophy of the olfactory epithelium, basal cell hyperplasia and nest-like infolds of the nasal epithelium. Although the mode of action for these non-neoplastic lesions is not established, irritation of the nasal tissues is considered to contribute to these extra extrathoracic effects.

Similar to ethylene oxide, PPO is a known mutagen which directly alkylates proteins and DNA. Numerous published studies have shown that PPO induces mutations in bacteria, yeast, fungi and insects. Chromosomal damage and aberrations and sister chromatid exchange were reported in mammalian cells *in vitro*. PPO tested negative for micronuclei induction in mice via the oral route and for dominant lethal assays in rats via the inhalation and in mice via oral route.

PPO induces several types of tumors depending on the route of exposure. PPO administered by oral gavage to rats produced tumors of the forestomach, which were mainly squamous-cell carcinomas. This study provides limited information on carcinogenicity effects in key tissues such as liver, kidney, thyroid etc. Further, it was conducted only in rats of one sex (females), and any sex specific effects were not determined.

In the carcinogenicity studies in rats via inhalation, equivocal evidence for mammary gland tumors (significant fibroadenoma with marginal tubulopapillary adenocarcinoma) in Wistar rats, and thyroid tumors (dose related increase in thyroid C-cell adenomas and carcinomas) and adrenal gland tumors (adrenal pheochromocytoma) in F344 rats was reported. The incidence of tumors in the nasal cavity was not significant in rats. However, in mice exposed by inhalation, PPO produced hemangiomas and hemangiosarcomas of the nasal cavity. The doses tested in the carcinogenicity studies were considered adequate based on inflammatory lesions in the nasal cavity and other systemic effects.

Although the incidence of forestomach tumors observed in PPO treated rats has a questionable relevance to humans, these tumors could not be excluded due to 1) evidence of mutagenicity in different organisms 2) chromosomal damage in mammalian cells *in vitro*, and 3) adduct formation *in vivo* in tissues distant from the site of administration.

PPO has been classified by the Agency as a B2 carcinogen (probable human carcinogen). The cancer slope factor is determined to be **0.15 (mg/kg/day)$^{-1}$** for forestomach tumors for the oral route of exposure. HED has derived an alternative cancer slope factor (Q*) of 0.000086 (mg/kg diet)$^{-1}$ using a concentration based approach. Use of an alternative

approach is based on the fact that forestomach tumors in the rat treated by gavage may be considered a portal of entry response. By analogy to the RfC methodology which considers the concentration of test material to be the most important determinant of response in portal of entry tumors, PPO dosage can be expressed as a concentration. The cancer slope factor for the inhalation route of exposure is **$3.5x10^{-6}$ $(\mu g/m^3)^{-1}$** for nasal cavity tumors for the inhalation route of exposure (USEPA, 1994). This assessment also discusses MOA data submitted by, and on behalf of the registrant, which provide the basis for use of an MOE approach for assessing inhalation cancer risks. After an initial analysis, EPA concludes that the MOA proposed by the registrant is quite plausible, and will review the proposed MOA in more depth, both within OPP and in conjunction other Agency offices. If the proposed MOA is accepted by the Agency, propylene oxide will not be regulated using a q* approach. Rather an MOE analysis will be conducted.

Propylene chlorohydrin

PCH, a major metabolite identified in spices and nutmeats sterilized with PPO, was considered separately for dietary risk assessment. The database for PCH is inadequate. PCH exists in two isomers, 1-chloro 2-propanol and 2-chloro-1-propanol. Most of the toxicity studies are done with a mixture of isomers containing predominantly 1-chloro-2-propanol.

There are no guideline studies (acute, subchronic, developmental, reproduction or chronic toxicity studies) submitted to the Agency. A search in the open literature provided a developmental toxicity study and a few subchronic studies in rats. These studies lacked sufficient study details or had deficiencies (poor stability of the test compound, studies conducted before GLPs were established) which precluded gleaning any useful information. However, the subchronic and chronic toxicity studies in rats and mice and the reproduction toxicity study in rats conducted by NTP provided minimum information to assess the dietary risk for PCH.

The available acute toxicity data indicate PCH as the Category II or III compound by the oral route and a Category II compound by dermal route and Category is undetermined for the inhalation route. Limited data suggest that PCH is a severe eye irritant but not a skin irritant. There are no data available on dermal sensitization effects.

The evidence suggests that PCH is widely distributed in tissues, metabolized and excreted following inhalation. Most of the administered radioactivity appears to be excreted in urine as glutathione conjugates. Also, biliary excretion is reported in rats exposed to PCH by inhalation. Following oral exposure, PCH is eliminated as a glucuronic acid conjugate in addition to glutathione conjugate.

Adequate developmental studies are not available. One reproduction study in rats found an increased percentage of abnormal sperm at the same dose which produced body weight changes in dams. The decreased pup weights observed at doses which did not produce toxic effects in dams indicate pups are more sensitive to the toxic effects of PCH compared to dams. However, the dose level selected for risk assessment with an

additional database uncertainty factor (10X) to the traditional 100X is considered to protect any potential increased susceptibility effects in children. No neurotoxic effects are evident in the available database for PCH.

In subchronic studies in rats and mice PCH produces cytoplasmic alteration and/or degeneration of acinar cells in the pancreas. In addition, atrophy of the bone marrow and spleen and hepatocellular vacuolization were reported in subchronic studies in rodents and these effects were not reported in the chronic studies. The doses used for the chronic studies are considered inadequate since no endpoints were established for systemic effects.

Inductions of mutations in bacteria and chromosomal aberrations as well as sister chromatid exchange in mammalian cells were reported for PCH. No evidence of carcinogenicity was reported in the chronic studies conducted with inadequate doses in both rats and mice.

Table 4 and 5 provide the toxicity profile of PPO* and PCH, respectively.

Table 4a- Acute Toxicity Profile of PPO

Study/ Species	MRID or Publication	Results	Classification
870.1100 Acute Oral, Rats Mice Guinea pigs	 Smyth et al. 1941 and Antonova et al., 1981 Antonova et al., 1981 Smyth et al. 1941 Antonova et al., 1981 (As cited in USEPA, 1987)	 LD_{50} 520-1140 mg/kg bw LD_{50} 630 mg/kg bw (males) LD_{50} 660-690 mg/kg bw	 Category III Category III Category III
870.1200 Acute Dermal, Rabbits	No study identified		
870.1300 Acute Inhalation, Rats Mice	 NTP, 1985 NTP, 1985	 LC_{50}(4h): 7697-8265 mg/m^3 (3207-3444 ppm) LC_{50}(4h): 2420-3540 mg/m^3 (1008- 1475 ppm)	 Category IV Category IV
870.2400 Primary Eye Irritation, Rabbits	Weil et al., 1963 (As cited in WHO, 1985)	Severe eye irritant	Category I
870.2500 Primary Skin Irritation, Rabbits	Rowe et al., 1956 (As cited in USEPA, 1987)	Severe skin irritant	Category I
870.2600 Dermal Sensitization, Guinea Pigs	No study identified	-	-
870.6200 Acute Neurotoxicity, Rats	No study identified	-	-

Table 4b: Subchronic, Chronic Toxicity Studies –PPO

Study/Species	MRID or Publication	Doses	Results/Classification

Table 4b: Subchronic, Chronic Toxicity Studies –PPO			
Study/Species	**MRID or Publication**	**Doses**	**Results/Classification**
Developmental/Reproduction Toxicity			
Developmental Toxicity Fischer 344 Rats	41750801	Doses (inhalation): 0, 100, 300, 500 ppm (GD 6-15)	**Maternal NOAEL: 300 ppm** **Maternal LOAEL: 500 ppm** Decreased body weight gain, food efficiency and food consumption **Developmental NOAEL: 300 ppm** **Developmental LOAEL: 500 ppm** Increased litter incidence of an accessory 7th cervical rib **Acceptable/Guideline**
Developmental Toxicity Sprague-Dawley Rats	41874102	Doses (inhalation): 0, 500 ppm (GD 7-16, GD1-16, GD1-16 with 3 week pregesational exposure)	**Maternal NOAEL: <500 ppm** **Maternal LOAEL: 500 ppm** Decreased body weight, body weight gain and food consumption **Developmental NOAEL: <500 ppm** **Developmental LOAEL: 500 ppm** Decreased mean fetal weight, decreased crown rump length in males and females and possibly increased fetal and litter incidence for the reduced ossification of the vertebra. **Unacceptable/Guideline** Use of one exposure level, and inadequate data reporting exposure)
Developmental Toxicity, New Zealand White Rabbits	41874102	Doses (inhalation) : 0, 500 ppm GD7-19; GD 1-19	**Maternal NOAEL: <500 ppm** **Maternal LOAEL: 500 ppm** Increased mortality, reduced food consumption, and microscopic changes in liver (minimal to mild portal mononuclear inflammation), lungs (minimal to mild portal mononuclear inflammation) and kidneys (mineralization of proximal and renal tubules, subacute/chronic nephritis) **Developmental NOAEL: <500 ppm** **Developmental LOAEL: 500 ppm** Increased resorptions, and/or increased incidence of minor skeletal abnormalities **Unacceptable/Guideline** Study deficiencies included low pregnancy rate, use of one exposure level, and inadequate data reporting. Complications by a possible Pasteurella infection.
Two-Generation Reproduction Study, Fischer 344 Rats	45292701	Doses (inhalation): 0, 30, 100, 300 ppm	**Parental NOAEL: 100 ppm** **Parental LOAEL: 300 ppm** Decreased body weights and weight gain in F0 and F1 males during premating and post mating periods and decreased body weight and weight gain in F0 and F1 females during premating period **Reproductive NOAEL: 300 ppm** **Reproductive LOAEL: >300 ppm** No reproductive effects at HDT **Offspring NOAEL: 300 ppm** **Offspring LOAEL: >300 ppm** **No offspring effects at HDT Acceptable/Guideline**
Subchronic Oral Toxicity			
Subchronic Toxicity, Rats, Strain not specified, 26-weeks	Antonova et al. 1981 (as cited in WHO, 1985)	Doses (drinking water): 0,	**NOAEL: 0.0052 mg/kg/day** **LOAEL: 0.052 mg/kg/day** Mild hematological abnormalities

Table 4b: Subchronic, Chronic Toxicity Studies –PPO			
Study/Species	**MRID or Publication**	**Doses**	**Results/Classification**
		0.00052, 0.0052, 0.052, 0.52 mg/kg/day	**Unacceptable/Non-Guideline** Secondary source and information could not be verified
Subchronic 24 days Females rats	Rowe et al. 1956 (as cited in USEPA, 1987)	Doses (oral): 0, 100, 200, 300 mg/kg	**NOAEL: 200 mg/kg** **LOAEL: 300 mg/kg** Slight decrease in body weight, gastric irritation, and slight liver damage **Unacceptable/Non-Guideline** Secondary source and information could not be verified
Subchronic Inhalation Toxicity			
Subchronic Neurotoxicity, Fischer 344 male Rats, 24 weeks	45292801	Doses (inhalation): 0, 30, 100, 300 ppm	**NOAEL: 300 ppm** **LOAEL: >300 ppm** No systemic and neurological effects at the HDT **Acceptable/Non-Guideline**
Subchronic Neurotoxicity, Wistar Rats, 7 weeks	Ohnishi et al., 1988	Doses (inhalation): 0, 1500 ppm	**NOAEL: Not Established** **LOAEL: 1500 ppm** Awkward gait during third and fourth week of exposure and more ataxia in all rats by 7th week; histo: axonal degeneration of the hindleg nerve and fasciculus gracilis and myelinated fibers in the sacral spinal root **Uncceptable/Non-Guideline** Only one dose was tested
Subchronic Toxicity, Fischer 344/N Rats, 12-14 days	NTP, 1985	Doses (inhalation): 0, 47, 99, 196, 487, 1433 ppm	**NOAEL: 487 ppm** **LOAEL: 1433 ppm** Decreased body weight gain, dyspnea, hypoactivity, gasping, ataxia, and diarrhea were observed at the highest dose; 20% mortality in males **Acceptable/Non-Guideline**
Subchronic Toxicity, B6C3F1Mice, 12-14 days	NTP, 1985	Doses (inhalation): 0, 20, 47, 99, 196, 487 ppm	**NOAEL: 99 ppm** **LOAEL: 196 ppm** Dyspnea **Acceptable/Non-Guideline**
Subchronic Toxicity, Fischer 344/N Rats, 13 weeks	NTP, 1985	Doses (inhalation): 0, 31, 63, 125, 250, 500 ppm	**NOAEL: 500 ppm** **LOAEL: Not established** **Acceptable/Non-Guideline**
Subchronic Toxicity, B6C3F1Mice, 13 weeks	NTP, 1985	Doses (inhalation): 0, 31, 63, 125, 250, 500 ppm	**NOAEL: 250 ppm** **LOAEL: 500 ppm** Decreased body weight (12.9% in males and 14.6% in females) **Acceptable/Non-Guideline**
Chronic Oral Toxicity			
870.4100 Chronic Toxicity-Female Sprague-Dawley Rats 2 years	Dunkelberg, 1982	Doses (oral): 0, 0(salad oil), 15 or 60 mg/kg by Gavage	**NOAEL: Not Established** **LOAEL: 15 mg/kg/day** Based on hyperkeratosis, hyperplasia and papillomas Combined incidences of hyperkeratosis, hyperplasia and papillomas were 0/50, 7/50, and 17/50 Forestomach tumors-primarily squamous cell carcinoma – incidence: 0/50 for both controls, 2/50, and 19/50 for low and high dose groups. Highest dose also had one adenocarcinoma of the pylorus and carcinoma *in situ* of the forestomach

Table 4b: Subchronic, Chronic Toxicity Studies –PPO			
Study/Species	**MRID or Publication**	**Doses**	**Results/Classification**
			Acceptable/Non-Guideline
Chronic Inhalation Toxicity			
870.4300 Combined/ Chronic Toxicity/ Carcinogenicity Study, Wistar Rats 123 weeks (Females) 124 weeks (Males)	Kuper et al. 1988 and 42039901	Doses (inhalation): 0, 30, 100 or 300 ppm	**Systemic NOAEL: 30 ppm** **Systemic LOAEL: 100 ppm** **BMD/BMDL$_{10}$:140/120 ppm** (moderate to marked effects) Increased incidences for basal cell hyperplasia, and nest-like infolds of the respiratory epithelium Cancer Effects No statistically significant nasal tumors in nasal cavity. However, 3 malignant tumors in nasal cavity were reported in males (one tumor of ameloblastic fibrosarcoma in low dose male, one squamous cell carcinoma in a low dose male and in a high dose male). Four males in the HDT had a carcinoma in the larynx or pharynx, trachea or lungs. Controls had no nasal tumors. Incidences of fibroadenomas of the mammary gland tumors are: 32/69(46%), 30/71(42%), 39/69(57%), 47/70 (67%) in control, low, mid and high dose groups respectively; significant at high dose ($p<0.04$). Historical control incidence of benign tumors in the mammary gland in the lab ranges 19-61%. Incidences of tubulopapillary adenocarcinoma: 3/69, 6/71, 5/69 8/70 ($p<0.01$) 70 in control, low, mid and high dose groups respectively. Historical control incidence of malignant tumors in the mammary gland in the lab ranges 0-15%. **Acceptable/Guideline Study**
870.4300 Combined Chronic Toxicity/ Carcinogenicity Male F344 Rats, 104 weeks	Lynch et al. 1984	Doses (inhalation): 0, 100, 300 ppm	**Systemic NOAEL: Not Established** **Systemic LOAEL: 100 ppm** Decreased body weight, increased hemoglobin, organ weights and extra thoracic (nasal suppurative rhinitis) effects. Cancer Effects Adrenal pheochromocytoma at both doses (8/78, 25/78, 22/80 in control, low and high dose groups, $p<0.05$)
870.4300 Combined Chronic Toxicity/ Carcinogenicity F344 Rats, 103 weeks	NTP, 1985	Doses (inhalation): 0, 200, 400 ppm	**Systemic NOAEL: Not Established** **Systemic LOAEL: 200 ppm** extra thoracic respiratory effects Cancer Effects At 400 ppm, 2/50 (m) and 3/50 (f) had papillary adenomas of the respiratory epithelium and submucosal glands of the nasal turbinates compared to none in low and control groups. An increase in the thyroid C-cell adenomas and carcinomas occurred at 400 ppm. In females the combined incidences of C-cell adenomas and carcinomas of the thyroid were 2/45, 2/35, 7/37 ($p=0.023$). NTP concluded that this tumor type does not provide unequivocal evidence of carcinogenicity for PPO in rats. **Acceptable/Non-Guideline**
870.4200 Combined Chronic Toxicity/ Carcinogenicity B6C3F1Mice, 103 weeks	NTP, 1985	Doses (inhalation): ppm 0, 200, 400 ppm	**Systemic NOAEL: Not established** **Systemic LOAEL: 200 ppm** extrathoracic respiratory effects HDT had decreased survival in males and females, decreased body weights in both sexes, sporadic metaplasia and hyperplasia and chronic inflammation in the nasal cavity.

Table 4b: Subchronic, Chronic Toxicity Studies –PPO			
Study/Species	**MRID or Publication**	**Doses**	**Results/Classification**
			Cancer Effects Nasal cavity: The combined incidences of hemangiomas and hemangiosarcomas in the nasal cavity were: males-0/50, 0/50, 10/50, p<0.001; females- 0/50, 0/50, 5/50, p=0.028) one squamous cell carcinoma and one papilloma were induced in nasal cavity at high dose (1 male each, not significant), adenocarcinomas in nasal cavity (2 females, not significant) NTP concluded as clear evidence of carcinogenicity for PPO in mice. **Acceptable/Non-Guideline**
870.4100 Chronic Toxicity-cynomolgus Monkeys 2 years	Sprinz et al. 1982 (As cited in EPA, 1994) and Setzer at al. 1996	Doses (inhalation): 0, 100 or 300 ppm	**NOAEL: Not established** **LOAEL: 100 ppm** Increased incidence for axonal dystrophy in the medulla oblongata and in the most distal portions of the fasciculus gracilus in all treated monkeys (2/2 in each PPO group) as compared to one (1/2) in controls. No dose related lesions between the treatments. **Acceptable/Non-Guideline Study**
Subchronic Dermal Toxicity			
21-Day Dermal Toxicity (Rats)	No Study identified		
Dermal Absorption	No Study identified		
Metabolism			
	WHO, 1985	-	-No data on absorption of propylene oxide. -Two metabolic pathways suggested: 1) conjugation with glutathione via glutathione epoxide transferase 2) hydrolysis by epoxide hydrolase to 1,2 propanediol (propylene glycol). Propanediol can be excreted as such or metabolized to lactic and pyruvic acid -Propylene oxide is a direct alkylating agent. Forms DNA (N-2-hydroxypropyl-guanosine, N-2-hydroxypropyl-guanosine) and protein adducts (hemoglobin alkylation at the cysteine, histidine or valine) residues. -Assuming a 100% alveolar absorption and first-order kinetics, a half-life of 40 minutes was estimated for the elimination of PPO in rats Under *in vitro* conditions, the half-life of propylene oxide in stomach (pH1 and 37°C) is reported approximately one minute.
Mutation/Genotoxicity			
	Multiple references as cited in IARC, 1994	-	Mutagenic in bacteria, fungi and insects; caused DNA damage in rat hepatocytes in vitro; caused chromosomal aberrations in vitro in mammalian cells; however, no increase in chromosomal aberrations of peripheral lymphocytes of male cynomolgus monkeys after long term exposure in vivo (up to 300 ppm for 2 years), inconsistent results in micronuclei formation in mice erythrocytes in vivo, negative results for dominant lethal assays in rats and mice.

*1 ppm = 2.4 mg/m^3 or 1 mg/m3 = 0.42 ppm

Table 5a: †Acute Toxicity of Propylene Chlorohydrin (1-chloro-2-propanol, 2-chloro-1-propanol)			
Study/ Species	**MRID or Publication**	**Results**	**Classification**

Table 5a: †Acute Toxicity of Propylene Chlorohydrin (1-chloro-2-propanol, 2-chloro-1-propanol)			
Study/ Species	**MRID or Publication**	**Results**	**Classification**
870.1100 Acute Oral, Rats Mouse Guinea pigs Dogs	 Smyth et al., 1941, US FDA, 1969 Weisbrod, 1981 Smyth et al., 1941 FDA, 1969 (as cited in TNO BIBRA International, 1994)	 Oral LD_{50} = 220 mg/kg Oral LD_{50} = 580 mg/kg Oral LD_{50} = 720 mg/kg At 200 mg/kg one of seven dogs died while 250 mg/kg or above was lethal to all six treated dogs	 Category II Category III Category III
870.1200 Acute Dermal, Rabbits	 Smyth et al., 1969 Weisbrod, 1981 (as cited in TNO BIBRA International, 1994)	 LD_{50} = 528 mg/kg LD_{50} = 440 mg/kg	 Category II Category II
870.1300 Acute Inhalation, Rats	 Smyth and Carpenter, 1969 (as cited in NTP, 1998)	 LC_{50} = Not Determined Inhalation of 500 ppm (1.94 mg/L) PPO resulted in death of 1/6 animals after 4 hours.	 Category Undetermined
870.2400 Primary Eye Irritation, Rabbits	 Carpenter and Smyth et al. 1946?) (as cited in NTP, 1998)	 Severe injury to the rabbit cornea following instillation of 0.005 ml propylene chlorohydrin	 -
870.2500 Primary Skin Irritation, Rabbits	 Smyth et al 1969 (as cited in TNO BIBRA International, 1994)	 Limited data-No irritation 24 hr following application of 0.01 ml propylene chlorohydrin in a rabbit	 -
870.2600 Dermal Sensitization, Guinea pig	 No study identified	 -	 -
870.6200 Acute Neurotoxicity, Rats	 No study identified	 -	 -

† Note: The strain of the animals used and type of PCH isomer used in acute tests are not specified.

Table 5b: Subchronic, Chronic Toxicity Studies - Propylene Chlorohydrin (1-chloro-2-propanol, 2-chloro-1-propanol)			
Study/Species	**MRID or Publication**	**Doses**	**Results/Classification**
Developmental/Reproduction Toxicity			
870.3700 Developmental Toxicity Rats (Strain not specified)	Exxon Chemical Company, 1980 (as cited in NTP, 1998)	Doses: 8, 20, 50 or 125 mg/kg GD 6-15 (gavage)	**Maternal NOAEL/LOAEL:** Could not be determined **Developmental NOAEL/LOAEL:** Could not be determined Maternal effects: Slight decrease in embryo survival in the 8 and 125 mg/kg groups Developmental effects: Two fetuses showed gross malformation (dose not specified) **Unacceptable/Non-Guideline** Data could not be verified; secondary source of

Table 5b: Subchronic, Chronic Toxicity Studies - Propylene Chlorohydrin (1-chloro-2-propanol, 2-chloro-1-propanol)			
Study/Species	**MRID or Publication**	**Doses**	**Results/Classification**
			information
870.3700 Developmental Toxicity Rabbits	No study identified		
870.3800 Two-Generation Reproduction Study, Rats	NTP, 1998	Doses: 0, 300, 650, 1300 ppm in drinking water (equivalent to 0, 30, 65, 130, mg/kg/day; determined assuming 30 ml as daily water consumption and average body weight of dams as 0.3 kg)	**Parental NOAEL:65 mg/kg/day** **Parental LOAEL: 130 mg/kg/day** Decreased body weight of F_0 dams during gestation and lactation, and F_1 dams during gestation **Reproductive NOAEL: Not determined** **Reproductive LOAEL: 130 mg/kg/day** Increased percentage of abnormal sperm **Offspring NOAEL: 30 mg/kg/day** **Offspring LOAEL: 65 mg/kg/day** Decreased F_1 male and female pup weights at PND 14 and 21 **Acceptable/Non-Guideline**
Subchronic Oral Toxicity			
Subchronic (22 weeks) Rats	USFDA, 1969 (as cited in TNO BIBRA International, 1994)	Doses: 0, 25, 50 or 75 mg/kg/day; Another group with 100-250 mg/kg/day Gavage	**NOAEL: <25 mg/kg/day** **LOAEL: 25 mg/kg/day** Increased liver weight in males **100% mortality at 250 mg/kg/day within 3 weeks**. **Unacceptable/Non-Guideline** Secondary reference and information could not be verified.
Subchronic (25 weeks) Rats	USFDA, 1969 (as cited in TNO BIBRA International, 1994)	Doses: 0, 1000, 2500, 5000 or 10000 ppm in diet (estimated as 0, 100, 250, 500, 1000 mg/kg/day)	**NOAEL: 250 mg/kg/day** **LOAEL: 500 mg/kg/day** Decreased body weight **Unacceptable/Non-Guideline** Secondary reference and information could not be verified.
Subchronic (14 days) F344 Rats	NTP, 1998	Doses: 0, 100, 330, 1000, 3300, 10,000 ppm in drinking water (determined by study authors as 0, 15, 45, 140, 260, 265 mg/kg/day)	**NOAEL: 45 mg/kg/day** **LOAEL: 140 mg/kg/day** cytoplasmic alteration and degeneration of the acinar cells in the pancreas and atrophy of the bone marrow in females **Acceptable/Non-Guideline**
Subchronic (14 days), B6C3F1 mice	NTP, 1998	Doses: 0, 100, 330, 1000, 3300, 10,000 ppm in drinking water (determined by study authors as 0, 20, 60, 175, 430, or 630 mg/kg/day in males and 0, 25, 95, 290, 640, or 940 mg/kg/day in females)	**NOAEL: 60 mg/kg/day** **LOAEL: 175 mg/kg/day** Increased liver weight relative to body weight in females and increased vacuolization of cytoplasm of hepatocytes in both males and females **Acceptable/Non-Guideline**
Subchronic (14 week) F344 Rats	NTP, 1998	Doses: 0, 33, 100, 330, 1000, 3300 ppm in drinking water	**NOAEL: 35 mg/kg/day** **LOAEL: 100 mg/kg/day** Increased incidences of the acinar cell

Table 5b: Subchronic, Chronic Toxicity Studies - Propylene Chlorohydrin (1-chloro-2-propanol, 2-chloro-1-propanol)			
Study/Species	**MRID or Publication**	**Doses**	**Results/Classification**
		(determined by study authors as 0, 5, 10, 35, 100, 220 mg/kg/day)	degeneration, and fatty change of the pancreas in males and females. **Acceptable/Non-Guideline**
Subchronic (14 week) B6C3F1 mice	NTP, 1998	Doses: 0, 33, 100, 330, 1000, 3300 ppm in drinking water (determined by study authors as 5, 15, 50, 170, 340 mg/kg/day in males and 7, 20, 70, 260 or 420 mg/kg in females)	**NOAEL: 50 mg/kg/day** **LOAEL: 170 mg/kg/day** Increased organ weights and increased incidence of renal tubule vacuolization in males **Acceptable/Non-Guideline**
Subchronic Dermal Toxicity			
Subchronic (21 days or 13 week)	No study identified		
Combined Chronic Carcinogenicity			
870.4300 Chronic (2 years) F344 Rats	NTP, 1998	Doses: 0, 150, 325, or 650 ppm in drinking water (determined by study authors as 0, 15, 30, or 65 mg/kg/day during beginning months and 0, 8, 17, or 34 mg/kg/day during remainder months)	**NOAEL: 65 mg/kg/day (HDT)** **LOAEL: Not established** No treatment related cancer or non-cancer effects. **Acceptable/Non-Guideline**
870.4300 Chronic (2 years) B6C3F1 mice	NTP, 1998	Doses: 0, 250, 500 or 1000 ppm in drinking water (determined by study authors as 0, 45, 75, or 150 mg/kg/day in males and 0, 60, 105, or 210 mg/kg/day in females during first few months and 0, 25, 50, or 100 mg/kg/day for remainder of the study)	**NOAEL: 210 mg/kg/day** **LOAEL: Not established** No effects at any of the doses tested. No evidence of carcinogenicity. **Acceptable/Non-Guideline**
Mutation/Genotoxicity			
	Multiple references (as cited in NTP, 1998)	-	-Weakly mutagenic in TA100 in the presence of S9 Positive in TA1535 with or without S9. -No mutagenic activity in TA97, TA98, and TA1537 with or without S9 extract. -CHO cells- caused high levels of chromatid exchanges and chromosomal aberration in the presence or absence of S9 extract. -No chromosomal aberrations in vivo. -Induced sex-linked recessive lethal mutations in Drosophila in injection but not by feed -Negative for germ cell reciprocal translocation in Drosophila -Negative for micronuclei formation in vivo in mice
Metabolism			
	Multiple	-	Absorption: No data

Table 5b: Subchronic, Chronic Toxicity Studies - Propylene Chlorohydrin (1-chloro-2-propanol, 2-chloro-1-propanol)			
Study/Species	**MRID or Publication**	**Doses**	**Results/Classification**
	references (as cited in NTP, 1998)		Metabolism: Following inhalation, PCH was widely distributed to tissues, rapidly metabolized and eliminated. Excretion: Following oral administration of propylene chlorohydrin in rabbits 11% was excreted in urine as glucuronic acid conjugate. In rats dosed orally with PCH the metabolites, 2-hydroxy propylmercapturic acid (N-acetyl-S-(2-hydroxy propyl)-cysteine) and beta-choloroacetate were identified in urine. In rats administered with PCH by inhalation most of the radioactivity (80%) was excreted in urine and in the expired air. Half-lives for elimination were 4 hours for breath and 5 hours for urine. Also, biliary excretion was reported as another major route of elimination (30% of inhaled dose) for PCH administered by inhalation. Metabolites related to glutathione conjugates, N-acetyl-S-(2-hydroxy propyl)-cysteine and/or S-(2-hydroxy propyl)-cysteine were identified in both liver and urine.

4.2 FQPA Hazard Considerations

4.2.1 Adequacy of the Toxicity Database

4.2.1.1 Propylene Oxide

The toxicology database for PPO is considered incomplete. The database includes acceptable developmental toxicity and reproduction toxicity, subchronic neurotoxicity (non-guideline), and chronic carcinogenicity in rats, all conducted via inhalation. There is no acceptable developmental study in rabbits. Also, the database lacks a chronic toxicity study in non rodents. In addition, there is a published study examining the carcinogenicity effects of PPO by the oral route. This chronic toxicity study via the oral route is inadequate since one sex alone was examined. Moreover, adequate systemic effects were not measured, and pathological examination of tissues is not complete. This study was the only chronic toxicity study available for the oral route and was considered for risk assessment.

4.2.1.2 Propylene Chlorohydrin

The database for PCH is inadequate. There are no guideline studies (acute battery of tests, subchronic, developmental, reproduction or chronic toxicity studies) submitted to the Agency. A search in the open literature provided information on reproductive toxicity and subchronic and chronic toxicities. One rat developmental toxicity study identified in the literature lacked sufficient study details to glean any useful information. A few subchronic oral toxicity studies in rats identified in the literature had deficiencies

such as poor stability of the test compound, and were conducted before GLPs were established. However, the subchronic and chronic toxicity studies in rats and mice and the reproduction toxicity study in rats conducted by NTP provided sufficient information to assess the dietary risk for PCH. The lack of acceptable developmental toxicity studies limited the ability to assess the fetal susceptibility effects under FQPA.

4.2.2 Evidence of Neurotoxicity

4.2.2.1 Propylene Oxide

In a subchronic inhalation neurotoxicity study (MRID 45292801), Fisher-344 male rats exposed to 0, 30, 100, or 300 ppm of propylene oxide (>99% active ingredient) for 6 hr/day, 5 days/week for the first 14 weeks and 7 days/week for the remainder of the study up to 24 weeks. No treatment-related mortalities or clinical signs of toxicity were reported. No treatment-related changes in body weight, FOB or motor activity or hind limb strength were seen. No treatment-related abnormalities were observed during handling and no gait or locomotor abnormalities were noted in the open field. Reflex and sensorimotor responses were similar between the treated and control groups. No gross necropsy and neuropathology were observed.

This study is classified as Acceptable/Non-Guideline and does not satisfy the requirements for a subchronic inhalation neurotoxicity study [OPPTS 870.6200 (§82-7)] in rats. The LOAEL for neurotoxic effects is not established. Validation of the laboratory neurotoxicity testing methods was not included and females were not tested. However, the study is sufficient for the purposes for which it was intended to assess the potential of propylene oxide to induce neurotoxicity in male rats following subchronic inhalation exposure.

Studies from the Open Literature

Wistar rats were exposed to 1500 ppm propylene oxide for 6 hours/day, 5 days/week for 7 weeks (Ohnishi et al., 1988). Awkward gait was apparent in exposed rats by the third to fourth week of exposure and all rats exhibited obvious ataxia by the seventh week. Histopathological examination revealed axonal degeneration of the hindleg nerve and fasciculus gracilis myelinated fibers, and myelinated fibers in the sacral spinal root. The LOAEL for this study was determined as 1500 ppm, the only dose tested. **This study is classified as Unacceptable-Non-Guideline.**

Sprinz et al. (1982; as cited in US EPA, 1994) treated male cynomolgus monkeys (2/group) at 0, 100, or 300 ppm propylene oxide, 7h/day, 5 days/week for 2 years. Nerve conduction velocity was measured throughout the exposure and at the termination of exposure; sections of peripheral nerves, spinal cord, and brain (19 regions) were examined. No exposure-related changes were observed in the peripheral nerves or the spinal cord. Axonal dystrophy was observed in the medulla oblongata and in the most distal portions of the fasciculus gracilus in one control monkey and in all four exposed monkeys. The extent of the lesion was similar in all affected monkeys and was not dose-

related. These findings are also reported in the publication by Setzer et al. (1996). **This study is classified as Acceptable-Non-Guideline.**

4.2.2.2 Propylene Chlorohydrin

There are no neurotoxicity studies available for PCH. Clinical signs of neurotoxicity are not evident in the available database.

4.2.3 Developmental Toxicity Studies

4.2.3.1 Propylene Oxide

Rats

Study1

In an inhalation developmental toxicity study (MRID 41750801), 25 pregnant Fischer 344 rats per group were administered propylene oxide (>99% a.i.; Lot : IRDC Nos. 8863C and 8863D) by whole body exposure to atmospheric concentrations of 0, 100, 300, or 500 ppm for 6 hours/day on gestation days (GD) 6-15, inclusive. On GD 20, dams were sacrificed, subjected to gross necropsy, and all fetuses examined externally. One-half of the fetuses were examined viscerally, and the remaining fetuses were examined for skeletal malformations/variations.

All animals survived to scheduled sacrifice. No treatment-related clinical signs of toxicity were observed in any treated animals during the study, nor were any treatment-related gross abnormalities observed at maternal necropsy. Maternal toxicity in the 500 ppm exposure group was evidenced by statistically significant decreases ($p < 0.05$; 0.01) in body weight gain (40% of control on GD 6-15), and food consumption (88-91% of controls during the various exposure intervals). In addition, food efficiency was substantially decreased during the exposure interval, GD6-16 (45% of controls), further indicating maternal toxicity. Absolute body weights in the 500 ppm group showed statistically significant decreases ($p < 0.01$), but these values represented only 95-96% of control values. No treatment-related differences in body weight, body weight gain, or food consumption were observed in animals exposed to 300 ppm propylene oxide or less.

Therefore, the maternal toxicity LOAEL is 500 ppm based on decreased body weight gains, food efficiency and food consumption and the maternal toxicity NOAEL is 300 ppm.

There were no differences between treated and control groups for number of corpora lutea/dam, implantation sites/dam, pre- or post-implantation loss, resorptions/dam, fetuses/litter, fetal sex ratios, gravid uterine or fetal body weights, or number of dead fetuses.

There were no statistically significant or treatment-related differences between control and treated groups regarding the number of external, soft-tissue, or skeletal malformations/variations with the exception of an increased litter incidence of an accessory 7th cervical rib in the 500 ppm group compared to the controls ($p < 0.01$) (2/17, 4/20, 3/22, and 11/21 for 0, 100, 300 or 500 ppm groups, respectively).

Therefore, the developmental toxicity LOAEL is 500 ppm based on an increased litter incidence of an accessory cervical rib and the developmental toxicity NOAEL is 300 ppm.

This study is classified as **Acceptable-Guideline** and satisfies the requirement for an inhalation developmental toxicity study in rats (§83-3; OPPTS 870.3700).

COMPLIANCE: Signed and dated Quality Assurance, Good Laboratory Practice Statements, Data Confidentiality and Flagging statements were included.

Study 2

In a developmental toxicity NIOSH sponsored study (MRID 41874102), Sprague-Dawley rats were whole-body exposed to filtered air (groups 1-3, 170 rats) or 500 ppm propylene oxide (≥99% a.i.; group 4 = 50 rats) for 7 hours/day by inhalation for a 3 week pregestation (pregestation day = PGD) period. Following this exposure interval, the group 1-3 animals were reallocated (45-48/exposure interval) and were exposed according to one of the following regimes: i) control group received filtered air from gestation days (GDs) 1-16; ii) group 2 received filtered air from GDs 1-6 and test chemical from GDs 7-16; and iii) group 3 received the test chemical from GDs 1-16. Group 4 continued to receive the test chemical from GDs 1-16 (in addition to the 3 week pregestational exposure). All dams were sacrificed on GD 21. No unscheduled deaths were reported.

When compared to controls, decreases ($p \leq 0.05$) were observed in group 4 body weights from GDs 6-21 (↓10-12%). Overall gestation body weight gain (GD 1-21), as calculated by reviewers and not analyzed for statistical significance, was reduced in all treated groups when compared to controls (group 2, ↓18%; group 3, ↓13%; group 4, ↓16%). Further, overall study body weight gain (PGD 3-GD 21) was reduced in all treated groups when compared to controls (group 2, ↓17%; group 3, ↓12%; group 4, ↓27%, calculated by reviewers).

When compared to concurrent controls, variations ($p \leq 0.05$) in absolute (g/rat/day) food consumption were observed in groups 2, 3, and 4, respectively, as follows: during pregestation week 2 (↑1, ↓1, and ↓14%); GDs 7-11 (↓33, ↓29, and ↓29%); GDs 12-16 (↓14, ↓15, ↓8%); and GDs 17-21 (↑12, ↑18, and ↓2%).

It was unconfirmed on page 10 of the evaluative summary of the study report that the animals were checked daily for clinical signs of toxicity; the study report does not indicate that nor any clinical signs data were provided. No gross pathology data were

provided. No treatment-related changes in organ weight or histopathological findings were noted at any exposure interval tested. Percent pre- and post-implantation losses were not reported and could not be calculated by reviewers due to the lack of total numbers of corpora lutea and implantation sites.

The maternal LOAEL is 500 ppm (only dose selected) on PGD 3-GD 21, based on decreased body weight, body weight gains, and food consumption.

Developmental effects were significant ($p<0.05$) decrease in mean fetal weights and decrease in crown-rump lengths in males and females at all exposure regimens in comparison to concurrent controls. The fetal as well as the litter incidence for the reduced ossification of the vertebra was significant ($p<0.01$) compared to controls in dams exposed to propylene oxide during GD1-16.

The developmental LOAEL based on the decreased mean fetal weights and crown-rump length in males and females and possibly reduced ossification of the vertebra is 500 ppm (only dose selected).

Study deficiencies included possible dermal absorption due to whole body exposure, use of one exposure level, inadequate data reporting and animal husbandry and no historical control data. Individual animal data were not reported. Therefore, this developmental toxicity study is classified as **Unacceptable/Guideline** and does not satisfy the guideline requirement for a developmental toxicity study in the rat. An acceptable rat developmental study (MRID 41750801) for inhalation of propylene oxide does exist.

COMPLIANCE: Signed and dated GLP, Data Confidentiality, Flagging, and Quality Assurance statements were provided.

Rabbits

In a developmental toxicity NIOSH sponsored study (MRID 41874102), New Zealand White rabbits (30/exposure interval) were whole-body exposed to 500 ppm propylene oxide (≥99% a.i.) for 7 hours/day by inhalation according to one of the following regimes: i) control group received filtered air from gestation days (GDs) 1-19; ii) group 2 received filtered air from GDs 1-6 and test chemical from GDs 7-19; and iii) group 3 received the test chemical from GDs 1-19. All does received filtered air from GDs 20-29 and were sacrificed on GD 30. All control animals survived to scheduled sacrifice.

In group 2, four rabbits died of pneumonia on GDs 19, 23, or 26. Decreases ($p\leq0.05$) in absolute (g/rabbit/day) food consumption were observed during GDs 11-15 (↓11%) and GDs 16-20 (↓13%). Regarding histopathological findings, the following minimal to mild findings were observed: portal mononuclear inflammation in the liver in 10/26 animals vs. 8/30 controls; subacute/chronic nephritis in 9/26 animals vs. 3/30 controls; and focal mononuclear inflammation of the lung in 11/26 animals vs. 5/30 controls.

In group 3, three rabbits died of pneumonia on GDs 15, 17, or 18. Overall body weight gain was reduced (↓34%, GDs 1-30) as was the gravid uterine weight (↓19%) when compared to the controls; both were calculated by reviewers and not analyzed for statistical significance. Decreases ($p \leq 0.05$) in absolute food consumption were observed during GDs 11-15 (↓38%) and GDs 16-20 (↓21%); additionally, food consumption in group 3 was different ($p \leq 0.05$) from group 2 during GDs 1-5 (↓22%) and GDs 11-15 (↓30%). The following minimal to mild findings were observed: portal mononuclear inflammation in the liver in 11/26 animals vs. 8/30 controls; mineralization of the proximal and distal renal tubules in 10/26 animals vs. 7/30 controls; subacute/chronic nephritis in 10/26 animals vs. 3/30 controls; and focal mononuclear inflammation of the lung in 10/26 animals vs. 5/30 controls.

It was unconfirmed on page 10 of the evaluative summary of the study report that the animals were checked daily for clinical signs of toxicity; however, no clinical signs data were provided. No treatment-related differences in maternal body weights or organ weights (absolute and relative to body) were observed. No gross pathology data were provided. An insufficient number of females (< 20 females) with implantation sites at necropsy in the control and group 2 (17 and 14 animals, respectively) and low pregnancy rates in all groups (47-67%) were observed. The number of implantations/doe, percent male, and fetal weights were similar between control and treated groups. Percent pre- and postimplantation losses were not reported and could not be calculated by reviewers due to the lack of total numbers of corpora lutea and implantation sites.

The maternal LOAEL is 500 ppm (only dose tested) on GDs 7-19, based on increased mortality, reduced food consumption, and microscopic changes in the liver, lungs, and kidneys.

In group 3, increases (not statistically significant) in the number of resorptions/doe (↑123%), number of early resorptions/doe (↑250%), and number of late resorptions/doe (↑34%) were observed. The following minor skeletal abnormalities were observed in the group 3 fetuses [% fetal incidence (% litter incidence)]: misaligned sternebrae [4.2 (23.5)]; fused sternebrae [2.5 (17.6)]; and forelimb flexures [2.5 (17.6)]. None of these findings were observed in the control animals. Bipartite sternebrae was observed in the group 3 fetuses [2.5 (17.6)] vs. controls [0.79 (6.7)].

The developmental LOAEL is 500 ppm (only dose tested) on GDs 7-19, based on increased resorptions and increased incidence of minor skeletal abnormalities.

Study deficiencies included low pregnancy rate, possible dermal absorption due to whole body exposure, use of one exposure level, inadequate data reporting and animal husbandry and no historical control data. Individual animal data was not reported. Further, the results of the study were complicated by a possible *Pasteurella* infection.

Therefore, this developmental toxicity study is classified as **Unacceptable/Non-Guideline** and does not satisfy the guideline requirement for a developmental toxicity study in the rabbit**.**

COMPLIANCE: Signed and dated GLP, Data Confidentiality, Flagging, and Quality Assurance statements were provided.

4.2.3.2 Propylene Chlorohydrin

Rats

There is no guideline developmental toxicity study conducted using rats. However, there is minimal information found from one rat developmental study was identified from the open literature.

Exxon Chemical Company, 1980 (as cited in NTP, 1998)

In the developmental study, rats (strain unspecified) were gavaged with PCH at 8, 20, 50 or 125 mg/kg during GD6-15. There was a slight decrease in the embryo survival in the 8 and 125 mg/kg groups. Two fetuses showed gross malformation at unspecified doses. No information on controls provided.

This study is classified as **Unacceptable/Non-Guideline Study** and does not satisfy the requirement for a developmental toxicity study in rats (§83-3, OPPTS 870.3700)**.**

Rabbits

There is no guideline developmental toxicity study available for rabbits.

4.2.4 Reproduction Toxicity Studies

4.2.4.1 Propylene Oxide

In a two-generation reproduction study (MRID 45292701), propylene oxide (30215 III, >99%, a.i.) vapor was administered to groups of 30 male and 30 female F_0 and F_1 Fischer 344 rats by inhalation at chamber concentrations of 0, 30, 100, or 300 ppm. Each group was exposed to room air (controls) or propylene oxide vapor for 6 hours/day, 5 days/week for 14 weeks (F_0) or 17 weeks (F_1) during the premating period and for 6 hour/day, 7 days/week during the mating, gestation, and lactation periods. The F_1 pups selected to parent the F_2 generation were exposed to room air or the same concentrations of propylene oxide vapor as their parents.

No treatment-related deaths, clinical signs, or gross lesions were observed in rats exposed to any concentration of propylene oxide vapor during premating and postmating periods for adult F_0 or F_1 males or during the premating period for adult F_0 or F_1 females. Adult F_0 and F_1 males exposed to 300 ppm of propylene oxide vapor weighed 4-10% ($p \leq 0.05$) and 7-18% ($p \leq 0.05$), respectively, less than controls for almost all the study including the premating and post mating periods. Both generations gained 13% less weight than controls during the entire study duration. F_0 males exposed to 30 and 100 ppm and F_1 males exposed to 30 ppm weighed significantly less (3-7%) than controls during the study, but these small differences are not considered toxicologically significant. F_0 females in the 300-ppm group weighed 3-6% ($p \leq 0.05$) less than controls and F_1 females weighed 7-10% ($p \leq 0.05$) less than controls during the premating period; weight gain was

12% and 18% less than controls for the F_0 and F_1 generations, respectively. No toxicologically significant effect was observed on body weights of F_0 or F_1 females exposed to any concentration of propylene oxide during the gestation or lactation periods; statistically significant differences were observed at 300 ppm but did not exceed 8% during gestation and 9% during lactation periods.

Exposure to concentrations up to 300 ppm had no exposure-related effect on reproductive performance (mating, fertility or gestation indices) of the adults or on offspring parameters [clinical signs, mean liter size at any time during lactation, survival indices (live birth, viability, or lactation), pup weights or gross and microscopic findings in weanlings].

The parental systemic LOAEL is 300 ppm, based on decreased body weights and weight gain in F_0 and F_1 males during premating and post mating periods and decreased body weights and weight gain in F_0 and F_1 females during premating period. The parental NOAEL is 100 ppm.

The reproductive NOAEL is 300 ppm, HDT. The reproductive LOAEL is not established.

The offspring NOAEL is 300 ppm, HDT. The offspring LOAEL is not established.

The animals were adequately exposed to assess the reproductive toxicity of propylene oxide based on reduced body weights of adult males and females in the F_1 generation. Estrous cycle, sexual maturation, and sperm parameters were not evaluated in this study. However, other reproductive parameters were not affected by exposure to propylene oxide.

The reproductive study in the rat is classified as **Acceptable/Guideline** and does satisfy the guideline requirement for a two-generation reproductive study [OPPTS 870.3800, (§83-4)] in the rat**.** Deficiencies were noted but they did not impact the overall evaluation of this study.

COMPLIANCE: A signed and dated Quality Assurance was provided; GLP, Data Confidentiality, and Flagging statements were not provided.

4.2.4.2 Propylene Chlorohydrin

In a two-generation reproduction study (NTP, 1998), PCH (approximately 75% 1-chloro-2-propanol and 25% 2-chloro-1-propanol) was administered to Sprague-Dawley rats (20/sex/group except controls 40/sex) at 0, 300, 650 and 1300 ppm in drinking water. Assuming 30 ml as daily drinking water consumption, and the average body weight as 0.3 kg, the daily intake values were estimated as 0, 30, 65 and 130 mg/kg/day respectively. F_0 adults were continued for five litters and the last litter was selected for F_1 adults. For F_2 generation, control and high dose animals from F_1 parents alone were treated and continued for one litter. Clinical observations, water consumption, pregnancy

index, litters per pair, cumulative number of days to litter, dam body weights, live pups per litter, proportion of pups born alive, sex of live pups, and pup body weights were recorded. Also, selected organ weights, epididymal spermatozoal measurements and estrous cycle parameters were measured.

At delivery of each litter, the mean body weights of F_0 dams in the MDT (except for the second litter) and the HDT were significantly less than those of the controls ($p<0.05$; ↓4-8% for MDT and $p<0.01$; ↓10-15% for HDT). Mean body weights of litter 5 F_0 dams in the MDT were significantly less than those of the controls from lactation days 0 to 14 ($p<0.05$; ↓4-8%), and the mean body weights of F_0 dams in the HDT were significantly less than those of the controls throughout lactation, PND 0 to 21 ($p<0.05$; ↓15-16%). The body weight changes in F_0 dams of MDT although statistically significant, was not considered biologically significant (<10% decrease). The mean body weight of F_1 dams of 1300 ppm, only dose tested, were significantly less ($p<0.01$; ↓17%) at delivery, compared to controls.

Mating, fertility and pregnancy indices in the 1-chloro-2-propanol treated groups were similar to controls. The average numbers of litters per pair of all exposed groups were not affected as compared to controls. The cumulative days to deliver were slightly higher in the HDT as compared to controls (116.7 days in controls to 118.7 days in HDT) for litter 5 but this was not affected in the other four litters. The days to litter in F_1 dams were not affected.

The survival of the final litters of exposed F_1 pups was similar to that of the controls throughout lactation. Male and female F_1 pup weights of HDT were significantly less than those of the controls on days 7, 14, and 21 ($p<0.05$; ↓10-23%) and of MDT on days 14 and 21 ($p<0.05$; ↓7-34%). The organ weights of the F_1 rats at HDT were similar to controls. The percentage of abnormal sperm was significantly greater in F_1 male rats of HDT compared to controls (↑210%; 0.78±0.11 in controls vs. 2.4±0.53 in HDT, $p<0.05$). There were no significant differences in estrous cycle parameters between control and F_1 females of HDT. The effects on sperm abnormalities and other reproductive measures at doses below HDT were not determined. Exposure of F_1 adults to HDT did not affect the sex ratio, or pup or organ weights.

The parental systemic LOAEL is 1300 ppm (130 mg/kg/day), based on decreased body weights of F_0 dams during delivery and lactation and F_1 dams during delivery. The parental NOAEL is 650 ppm (65 mg/kg/day).

The reproductive LOAEL is 1300 ppm (130 mg/kg/day) based on increased percentage of abnormal sperm in F_1 rats. The reproductive NOAEL is not established.

The offspring LOAEL is 650 ppm (65 mg/kg/day) based on decreased F_1 pups weights for males and females during PND 14 and 21. The offspring NOAEL is 300 ppm (30 mg/kg/day).

The study is classified as **Acceptable/Non-Guideline**.

4.2.5. Pre-and/or Postnatal Toxicity

4.2.5.1 Propylene Oxide

Determination of Susceptibility

There is no quantitative susceptibility between the rat fetuses and the dams from the rat developmental study (MRID 41750801). The study indicated a possible qualitative susceptibility since the skeletal variations (increased litter incidence for the accessory 7th cervical rib) were observed at the same dose which produced maternal toxic effects (decreased body weight gain, food consumption and food efficiency).

Susceptibility in rabbits could not be adequately ascertained due to the absence of an acceptable rabbit developmental study.

In the two-generation reproduction study, there is no evidence for quantitative or qualitative susceptibility in pups exposed to PPO since no offspring effects were seen at doses which produced significant systemic toxicity in parents.

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

The degree of concern for the qualitative susceptibility effects seen after *in utero* exposures in rats was low since the effects (increased incidence of the7th cervical rib) are 1) skeletal variations and not malformations 2) they were seen in the presence of maternal toxicity and 3) this endpoint is used for assessing potential acute dietary risk to the population of concern (Females 13-49).

The concern for the lack of an acceptable developmental toxicity study in rabbits is addressed with the retaining of the 10X database uncertainty factor for risk assessments. The database uncertainty factor is considered an FQPA factor.

4.2.5.2 Propylene Chlorohydrin

Determination of Susceptibility

There is no adequate data to determine the fetal susceptibility following *in utero* exposures in rats or rabbits for PCH.

In the reproduction study (NTP, 1998), quantitative susceptibility effects were evident since decreased pup weights were seen at dose which had no systemic toxicity in dams.

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

The degree of concern is low for the quantitative susceptibility seen in the reproduction study since the dose and the endpoint of this study is used for assessing chronic dietary risk in conjunction with the retaining of the 10X database uncertainty factor. The database uncertainty factor is considered to be an FQPA factor.

4.2.6 Recommendation for a Developmental Neurotoxicity Study

4.2.6.1 Propylene Oxide

Evidence that supports requiring a Developmental Neurotoxicity Study

In a subchronic study identified in the open literature, Wistar rats exposed to PPO at 1500 ppm for 7 weeks exhibited awkward gait during third and fourth week of exposure and more ataxia in all rats by 7^{th} week. Also, histopathological evidence such as axonal degeneration of the hindleg nerve and fasciculus gracilis and myelinated fibers in the sacral spinal root were observed.

In a chronic study axonal dystrophy in the nucleus gracilis was reported in monkeys exposed to PPO for 2 years.

Evidence that supports not requiring a Developmental Neurotoxicity Study

No evidence of neurotoxicity was reported in the subchronic neurotoxicity conducted up to 300 ppm and no evidence neurotoxicity signs were observed in developmental, reproductive, subchronic or chronic toxicity studies. Since the nasal epithelial effects (e.g., hyperplasia) occur at low dose level (100 ppm) compared to the developmental, reproductive effects or neurotoxic effects ($\geq$ 300 ppm), it is unlikely that the data that would be derived from the developmental neurotoxicity study would be helpful for risk assessment. Therefore, the requirement for a developmental neurotoxicity study is not recommended.

4.2.6.2 Propylene Chlorohydrin

Evidence that supports requiring a Developmental Neurotoxicity Study

None.

Evidence that supports not requiring a Developmental Neurotoxicity Study

No neurotoxic effects found from the available database.

4.2.7 Rationale for the UFDB

4.2.7.1 Propylene Oxide

There is a data gap in the toxicology database for PPO (developmental toxicity study in rabbits and chronic study in non-rodents by oral route). This necessitates the use of 10X database uncertainty factor (UF_{DB}) for PPO dietary risk assessment. The UF_{DB} is considered an FQPA factor.

4.2.7.2 Propylene Chlorohydrin

The database for PCH is incomplete. There is a need for developmental toxicity study in rats and rabbits and chronic toxicity study in nonrodents. In addition, there is a need for the chronic carcinogenicity studies in rats and mice since the doses used in the existing studies found in the literature are inadequate. A 10X database uncertainty factor (UF_{DB}) is applied for PCH dietary risk assessment.

4.3 Additional FQPA Safety Factor

Based on the discussion in 4.2.5., no additional FQPA Safety Factor (i.e., 1X) is required for PPO or PCH since there are no residual uncertainties for pre and/or post-natal toxicity for PPO and the doses selected for PCH are considered to protect the effects for children. It is assumed that the exposure databases are complete and the risk assessment does not underestimate the potential risks for infants and children. The FQPA SF has been retained as a data base uncertainty factor.

4.4 Hazard Identification and Toxicity Endpoint Selection

4.4.1 Acute and Chronic Reference Doses for Propylene Oxide

4.4.1.1 Acute Reference Dose (aRfD) – Females 13-49 Years

Study Selected: Developmental Toxicity Study in Rats § 83-3; OPPTS 870.3700

Executive Summary: MRID 41750801 (See section 4.2.3.1)

Dose and Endpoint Selected for Establishing Acute RfD (Gen Population): The NOAEL of 300 ppm ([1]oral equivalent to 209 mg/kg/day) based on the increased litter incidence of an accessory 7th cervical rib.

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

[1] Extrapolation from inhalation to oral route: mg/kg/day = (mg/L x absorption factor x respiratory volume in L/hr x duration of daily animal exposure x activity factor) /mean body weight in kg; The oral equivalent dose for 300 ppm =[(300x 58.08/24.4x1000) mg/L x 1x 6.06 L/hr x 6 h/day x 1 / (0.124 kg)] = 209 mg/kg/day.

Comments about Study/Endpoint/Uncertainty Factor:

The study is considered appropriate for the population of concern. The developmental effects could be attributed to a single dose. In addition to the developmental effects, the same dose level also caused maternal toxic effects.

Acute RfD (Females 13-49 years) =	**209 mg/kg/day (NOAEL)** / **1000 (UF)**	**=**	**0.21 mg/kg/day**

4.4.1.2 Acute Reference Dose (aRfD) – General Population

No endpoint of concern is found suitable to assess risk for this population.

4.4.1.3 Chronic Reference Dose (cRfD) – General Population

Study Selected: Chronic Carcinogenicity Study in Rats- Oral §83-5; OPPTS 870.3700

Executive Summary: Dunkelberg, 1982 (See Section 4.4.10.1)

Dose and Endpoint Selected for Establishing Chronic RfD (Gen Population): BMD_{10} of 1.4 mg/kg/day based on the increased incidence for the hyperkeratosis, hyperplasia and papillomas in forestomach in PPO administered rats.

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

Comments about Study/Endpoint/Uncertainty Factor: The study selected is appropriate for the duration and route of exposure. This was the only chronic study available for PPO by oral route. Since the study did not establish a clear NOAEL, bench mark dose modeling (BMD) was used. Although the data fitted well for several dichotomous models, the $BMDL_{10}$ (the lower confidence limit on the dose that produced 10% effects) from the log logistic model was used to derive cRfD since it provided the conservative dose as compared to other dichotomous models.

Chronic RfD (General Population) =	**1.4 mg/kg/day (BMDL)** / **1000 (UF)**	**=**	**0.001 mg/kg/day**

4.4.2 Acute and Chronic Reference Doses for Propylene Chlorohydrin

4.4.2.1 Acute Reference Dose (aRfD) – Females 13-49 Years and General Population

No endpoint of concern is found suitable to assess risk for this population.

4.4.2.2 Chronic Reference Dose (cRfD) – General Population

Study Selected: Two-generation Reproduction Study, Rats § 83-4; OPPTS 870.3800

Executive Summary: NTP, 1998 (See Section 4.2.4.2)

Dose and Endpoint Selected for Establishing Chronic RfD (Gen Population): The offspring NOAEL of 30 mg/kg/day based on decreased F_1 pup weights in males and females during PND 14 and 21 at 65 mg/kg/day.

Uncertainty Factor (UF): 1000X (10X interspecies extrapolation, 10X intraspecies variation and 10X database uncertainty factor for the data gaps in toxicity studies).
Comments about Study/Endpoint/Uncertainty Factor: The study selected is appropriate for the route and duration of the exposure. The doses selected are comparable to the NOAELs established for pathological changes in pancreas, spleen or bone marrow in subchronic studies conducted using adult rats and mice (NOAEL of 35 to 45 mg/kg/day in rats and 50-60 mg/kg/day in mice) and conservative to the endpoints observed in the chronic studies (NOAEL of 65 mg/kg/day, HDT for rats and NOAEL of 210 mg/kg/day, HDT for mice. The discrepancy in the pathological changes reported between the subchronic and chronic exposures using the same strain of animals and identical test compound is not understood (NTP, 1998). However, the potential for any such pathological changes in the offspring could be protected by the dose selected and the application of 10X database uncertainty factor.

Chronic RfD (General Population) = $\frac{\text{30 mg/kg/day (NOAEL)}}{\text{1000 (UF)}}$ = 0.03 mg/kg/day

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

There are no residential uses for propylene oxide and therefore, the endpoints for the incidental oral exposure are not derived.

4.4.4 Dermal Absorption

Studies on dermal absorption are unavailable.

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

Dermal exposure was not assessed.

4.4.6 Inhalation Exposure

4.4.6.1 Acute (1-day)

Study Selected: Rabbit Developmental Study § 83-4; OPPTS 870.3700

Executive Summary: MRID 41874102 (See Section 4.2.3.1)

COMPLIANCE: Signed and dated GLP, Data Confidentiality, Flagging, and Quality Assurance statements were provided.

Dose and Endpoint Selected: The LOAEL of 500 ppm based on increased resorptions, and/or increased incidence of minor skeletal abnormalities.

Comments about Study/Endpoint: Although there are concerns for this study, primarily because it is a single dose study with no NOAEL, the study is appropriate for the route and duration of exposure, and the study is considered adequate for assessment of acute inhalation risk if an additional uncertainty factor of 10X is included in the derivation of a concern level. The rat developmental inhalation study is also appropriate to assess acute inhalation risks; however, the rabbit study provides a more conservative point of departure when the additional uncertainty factor is included.

4.4.6.2 Short-Term (1-30 days) and Intermediate-Term (1-6 months)

Study Selected: Two generation Reproduction Study in Rats § 83-4; OPPTS 870.3800

Executive Summary: MRID 45292701 (See Section 4.2.4.1)

COMPLIANCE: A signed and dated Quality Assurance was provided; GLP, Data Confidentiality, and Flagging statements were not provided.

Dose and Endpoint Selected: The NOAEL of 75 ppm based on decreased body weight and weight gain in both F_0 and F_1 males and females during premating periods at 225 ppm.

Comments about Study/Endpoint:

The study selected is appropriate for the route of exposure. It must be noted that the study NOAEL/LOAEL of 100/300 ppm is converted to human equivalent concentrations of 75/225 ppm for occupational scenarios. For example, the human equivalent NOAEL of 75 ppm is derived after adjusting the 6 hour exposure per day in the animal study to 8 hours per day for humans (100 ppm x 6h/8h = 75 ppm). Similarly, 225 ppm is derived from the animal LOAEL of 300 ppm (300 ppm x 6h/8h = 225 ppm).

4.4.6.3 Inhalation Exposure Long -Term (>6 months)

Study Selected: Two year combined carcinogenicity study § 83-5; OPPTS 870.4300

Executive Summary: MRID 42039901 (See Section 4.4.10.1)

Dose and Endpoint Selected: The NOAEL of 30 ppm based on increased incidences of basal cell hyperplasia, and nest-like infolds of the respiratory epithelium at 100 ppm. A Benchmark Dose analysis was performed on the data, and the most appropriate point of departure was determined to be a BMD of 140 ppm based on moderate to marked nest-like infolds of the respiratory epithelium in male rats. The corresponding $BMDL_{10}$ is 120 ppm.

Comments about Study/Endpoint:

The study selected is appropriate for the route of exposure and duration. The $BMDL_{10}$ of 120 ppm is converted to a human equivalent concentration of 90 ppm to reflect an occupational scenario, i.e., the difference between the study duration of 6 hours and an 8-hour workday for typical workers. The previous version of this risk assessment had included an additional dosimetric adjustment factor, the regional gas dose ratio (RGDR), of 0.23 to further reduce the human equivalent concentration; however, in its review of the RfD and RfC processes, the Agency has questioned whether the default RGDR calculation for the extrathoracic region is appropriate, and indicates that the interspecies dosimetric adjustment factor for extrathoracic effects may be closer to 1 (EPA, 2002, page 4-33).

4.4.7 Margins of Exposure

Summary of target Margins of Exposure (MOEs) for risk assessment.

Route Duration	Acute (1-day)	Short-Term (1-30 days)	Intermediate Term (1-6 months)	Long Term (>6 Months)
Occupational & Residential Exposure				
Dermal	N/A	N/A	N/A	N/A
Inhalation	300	30	30	30

The occupational and residential MOE for short, intermediate and long term for occupational exposure is based on a combined uncertainty factor of 30X (3X interspecies factor and 10X intraspecies factor). The MOE for acute inhalation exposure includes an extra 10x factor for database uncertainties. The traditional interspecies factor of 10X is reduced to 3X since the animal doses are converted to human equivalent concentrations.

4.4.8 Recommendation for Aggregate Exposure Risk Assessments

As per FQPA, when there are potential residential exposures to the pesticide, aggregate risk assessment must consider exposures from residues in food commodities and drinking

water as well as exposures arising from non-dietary sources (e.g., incidental oral, dermal and inhalation routes). The residues from drinking water are negligible since PPO is used only indoors. PPO has no direct residential uses; however residential bystanders may be exposed to emissions from fumigation facilities or structures. Dietary and bystander exposure cannot be combined for this assessment, however, because the endpoints selected for these exposures are not based on a common effect. Therefore, the aggregation of risk from dietary and inhalation routes is not performed.

4.4.9 Classification of Carcinogenic Potential

4.4.9.1 Propylene Oxide

Animal Studies

Rats – Oral

Study 1 (Dunkelberg, 1982)

In a chronic carcinogenicity study (Dunkelberg, 1982), female Sprague-Dawley rats (50/group) were administered with 0, 0 (salad oil as vehicle control), 15 or 60 mg/kg bw propylene oxide (99.7% pure) by gavage twice a week for 109.5 weeks (determined from 219 times of dosing) and observed for 150 weeks. The average total doses in the low and high propylene oxide treated groups were reported as 2714 or 10798 mg/kg bw, respectively. Adjusting the doses to the whole study period of 150 weeks, the average daily doses are estimated as 2.58 and 10.28 mg/kg/day, respectively. Between the 79th and 82nd week several rats in the various groups were affected with pneumonia and during which time the administration was interrupted. Survival rates were not affected by propylene oxide treatment. The first tumor was observed in the 79th week of the treatment. A dose dependent increase in the incidence of forestomach tumors (mainly squamous-cell carcinomas) were observed in the propylene oxide treated animals (0/50, 0/50, 2/50, 19/50 in the control, vehicle control, low and high propylene oxide treatment groups, respectively). Further, one animal in the high dose group had a carcinoma in situ and another animal in the high dose group had an adenocarcinoma of the glandular stomach. In addition to the neoplastic lesions, a dose dependent increase in the combined incidences of papilloma, hyperplasia and hyperkeratosis of the stomach (0/50, 0/50, 7/50, 17/50 in control, vehicle, low dose and high dose, respectively) was reported.

The LOAEL is determined as 2.58 mg/kg/day based on increased combined incidences for hyperkeratosis, hyperplasia and papillomas. The NOAEL is not established.

The carcinogenicity study is limited by inadequate pathological data because pathological examination in several tissues including lung, liver, kidney and thyroid tissues were not reported. The study examined only female rats and any sex specific effects were not determined. It must be noted this is the only chronic study available for PPO by oral route and used for chronic reference dose and chronic cancer risk determination. The

lack of adequate measurements on systemic effects such as body weights, food consumption, clinical measurements, organ weights etc. along with the inadequate pathological examinations and lack of determination of any sex specific effects limit to classify this study as combined chronic toxicity/carcinogenicity guideline study (OPPTS No. 870.4300). Therefore, the study is classified as **Acceptable/Non-Guideline**.

Rats – Inhalation

Study 1 (MRID 42039901)

In a chronic inhalation toxicity study (MRID 42039901), 100 Wistar rats/sex/exposure group were exposed to 1,2-propylene oxide gas (technical grade, 99.9903% a.i.; Lot Nos. - not provided) at target exposure concentrations of 0, 30, 100, or 300 ppm for 6 hours/day, 5 days/week for up to 28 months. Seventy rats/sex/exposure group were in the main group, and 10 rats/sex/exposure group were in each of three satellite groups killed after 12, 18, or 24 months to provide interim toxicological data.

The mortality rate was statistically increased at the end of the study in 300 ppm group males (79% vs. 46% for controls) and 100 and 300 ppm group females (61 and 79%, respectively, vs. 43% for controls) as compared to controls. It appears that the decreased survival in high dose females is evidence that the MTD was exceeded in the study. Statistically significant decreases in absolute body weights in 300 ppm males during weeks 1-71 and 99-111 and 300 ppm females during weeks 1-67, with the body weight means ranging from 90-97% of controls for males, and 92-98% of controls for females, were reported. Mean body weight gains in the high dose level males (↓16%) and females (↓22%) during the first four weeks and in 300 ppm males during weeks 13-59 (↓12%) were decreased as compared to respective controls. During weeks 59-99, 100 and 300 ppm males and 300 ppm females had an increased body weight gain, suggestive of a compensatory effect. Food consumption was marginally decreased during the first two weeks of the study ($p < 0.02$) in high level males (94%) and during the first week in high dose level females (89%).

There were no treatment-related changes observed in hematology and clinical chemistry parameters or in organ weights. Macroscopic evaluation revealed that females in the 300 ppm group had an increased incidence of adrenal enlargement, which may be related to treatment.

Microscopic examination revealed an increased incidence of degenerative and hyperplastic changes in the nasal mucosa of exposed rats as compared to controls. The 300 ppm male and female satellite groups had statistically significant ($p < 0.05$; 0.01) increase in the incidences of olfactory epithelium atrophy at 12 months (males: 4/10 vs. 0/10 controls; females: 5/9 vs. 0/10 controls) and basal cell hyperplasia of the olfactory epithelium at 12 months (males: 5/10 vs. 0/10 controls; females: 7/9 vs. 0/10 controls), 18 months (males: 6/10 vs. 1/10 controls; females: 6/10 vs. 0/10 controls), and 24 months (males: 4/10 vs. 0/10; females: 5/9 vs. 0/9 controls) compared to controls. The incidences of nest-like infolds of respiratory epithelium were increased ($p < 0.05$; 0.01) in

300 ppm males at 12 months (9/10 vs. 1/10 controls), 18 months (9/10 vs. 0/10 controls) and 24 months (7/10 vs. 0/10 controls); and 300 ppm females at 12 months (9/9 vs. 0/10 controls), 18 months (10/10 vs. 0/10 controls), and 24 months (7/9 vs. 0/9 controls). The incidences of these nasal lesions were similar in animals from the main study (28 months). Atrophy of the olfactory epithelium was increased ($p < 0.01$) in 300 ppm males (21/63 vs. 5/66 controls) and females (26/65 vs. 7/64). Both 100 and 300 ppm males and females had increased incidences ($p < 0.05$; 0.01) of basal cell hyperplasia (males: 10/62 and 24/63 vs. 4/66 controls; females: 9/62 and 33/65 vs. 0/64 controls) and nest-like infolds of the respiratory epithelium (males: 29/62 and 47/63 vs. 5/66 controls; females: 20/62 and 43/65 vs. 4/64 controls). The nest-like infolds showed a clear concentration-response relationship. Other microscopic changes that may be related to exposure to 300 ppm 1,2-propylene oxide include increased incidence of thrombi in the heart in males, and myocardial degeneration in females.

The LOAEL is 100 ppm based on increased incidences for basal cell hyperplasia, and nest-like infolds of the respiratory epithelium. The NOAEL is determined as 30 ppm.

There were incidences of fibroadenomas (control, 32/69; low dose, 30/71; mid dose, 39/69; high-dose 47/70, $p<0.05$) and tubulopapillary carcinomas (control, 3/69; low dose, 6/71; mid dose, 5/69; high-dose 8/70, $p<0.05$) in the mammary glands of females. Multiplicity of fibroadenomas was significantly increased at all doses ($p<0.01$). However, the study was conducted for 28 months and the high dose incidence of 67%, although exceeding the historical control range 19-61%, is of questionable usefulness, since the usual proliferation of mammary gland fibroadenomas, the most common type of female tumor, is expected to be significantly enhanced at this point in the study. These facts, in part, support the conclusion that the fibroadenoma data do not provide unequivocal evidence that PPO is a systemic carcinogen.

Three malignant tumors were found in the nasal cavity of treated males: one tumor described as 'ameloblastic fibrosarcoma' in a low dose male, one squamous cell carcinoma in a low dose male and one in a high dose male. Four males in the high dose group had a carcinoma in the larynx or pharynx, trachea or lungs with none in controls or low-dose males.

Dosing was considered adequate based on increased mortality and decreased body weight in males and females at the highest concentration and increased incidences of nasal lesions at all exposure concentrations.

This combined chronic/oncogenicity toxicity study is **Acceptable/Guideline** (§83-5; OPPTS 870.4300*)* and does satisfy the guideline requirement for a combined chronic/oncogenicity study in rats.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

Study 2 (NTP, 1985)

In a chronic carcinogenicity study (NTP, 1985), F344 rats (50/sex/group) were exposed via inhalation to 99.9% pure propylene oxide at concentrations of 0, 200, and 400 ppm for 6 hours/day, 5 days/week for 103 weeks. Hematology, serum chemistry, urinalysis, and histopathology were performed. Survival in the rats was unaffected by exposure to propylene oxide, and terminal body weights were slightly depressed in the high-dose male (8%) and female (9%) rats. The respiratory epithelium of the nasal turbinates was the primary tissue affected by propylene oxide exposure in rats. Exposure-related increases in suppurative inflammation of the nasal cavity (7/50, 19/50, and 33/50 in the control, 200, and 400 ppm males, respectively, and 3/50, 5/50, and 20/50 in the control, 200, and 400 ppm females, respectively) in addition to exposure-related increases in epithelial hyperplasia (0/50, 1/50, and 11/50 in males; 0/50, 0/48, and 5/48 in females in respective dose groups) and squamous metaplasia (1/50, 3/50, and 21/50 in males; 1/50, 2/48, and 11/48 in females in respective dose groups) were reported at the end of the treatment.

The LOAEL is determined as 200 ppm based on the extrathoracic effects. The NOAEL is not established.

Papillary adenomas of the nasal cavity occurred in 0/50 control, 0/50 low dose and 3/50 high dose females, and in 0/50 control, 0/50 low dose and 2/50 high dose males. In historical controls from five different laboratories for the same strain of rats, the incidences for nasal cavity tumors were reported as 3/1523 for females and 1/1477 for males. However, although the incidence of papillary adenomas of the nasal cavity occurred at increased frequency, the occurrence of these tumors was not statistically significant by pair wise comparison with the controls, and are not considered treatment related. A increase in thyroid C-cell adenoma and carcinoma ($p=0.023$) occurred in females and the incidences are 2/45, 2/35, 7/37 in control, low dose and high dose groups, respectively. Since these tumors are relatively common in female F334/N rats, the combined incidence of C-cell adenomas and carcinomas in this study is considered to be unrelated to the administration of propylene oxide. The incidences in historical control females for C-cell adenoma or carcinoma ranged from 1/49 (2%) to 9/50 (18%) and the total incidence corresponded to 122/1472 (8.3%±4.3%) based on the data collected from five different laboratories. The incidence in the 400 ppm PPO group was similar to that observed for the historical controls at the high end (19%) but greater than the overall or total incidence for thyroid gland tumors.

The doses tested are considered adequate based on the extrathoracic effects in propylene oxide treated groups.

The study is classified as **Acceptable/Non-Guideline**.

Study 3 (Lynch et al. 1984)

In a chronic carcinogenicity study male F344 rats were exposed via inhalation to propylene oxide (80/group) at 0, 100, or 300 ppm propylene oxide for an average of 6.9 hours/day, 5 days/week for 104 weeks. A statistically significant ($p<0.01$) increase in

mortality was observed at the high dose compared to controls. The median survival time was 720, 705, and 675 days for control and 100 and 300 ppm groups, respectively. The mean body weights were significantly ($p<0.05$) reduced in both 100 and 300 ppm treatment groups, compared to controls. Hemoglobin concentrations were increased significantly in both groups of propylene oxide-treated rats ($p<0.025$) compared to controls. Absolute and/or relative weights to the body weights were reported increased for lungs and adrenal glands and decreased for testes, in both treatment groups. The incidences for complex epithelial hyperplasia (0/76, 2/77, 11/78 in control, 100 and 300 ppm groups; significant only in 300 ppm group, $p<0.05$) and suppurative rhinitis in the nasal cavity (12/76, 21/77, 44/78 in control, 100 and 300 ppm groups; significant in both groups, $p<0.05$) were higher in treated groups compared to controls. The skeletal muscle atrophy in the absence of sciatic nerve neuropathology was noticed in 300 ppm group compared to controls.

The only noticeable neoplastic lesion was adrenal pheochromocytomas and the incidences were 8/78, 25/78, 22/80 in control, 100 and 300 ppm groups, respectively.

The LOAEL is determined as 100 ppm based on decreased survival, decreased body weights, increased hemoglobin, extra thoracic effects (nasal suppurative rhinitis) and systemic effects such as decreased body weight, increased hemoglobin, and organ weight changes. The NOAEL is not established.

The study is classified as **Acceptable/Non-Guideline**. The study was conducted using only one sex and with two doses only. No individual animal data or interim sacrifice data were provided. Also, limited clinical parameters were measured. The findings of this study are complicated by the outbreaks of Mycoplasma pneumonia infection which occurred at 8, 16, and 20 months of the study.

Mice – Inhalation

NTP (1985)

In a chronic carcinogenicity study (NTP, 1985), B6C3F1 mice (50/sex/treatment) were exposed to 99.9% pure propylene oxide at concentrations of 0, 200, and 400 ppm for 6 hours/day, 5 days/week for 103 weeks. Survival tended to be adversely affected in all treated groups (males: controls, 42/50; low-dose, 34/50; high dose, 29/50 and females: controls, 38/50; low-dose, 29/50; high dose, 10/50), but the decrease was statistically significant only for male and female mice in the 400 ppm group. Terminal body weights were 10% below control values for the high-dose female mice and 22% below control values for the high-dose male mice. Chronic inflammation of the nasal cavity was observed in 1/50, 13/50, and 38/50 of the male mice and in 0/50, 13/50, and 17/50 of the female mice exposed to 0, 200 ppm, and 400 ppm, respectively. Hyperplasia and metaplasia were also observed sporadically in mice exposed to 400 ppm propylene oxide. These lesions were most pronounced in the anterior portion of the nasal cavity and on the greater curvatures of the nasal maxillary turbinates. No consistent effect was observed in

the tracheobronchiolar or pulmonary region of the respiratory tract, or in skeletal muscle, bronchial lymph nodes, or central nervous system.

The LOAEL is determined as 200 ppm based on extra thoracic effects. The NOAEL is not established.

The combined incidences of hemangiomas and hemangiosarcomas in the nasal cavity were significantly elevated in the high dose group (males: controls, 0/50; low-dose, 0/50; high dose, 10/50, $p<0.001$ and females: controls, 0/50; low-dose, 0/50; high dose, 5/50, $p=0.03$). One squamous cell carcinoma and one papilloma were induced in nasal cavity of high dose males and adenocarcinomas in two high dose females, but these effects were not statistically significant. Doses tested were considered adequate based on the extra thoracic effects.

The study is classified as **Acceptable/Non-Guideline**.

Mutagenicity Studies

No mutagenicity studies were submitted to the Agency. However, there are several reports published in the literature. The following summary provides a brief over view of the studies available in the open literature.

Propylene oxide induced reverse mutations in *Salmonella typhimurium* TA100, TA1535 strains consistently in the absence of S9 activation (S9 was not included in most of the tests). Mutations were also induced in *E.coli* (WP2, WP2 *uvr*A), yeast (*Saccharamyces cerevisiae* and *Schizosaccharomyces pombe*), and fungi (*Neurospora crassa*). PPO caused sex-linked recessive lethal mutations in *Drosophila melanogaster*. Propylene oxide induced DNA single strand breaks in rat hepatocytes, and caused gene mutations in Chinese hamster ovary cells and mouse L5178Y cells, *in vitro*. Propylene oxide induced sister chromatid exchange in Chinese hamster ovary cells, rat liver cells and human lymphocytes and chromosomal aberrations in cultured human lymphocytes (as reviewed in IARC, 1994).

Chromosomal aberrations and sister chromatid exchange were induced in mouse bone-marrow cells after intraperitoneal injection. In one chronic study, no significant increase in sister chromatid exchange or chromosomal aberrations in peripheral blood lymphocytes was reported in cynomolgus monkeys exposed to 300 ppm PPO for 7h/day, 5days/week for two years. Micronuclei were not induced in bone-marrow cells of mice administered PPO by gavage but were induced in mice receiving PPO by intraperitoneal injection. Dominant lethal mutations were not induced in mice exposed to PPO orally or rats exposed to PPO by inhalation (as reviewed in IARC, 1994).

DNA adducts were reported *in vitro* when calf thymus DNA was incubated with propylene oxide. Increased DNA adducts (7-(2-hydroxy propyl)guanine) in DNA hydrolysates of various organs were formed in male mice 3h and 10h after intraperitoneal injection of ^{14}C-propylene oxide. In mice, rats and dogs, the levels of DNA adducts in

liver were greater after intraperitoneal or intravenous injection as compared to inhalation. Male Fischer rats exposed to tritiated propylene oxide via inhalation at 46 ppm for 2 hours had 17, 5.8, 3.3 adducts/10^6 base in nasal cavities, trachea and lungs, respectively. The persistence of the radiolabel was seen in trachea and lungs as compared to nasal cavities. The elimination of the radiolabel from nasal cavities appears to be biphasic with half-lives of 8h and 5.3 days (as reviewed in IARC, 1994).

Cancer Classification

Oral

PPO has been classified by the Agency as a B2 carcinogen (probable human carcinogen). The cancer slope factor for the oral route **is 0.15 (mg/kg/day)$^{-1}$** based on the Dunkelberg study which showed forestomach tumors in rats.

HED has derived an alternative cancer slope factor (Q*) of 0.00086 (mg/kg dose)$^{-1}$ using a concentration based approach. Use of an alternative approach is based on the fact that forestomach tumors in the rat treated by gavage may be considered a portal of entry response. By analogy to the RfC methodology which considers the concentration of test material to be the most important determinant of response in portal of entry tumors, PPO dosage may be expressed as a concentration. A detailed description of the derivation of the alternate slope factor is provided in Appendix 5.0. The Agency is considering mode of action data relevant to both oral and inhalation routes of exposure. If the proposed MOA is adopted, characterization of cancer risks is likely to change from a low-dose linearity approach to a threshold approach.

Inhalation

The cancer slope factor based on nasal tumors in mice for the inhalation route is **3.5x10^{-6} (µg/m^3)$^{-1}$** using RfC methodology and assuming linearity at low doses.

As previously noted, the registrant and consultants to the registrant have submitted a large amount of information supporting a threshold carcinogenic mode of action (MOA) of PPO. The Agency has done an initial review of the data supporting the proposed MOA and finds it highly plausible. The key points of the proposed MOA are described in Appendix 6.0

4.4.9.2 Propylene Chlorohydrin

Animal Studies

Rats – Oral

In a chronic carcinogenicity study (NTP, 1998), groups of 50 male and 50 female F344/N rats were administered drinking water containing 0, 150, 325, or 650 ppm PCH (75% 1-chloro-2-propanol and 25% 2-chloro-1-propanol; equivalent to average daily

doses of approximately 15, 30, or 65 mg/kg during the first several months of the study and 8, 17, or 34 mg/kg for the remainder of the 2-year study) for up to 105 weeks. Survival of all exposed groups was similar to that of the controls. Mean body weights of exposed rats were generally similar to those of the controls throughout most of the study. Water consumption by all exposed groups was similar to that by the controls. No treatment-related neoplasms or nonneoplastic lesions were observed in this study. **The NOAEL is determined as 65 mg/kg/day (HDT) and the LOAEL is not established.**

The study is classified as **Acceptable/Non-Guideline**. The NTP concluded that there was no evidence of carcinogenicity.

Mice – Oral

In a chronic carcinogenicity study (NTP, 1998), groups of 50 male and 50 female B6C3F mice were administered drinking water containing 0, 250, 500, or 1,000 ppm PCH (75% 1-chloro-2-propanol and 25% 2-chloro-1-propanol) (equivalent to average daily doses of approximately 45, 75, or 150 mg/kg to males and 60, 105, or 210 mg/kg to females during the first several months of the study and 25, 50, or 100 mg/kg for the remainder of the 2-year study) for up to 105 weeks. Survival of all exposed groups was similar to that of the controls. The mean body weights of all exposed mice were generally similar to those of the controls throughout the study. Water consumption by all exposed groups was similar to that by the controls. No treatment-related neoplasms or nonneoplastic lesions were observed in this study.

The NOAEL is determined as 210 mg/kg/day (HDT) and the LOAEL is not established.

The study is classified as **Acceptable/Non-Guideline**. No evidence of carcinogenicity was reported. The doses used in the study are inadequate. Consequently, no conclusions can be made as to the carcinogenicity of PCH.

Mutagenicity Studies

PCH (1-Chloro-2-propanol) is a demonstrated mutagen *in vitro*. It was weakly mutagenic in *Salmonella typhimurium* strain, TA100 in the presence of hamster or rat liver S9 activation enzymes and was positive, with and without S9, in TA1535. No mutagenic activity was detected in strains TA97, TA98, and TA1537, with or without S9. PCH was positive in *E.coli polA* assay for DNA damage (as reviewed in NTP, 1998).

In cytogenetic tests with Chinese hamster ovary cells, PCH induced high levels of sister chromatid exchanges and chromosomal aberrations in the presence and the absence of S9. Positive results were reported when PCH was tested in L5178Y mouse lymphoma cells with and without S9 (as reviewed in NTP, 1998).

PCH induced sex-linked recessive lethal mutations in germ cells of male *Drosophila melanogaster* when administered via injection; however, negative results were obtained

when males were administered PCH in feed. A subsequent germ cell reciprocal translocation test in D. melanogaster yielded negative results. Further, no induction of micronucleated erythrocytes was observed in peripheral blood of male and female mice administered PCH via drinking water for 14 weeks (as reviewed in NTP, 1998).

4.4.10 Summary of Endpoints Selected for Risk Assessment

Table 6: Summary of Toxicological Doses and Endpoints Use in Human Risk Assessments

Exposure Scenario	Dose Used in Risk Assessment, UF	Additional FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Propylene Oxide			
Acute Dietary (Females, 13-49 years)	NOAEL = #209 mg/kg/day (300 ppm) UF =1000 Acute RfD = 0.21 mg/kg/day	FQPA SF = 1X aPAD = acute RfD FQPA SF = 0.21mg/kg/day	Developmental Toxicity, Rats (MRID 41750801) Developmental LOAEL: #349 mg/kg/day (500 ppm) Increased litter incidence of an accessory 7th cervical rib
Acute Dietary (General populations)	No endpoint of concern is found suitable to assess risk for this population		
Chronic Dietary (All populations)	†BMDL10= 1.4 mg/kg/day UF = 1000 Chronic RfD = 0.001 mg/kg/day	FQPA SF = 1X cPAD = chronic RfD FQPA SF = 0.001 mg/kg/day	Chronic carcinogenicity study, Rats (Dunkelberg, 1982) †Systemic LOAEL = 2.6 mg/kg/day Increased combined incidence for hyperkeratosis, hyperplasia and papillomas.
Incidental Oral Exposure, Short-Term (1 - 30 days) Intermediate-Term (1 - 6 months)	No hand to mouth exposure is expected for children. Therefore, this scenario is not applicable.		
Dermal, Short-Term, Intermediate-Term, and Long-Term (> 6 months)	Propylene oxide is a severe skin irritant and therefore, care must be taken to avoid direct contact with the skin.		
Inhalation – acute (1-day) Residential	LOAEL = 500 ppm UF = 30	FQPA SF = 10x (UF_L) Residential MOE = 300	Developmental toxicity in rabbits (MRID 41874102). Increased resorptions, and/or increased incidence of minor skeletal abnormalities.
Inhalation – acute (1-day) Occupational	LOAEL = 500 ppm UF = 30 UF_L = 10	FQPA SF = 1x Occupational MOE = 300	
Inhalation Short-Term (1 - 30 days) and Intermediate-Term (1 - 6 months)	¶ NOAEL= 75 ppm (180 mg/m^3) Inhalation Absorption Rate = N/A	Residential MOE =N/A Occupational MOE = 30	Two-generation Reproduction Study in Rats (MRID 45292701) ¶ LOAEL = 225 ppm (540 mg/m3) Decreased body weight and body weight gain in both F0 and F1 males and females during premating periods

Table 6: Summary of Toxicological Doses and Endpoints Use in Human Risk Assessments			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**Additional FQPA SF* and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Inhalation Long-Term (> 6 months)	[§] $BMDL_{10}$ = 120 ppm (90 ppm HEC) Inhalation Absorption Rate = N/A	Residential MOE =N/A Occupational MOE = 30	Two year combined chronic carcinogenicity study, Rats (MRID 42039901) Increased incidences of basal cell hyperplasia, and nest-like infolds of the respiratory epithelium
Cancer (Oral)	Traditional cancer slope factor (oral- forestomach tumors in rats) = 0.15 (mg/kg/day)-1; Alternate cancer slope factor using concentration based approach = 0.000086 (mg/kg diet)-1 **		
Cancer (Inhalation)	Traditional cancer slope factor (inhalation - hemangioma and hemangiocarcinoma in mice) = 3.5x10-6 $(\mu g/m^3)^{-1}$ Note: if a proposed MOA is accepted, inhalation cancer risks will be likely equal to non-cancer risks.		
Propylene chlorohydrin			
Acute Dietary (Females, 13-49 years) and (General populations)	No endpoint of concern is found suitable to assess risk for these populations		
Chronic Dietary (All populations)	NOAEL= 30 mg/kg/day UF = 1000 Chronic RfD = 0.030 mg/kg/day	FQPA SF = 1X cPAD = chronic RfD / FQPA SF = 0.030 mg/kg/day	Two-Generation Reproduction Study, Rats (NTP, 1998) Offspring LOAEL: 65 mg/kg/day Decreased F1 male and female pup weights at PND 14 and 21.
Cancer (Oral and Inhalation)	Data is inadequate to determine the carcinogenic effects.		

UF = uncertainty factor, FQPA SF = 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

[#]Extrapolation from inhalation to oral route: mg/kg/day = (mg/L x absorption factor x respiratory volume in L/hr x duration of daily animal exposure x activity factor) /mean body weight in kg; The oral equivalent dose for 500 ppm =[(500x (58.08/24.4)x1000) mg/L x 1x 6.06 L/hr x 6 h/day x 1 / (0.124 kg)] = 349 mg/kg/day; similarly 300 ppm corresponds to 209 mg/kg/day. In the equation the default value of 1 is used for both absorption factor and animal activity factor.

[†] Study gavage doses of 15 and 60 mg/kg/day administered twice a week (corresponding average total doses are 2714 and 10798 mg/kg bw) are adjusted for experimental duration of 150 weeks to 2.58 and 10.28 mg/kg/day, respectively. These adjusted doses were used for bench mark dose modeling ($BMDL_{10}$; Log Logistic Model had a good fit of the data).

[£]Study LOAEL of 500 ppm needs no adjustment to a human equivalent dose for residential bystander scenario, since the study duration of 7 hrs is assumed to be equivalent to the human exposure interval.

[¶]Study NOAEL and LOAEL are adjusted to human equivalent doses for occupational scenario only. e.g., animal NOAEL of 100 ppm (6h/day, 5d/week) is adjusted to human NOAEL of 75 ppm (8 h/day, 5d/week), assuming the regional gas dose ratio (RGDR) is similar between animals and humans for systemic effects (100 ppm x 6h/8h =75 ppm);

[§] Study POD is adjusted to human equivalent dose for occupational scenario only; ie., animal $BMDL_{10}$ of 120 ppm is adjusted to human NOAEL of 90 ppm, by correcting for differences in study (6 h/day, 5 d/week) and exposure (8 h/day, 5d/week) durations. (120 ppm x 6h/8h = 90 ppm).

* Refer to Section 4.3

** Slope factor used for dietary exposure assessment

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 the reaction product of propylene oxide, PCH, there was increased percentage of abnormal sperm in the subchronic and reproduction toxicity studies. When additional appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, PCH may be subjected to further screening and/or testing to better characterize effects related to endocrine disruption.

5.0 INCIDENT REPORT

Scientific literature reports a few cases of contact dermatitis from exposure in workplace settings, although these occurrences were in laboratories, not sterilization/fumigation facilities or food processing facilities. Information from the Poison Control Center showed evidence of throat and skin irritation. One reported case in California described an almond fumigator experiencing lightheadedness, coughing, and skin sores from changing cylinders.

6.0 DIETARY EXPOSURE/RISK PATHWAY

6.1 Residue Profile

Residue data are adequate to support the fumigant uses on spices and herbs (as defined by the Agency’s crop groups), cocoa bean, and nutmeats (except peanut). The existing 300 ppm PPO tolerances for “spices processed” should be clearly defined in regard to what spice/herb commodities are fumigated. The proposed PPO tolerances in/on spices are based on residue data collected 2 days after treatment. A 1500 ppm tolerance should be established for residues of PCHs in/on spices and herbs (dried) (except basil) based on residues at 2 day sampling. A 6000 ppm PCH tolerance should be established for basil. A 6000 ppm PCH tolerance should be established for dried onion and dried garlic powders. Magnitude of the residue studies found minimal PBHs levels in cocoa powder, nutmeats (almond, pecan, walnut), spices (black pepper, chili powder, celery seed), dried

basil, dried onion powder, and dried garlic powder. Therefore, HED suggests that a tolerance be established based on PCHs residue levels which should cover any expected PBHs residues.

The existing 300 ppm PPO tolerance for nutmeats is adequate based on existing and newly submitted residue data. New data on anticipated residues of PPO in nutmeats has been submitted to and evaluated by HED for this revised assessment. According to the registrant and industry representatives, actual application rates for nutmeats are significantly lower than the maximum allowable label rate of 2.4 oz PPO/ft^3. The new residue data for nutmeats reflect actual maximum application rates (0.5-0.7 oz PPO/ft^3), as well as actual fumigation parameters (e.g., temperature, duration) which also differ from those provided in the current label. Tolerances in/on nutmeats for residues of PCHs are proposed at a 10 ppm level.

The tolerance levels for PPO and PCHs in/on cocoa bean should be established at 200 ppm and 20 ppm, respectively. The existing 300 ppm tolerance for vegetable gums should be revoked based on the registrant's submission of request for voluntary cancellation of PPO use on edible gums pursuant to FIFRA Section 6(f). PPO tolerances should be established for fig, prune, and raisin at 3 ppm, 2 ppm, and 1 ppm, respectively. PCHs tolerances should be established for fig, prune, and raisin at 3 ppm, 2 ppm, and 4 ppm, respectively.

Presently in 40 CFR §180.491(a)(2), application directions are listed including time and temperature conditions. This section (a)(2) should be removed. All treatment parameters should be on the label only. The Registration Division should request revised labels from the registrant of PPO formulations to reflect the proposed lower maximum rate tree nuts as well as any other proposed changes to fumigation parameters. All labels must be amended to match the conditions of the study.

The PPO tolerance for nutmeats should remain at 300 ppm until the maximum label rate is lowered from 2.4 oz PPO/ft^3 to 0.5-0.7 oz PPO/ft^3 for treatment of tree nuts. At such time, it may be possible to decrease the existing tolerance. However, since the newly submitted data are only preliminary, HED will require additional adequate confirmatory residue data (with adequate sampling) to support any change to the existing 300 ppm tolerance. Any study submitted must be run under GLP conditions. Residue chemistry requirements are provided in more detail in the residue chemistry assessments. (J. Stokes, D316571, 9/22/05; D316573, 6/22/06)

Table 7 provides the summary of the tolerances assessments or reassessments for PPO and the PCH.

Table 7. Tolerance Reassessment for Propylene Oxide and Propylene Chlorohydrin				
Tolerances Established Under 40 CFR §180.491				
	Propylene Oxide		Propylene Chlorohydrin	
Commodity	Current Tolerance (ppm)	Reassessed Tolerance (ppm)	Current Tolerance (ppm)	Reassessed Tolerance (ppm)
Basil	--	--	--	6000
Spices/herbs	300	300	--	1500
Dried onion[1]	--	--	--	
Dried garlic[1]	--	--	--	
Processed nutmeats	300	300	--	10
Figs	--	3	--	3
Prunes	--	2	--	2
Raisins	--	1	--	4
Gum, edible	300	*Revoke*	--	--
Cacoa bean	300	200	--	20

[1] Tolerance based on data given for basil

6.2 Acute and Chronic Dietary Exposure and Risk

Refined acute and chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID™, Version 2.03), and the Lifeline Model Version 3.0 which use food consumption data from the USDA's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. The dietary exposure and risk assessment for cancer has been revised to incorporate new residue and percent crop sterilized data and to exclude edible gums as a fumigated commodity. Only the dietary cancer assessment has been revised for this analysis because only that scenario produced risk estimates above EPA's level of concern based previous dietary assessments. Other acute and chronic dietary exposure assessments resulted in risks well below HED's level of concern and incorporation of new data would result in risks $\leq$ previously estimated risks.

Residue data obtained from studies on propylene oxide sterilization of nutmeats, cocoa powder, herbs and spices, figs, prunes and raisins were used for the acute and chronic assessments. Residue distribution data from PPO sterilization studies were used for the acute dietary analysis of propylene oxide. Tolerance level residues were used for the chronic dietary analysis of propylene chlorohydrin. Average residues from the sterilization study data were used for the chronic and cancer assessments of propylene oxide. Percent crop treated data provided by BEAD were used for the acute and chronic/cancer analyses. EPA concluded that a drinking water exposure assessment was not necessary because based on use patterns and physical-chemical properties of PPO, none of the uses of PPO are expected to result in significant exposure from drinking water.

An acute dietary assessment was conducted for PPO only. A refined probabilistic acute dietary exposure assessment was conducted for all supported propylene oxide food uses

for the population subgroup females 13-49. This assessment concludes that for all supported commodities, the acute dietary exposure estimates for propylene oxide are below HED's level of concern. The DEEM and LifeLine acute dietary exposure estimates for a single treatment for females 13-49, the only population subgroup assessed for acute dietary exposure, were 6% and 7 % of the aPAD respectively.

Refined chronic dietary exposure assessments were conducted for all supported propylene 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 propylene oxide are below HED's level of concern. The DEEM and Lifeline model chronic dietary exposure estimate for the highest exposed population subgroup, children 1-2 years of age were 16% and 13% of the cPAD respectively. The results of the DEEM and Lifeline acute and chronic non cancer dietary exposure analyses and risk estimates for PPO are reported in Table 8.

Table 8. Acute and Chronic Dietary Exposure and Risk Estimates for Propylene oxide

Population Subgroup	PAD, mg/kg/day	DEEM-FCID		Lifeline	
		Exposure, mg/kg/day	% PAD	Exposure, mg/kg/day	%PAD
Acute Dietary Estimates (99.9th Percentile of Exposure)					
Females 13-49 years old	0.21	0.0131	6	0.0141	7
Chronic Dietary Estimates					
General U.S. Population	0.0014	0.0001	6	0.0001	7
All infants (< 1 yr)	0.0014	0.0001	3	0.0001	2
Children 1-2 yrs	**0.0014**	**0.0002**	**16**	**0.0002**	**13**
Children 3-5 yrs	0.0014	0.0002	15	0.0002	14
Children 6-12 yrs	0.0014	0.0001	10	0.0001	10
Youth 13-19 yrs	0.0014	0.0001	5	0.0001	6
Adults 20-49 yrs	0.0014	0.0001	5	0.0001	6
Adults 50+ yrs	0.0014	0.0001	6	0.0001	7
Females 13-49 yrs	0.0014	0.0001	5	0.0001	7

The cancer assessment for PPO has been revised to incorporate new residue and percent crop treated data for nutmeats and to omit guar (edible gums) as a fumigated commodity. Revisions to the cancer analysis resulted in a DEEM chronic exposure estimate for the general population of 0.0001 mg/kg/day. Cancer risks for dietary exposure to PPO were estimated using this revised chronic exposure estimate and the alternative cancer slope factor derived using a PBPK or concentration based approach. The revised chronic dietary exposure assessments conducted for all supported propylene oxide food uses for the general U.S. population concludes that the cancer dietary risk estimates for propylene oxide are below HED's level of concern. Based on the revised assessment, excess lifetime risk estimates for the U.S. general population are $4x10^{-7}$. The results of the cancer analysis conducted using the alternative cancer slope factor are provided in Table 9.

Conclusions of the cancer dietary risk assessment only are based on residue data supplied by Aberco, Inc. and industry representatives that reflect typical application rates. Although the typical application rates are lower than the agreed-upon maximum application rate of 2.0 oz ai/ft3, the conclusion of the dietary risk assessment will not change if the maximum rate for nuts is 2.0 oz ai/ft3. In other words, cancer risk estimates would not exceed EPA's level of concern. In addition, the registrant has proposed reducing the maximum application rate from 2.4 to 2.0 oz ai/ft3 for herbs, spices, dried onion, dried garlic, cocoa beans, and cocoa powder.

Table 9. Cancer Dietary Exposure and Risk Estimates for Propylene oxide

Population Group	Slope Factor (mg/kg diet)	DEEM-FCID Exposure mg/kg/day	mg PPO/kg Diet [1]	Estimated Cancer Risk [2]
General U.S. Population	0.000086	0.0001	0.0047	$4x10^{-7}$

[1] mg PPO/kg Diet = 0.0001 mg/kg/day chronic dietary exposure x 70 kg bw ÷ 1.5 avg kg food consumed/day*
[2] Estimated Cancer Risk = slope factor 0.000086 $(mg/kg\ diet)^{-1}$ x 0.0047 mg PPO/kg diet
* American Industrial Health Council (AIHC), 1994 Exposure Factors Sourcebook Washington DC., AIHC

An acute RfD was not established for propylene chlorohydrin because an endpoint attributable to a single (or few) day exposure was not identified from the available database. The results of both the DEEM and Lifeline chronic dietary exposure analyses for propylene chlorohydrin are reported in the Table 10. These assessments for PCH 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 25% and 29% of the cPAD respectively.

Table 10. Result of Chronic Dietary Exposure and Risk Estimates for Propylene chlorohydrin

Population Subgroup	cPAD, mg/kg/day	DEEM-FCID		Lifeline	
		Exposure, mg/kg/day	% PAD	Exposure, mg/kg/day	%PAD
U.S. Population	0.03	0.0018	6	0.0034	11
All infants (< 1 yr)	0.03	0.0017	6	0.0027	9
Children 1-2 yrs	**0.03**	**0.0074**	**25**	**0.0087**	**29**
Children 3-5 yrs	0.03	0.0062	21	0.0080	27
Children 6-12 yrs	0.03	0.0037	12	0.0054	18
Youth 13-19 yrs	0.03	0.0015	5	0.0035	11
Adults 20-49 yrs	0.03	0.0010	4	0.0030	10
Adults 50+ yrs	0.03	0.0011	4	0.0030	10
Females 13-49 yrs	0.03	0.0011	4	0.0036	12

7.0 RESIDENTIAL EXPOSURE/RISK PATHWAY

There are no residential uses for PPO. However, exposure to PPO is expected to occur to the subjects residing near the PPO fumigation facilities. PPO emissions monitoring data

necessary to quantitatively estimate exposures and risks from sterilization/fumigation facilities are unavailable. Therefore, a qualitative assessment was conducted comparing the risks associated with emissions from the use of a similar chemical, ethylene oxide (ETO), in similar commercial sterilization/fumigation scenarios. Additionally, a quantitative assessment of residential bystander risk associated with emissions from outdoor commodity fumigation in stationary commercial sterilization chambers which have no emission controls and in temporary structures with the recently registered product Propoxide 892.

7.1 Emissions from Commercial Sterilization Chambers with Emission Controls

EPA's Office of Air Quality Planning and Standards (OAQPS) has recently conducted a residual risk assessment for fugitive and point source emissions of ETO in the commercial sterilization source category (Mark Morris, OAR, 2/25/05). OAR's residential risk assessment estimated cancer as well as short and long term non-cancer risk to the general population. The results of OAR's assessment were included in HED's ETO risk assessment (D316794, May 18, 2005). Based on the results of its residential exposure assessment, OAR concluded that potential cancer and non-cancer (acute and chronic) risk indicate that no further regulatory action is necessary at this time.

Because of the similarity in chemical characteristics (e.g., vapor pressure) and usage scenarios, the results and conclusions from the ETO assessment can be compared, qualitatively, with PPO use in commercial sterilization facilities that have emission controls comparable to those required for ETO. To further refine or attempt a quantitative assessment specific for PPO, use of similar air modeling techniques and emissions monitoring data would be required.

Using various data sources, including EPA's Toxic Release Inventory (TRI) and the National Emissions Inventory (NEI) point source database, OAR estimated that the facility with the highest annual ETO usage (500 tons) would have total annual emissions of 10 tons (20,000 lbs) and these emissions are further corroborated by a 2003 TRI report. Using modeling techniques, OAR concluded that no source poses a lifetime cancer risk greater than 100 in a million and that chronic non-cancer effects are unlikely to occur because no source emitted ETO in quantities that resulted in exposures that approached the inhalation reference concentration of 30 $\mu g/m^3$.

A qualitative comparison with the results from the residual risk assessment for ETO concludes that the residual cancer risks for PPO emissions would be significantly less than those reported by OAR for ETO due to the difference in the chemicals' risk factors and the less annual usage for PPO compared to ETO. Assuming the source with the highest emissions, 20,000 lbs, OAR found no ETO source posing a cancer risk greater than 100 in a million with a unit risk estimate (Q_1* or cancer slope factor) of 0.16 ppm^{-1}). The existing cancer slope factor for PPO (Q_1* = 0.0084 ppm^{-1}) is approximately 20-fold less compared to that for ETO. In addition to the reduction in cancer slope factors, the annual usage for PPO is found approximately 14 times less compared to ETO usage (4000 tons versus 285 tons) (J. Faulkner, EPA/OPP/BEAD Quantitative Usage Analysis).

Based on the reduction in usage and cancer slope factors, the cancer risk for PPO exposure is significantly less than ETO.

For acute risk, OAR conducted a screening assessment of potential risk from short-term emissions from ethylene oxide commercial sterilization sources using three acute endpoints, the Acute Exposure Guideline Level-2 (AEGL) of 81 mg/m^3(45 ppm), the Emergency Response Planning Guideline (ERPG) of of 90 mg/m^3 (50 ppm), and the OSHA Immediately Dangerous to Life and Health (IDLH/10) Level of 140 mg/m^3 (78 ppm). OAR concluded that results of the acute exposure assessment indicate that estimated acute exposures are not of concern. The level of concern (daily TWA) for acute risks from both ETO and PPO is 1.7 ppm. Therefore, risks from PPO for the acute exposure scenario would be similar to those for ETO. For non cancer risk, OAQPS used a Reference Exposure Level (REL) developed by California EPA of 30 µg/m^3 or 0.02 ppm and determined that potential for non cancer risks are also not of concern. Since the chronic reference concentration for PPO is higher than the ETO RfC and the annual usage is less for PPO, chronic non-cancer risks are not expected to be of concern.

7.2 Emissions from Stationary Sources with No Emission Controls and Outdoor Commodity Fumigation with Propoxide 892

This assessment addresses residential bystander risk from commodity fumigations conducted in stationary fumigation chambers that do not have emission controls and from commodity fumigation scenarios outlined in the registered product Propoxide 892 (EPA Reg. No. 47870-3). (M. Crowley, D316545, 7/31/06) Fumigation with Propoxide 892 differs from fumigation with other PPO products in that the Propoxide 892 label allows for fumigation of commodities in a variety of outdoor containment structures. These structures include trailers, air/sea containers, railcars, tents, and tarps. The use pattern for Propoxide 892 closely follows that of methyl bromide for which a quantitative commodity fumigation bystander risk assessment has been conducted (J. Dawson, D304623, 3/10/06). Therefore, due to the similarities in use pattern, the bystander assessment for propylene oxide fumigation is generally consistent with the methodologies used to assess residential bystander risk for methyl bromide – although certain aspects and assumptions differ.

7.2.1 Modeling Methodology

The PERFUM (Probabilistic Exposure and Risk model for FUMigants PERFUM V 2.1.2; http://www.sciences.com/perfum/index.html) was used to assess potential risk to residential bystanders from two additional fumigation scenarios; 1) commodity fumigations in commercial sterilization chambers that do not have emission controls and 2) commodity fumigations with Propoxide 892. The PERFUM model was used for this assessment because HED believes it provides the most refined, scientifically defensible approach for calculating and characterizing risks. PERFUM uses as its core processor the proven technology of ISCST3 (Industrial Source Complex: Short-Term Model (http://www.epa.gov/scram001/). It incorporates actual weather data, and links flux profiles to the appropriate time of day when calculating results.

7.2.2 Exposure Scenarios

The scenarios modeled are assumed to represent typical PPO use scenarios and are similar to those modeled for methyl bromide. The exposure scenario evaluated for this assessment were developed based on a set of critical factors including the nature of the buildings, chambers, or structures being treated; application rates and treatment durations; and emission rates and factors. Based on the available information regarding likely use patterns for Propoxide 892, the most conservative scenario in which no stack is assumed (e.g., opening doors to railcars for aeration) was modeled for this assessment. This scenario represents leakage from a structure during treatment as it is assumed for certain structures (i.e., railcars or air/sea containers) that fugitive emissions are possible. Based on likely use patterns, PPO fumigation conducted in non-stationary sources (e.g., temporary structures such as railcars, tents, tarps) is expected to be infrequent and intermittent. Therefore, long term exposures to bystanders from this scenario are not expected. Emission controls are not required for sterilization conducted with PPO. Therefore, HED also evaluated residual risk to bystanders from fumigations conducted in commercial sterilization chambers without emission controls. Only acute exposures were assessed for this scenario because protecting for acute effects at the acute daily TWA level of concern of 1.7 ppm will also protect against effects from chronic exposure.

7.2.3 PERFUM Model Inputs

In order to assess the potential levels of exposures that could be associated with the exposure scenarios described above, HED has developed a series of input parameters for the PERFUM modeling that is meant to bracket the range of possible exposures associated with PPO treatment of commodities under various common use practices. Again, these conditions are generally modeled after the MeBr commodity fumigation assessment. The factors which have been used include:

- **Treatment Concentration**
  - 2.8 lb lb ai/1000 ft3 (0.0448 oz/ft3) (Propoxide 892)
  - 31.25 lb ai/1000 ft3 (0.5 oz/ft3)
  - 43.75 lb ai/1000 ft3 (0.7 oz/ft3)
  - 75 lb ai/1000 ft^3 (1.2 oz/ft3)
  - 150 lb ai/1000 ft^3 (2.4 oz/ft3)
- **Retention and Emission Rates (expressed as % of treatment concentrations)**
  - During Treatment (Scenario 1): 1, 5, 10, 25, and 50% of treatment concentration; Aeration (Scenarios 2-3): 50, 75, 90, 95, 99, and 100% of treatment concentration is released and varies based on how airtight the chamber is and/or how much is absorbed.
- **Structure Volume**
  - Small scale: 1000, 2000, 5000 cubic feet;
- **Structure Height**
  - Small scale: 1000 cu. ft = 10 feet tall, 2000 cu. ft. = 12 feet tall, 5000 cu. ft. = 17 feet tall;

- **Stack and Release Heights**
  - All fixed stack heights = 10 feet stack affixed to chambers or structures [Note: absolute release height then varies when added with specific building height]
- **Active Air Exchange Rates**
  - 4 air exchanges/hour representing full ventilation or exit velocity [Note: this is based on the Propoxide 892 label whose aeration instructions include 4 chamber volumes of fresh air and an aeration time of one hour for atmospheric and vacuum fumigation.]
  - 2 air exchanges/hour representing 50% of full exit velocity;
  - 0.2 air exchanges/hour representing 5% of full exit velocity.
- **Stack Diameters**
  - PERFUM can only accommodate a single stack so the diameters are varied to achieve the proper cross sectional ventilation areas for each combination of chamber/structure size and air exchange value. The results for larger chambers or high concentration treatments, therefore, may be based on very large diameter stacks which would not occur in reality to achieve proper ventilation (i.e., 0.2 m to 5 m). Under actual conditions, multiple stacks would be used in order to achieve target air exchange rates. This approach is not expected to be a negative bias in the results. In fact, this approach is likely a conservative method because all emitted PPO is forced out at one location making the predicted distances higher.
- **Hazard Concerns**
  - Threshold Level of Concern: 1.7 ppm.
- **Treatment Frequency and Emission Profiles**
  - A number of frequency and emission profiles were considered in order to simulate the practices associated with PPO commodity use. Only those emission profiles that are assumed to represent current PPO use in commodity fumigations are presented below. In most applications the active application duration is 16–48 hours followed by aeration on the order of 1 hour. Based on this information, HED considered 2 frequency and emission profiles in the assessment:
    -- 1-hour single emission: based on a single application and short-lived emission period such as 15 minutes, actual modeling of a 15 minute emission profile was not done since PERFUM accepts emission terms in 1 hour intervals and the concentration that it is compared to is 8 hours so the 1-hour time-frame is a better comparison;
    -- 4-hour single emission: based on a single application and short-lived emission period such as 15 minutes as the 1-hour emission described above but 3 additional hours of no emissions were also included (i.e., a 4-hour time-weighted average) in order to develop a better comparison to the human equivalent concentration.

7.2.4 Residential Bystander Exposure and Risk Estimates

There is potential for exposure and risk to propylene oxide (PPO) for non-occupational/residential bystanders as a result of both commodity fumigations conducted in non-emission controlled commercial sterilization chambers and in those conducted

with the registered product Propoxide 892. The PERFUM results are generated in the form of buffer distances. The range of buffer zones corresponds to a range of assumptions regarding key input parameters including, structure size, emission rate, and ventilation rate. The "Maximum Buffer" distribution is based on the maximum distance needed to reach the threshold level of concern for each of 1825 days (i.e., a distribution of the farthest single points on the irregular line as seen in Figure 1 for each of 1825 days). The "Whole Field Buffer" distribution is also based on values from each day, except the distances on which the distribution is based includes those on each spoke where the threshold concentration or level of concern is achieved for each day. For both types of buffer distances, results from selected percentiles from the distribution have been reported. PERFUM results for aeration of structures (i.e., chamber, tarp, or railcar) using Propoxide 892 are presented in Table 11. PERFUM results for commercial sterilization chambers with no emission controls are presented in Table 12. Buffer distances (in meters) are presented from the 90th percentile to the 99.9th percentile and are based on 95% and 75% of the application rate emitted upon aeration.

Table 11. Propoxide 892 - PERFUM Buffer Distances (meters) 4 hour Exposure Duration, 2.8 lb/1000 cubic feet Application Rate

Aeration Type	Percentile	1000 Cubic Feet		2000 Cubic Feet		5000 Cubic Feet	
		95% Mass Release	75% Mass Release	95% Mass Release	75% Mass Release	95% Mass Release	75% Mass Release
During Aeration							
Maximum Buffer Distances							
Minimum Stack (4 xch/hr)	90	10	0	35	30	40	30
	95	15	10	40	30	45	35
	99	20	15	50	40	50	40
	99.9	20	15	55	40	55	45
No Stack	90	40	30	75	60	150	130
	95	45	35	85	70	170	145
	99	55	40	100	80	185	160
	99.9	60	45	105	85	195	165
Whole Field Buffer Distances							
Minimum Stack (4 xch/hr)	90	0	0	0	0	0	0
	95	0	0	0	0	0	0
	99	0	0	0	0	20	0
	99.9	15	10	35	30	40	35
No Stack	90	0	0	0	0	0	0
	95	0	0	0	0	5	0
	99	10	0	25	20	55	45
	99.9	40	30	80	65	160	135
During Treatment							
Maximum Buffer Distances							
No Stack	95	0	0	0	0	0	0
	99	0	0	0	0	0	0
	99.9	0	0	0	0	0	0
Whole Field Buffer Distances							
No Stack	95	0	0	0	0	0	0
	99	0	0	0	0	0	0
	99.9	0	0	0	0	0	0

Table 12. Commercial Sterilization w/o Emission Control - PERFUM Buffer Distances (meters) 4 hour Exposure Duration, 5000 ft^3 Treated Volume			
Aeration Type	**Percentile**	**95% Mass Release**	**75% Mass Release**
Application Rate 150 lb/1000 ft^3			
Maximum Buffer Distances			
Minimum Stack (4 xch/hr)	90	1440	1410
	95	1440	1440
	99	1440	1440
	99.9	1440	1440
Whole Field Buffer Distances			
Minimum Stack (4 xch/hr)	90	0	0
	95	45	40
	99	545	470
	99.9	1440	1440
Application Rate 75 lb/1000 ft^3			
Maximum Buffer Distances			
Minimum Stack (4 xch/hr)	90	1015	180
	95	1155	965
	99	1330	1120
	99.9	1370	1150
Whole Field Buffer Distances			
Minimum Stack (4 xch/hr)	90	0	0
	95	35	30
	99	350	300
	99.9	1085	915
Application Rate 43.75 lb/1000 ft^3			
Maximum Buffer Distances			
Minimum Stack(4 xch/hr)	90	680	560
	95	775	645
	99	870	735
	99.9	920	770
Whole Field Buffer Distances			
Minimum Stack (4 xch/hr)	90	0	0
	95	25	25
	99	245	205
	99.9	720	600
Application Rate 31.25 lb/1000 ft^3			
Maximum Buffer Distances			
Minimum Stack (4 xch/hr)	90	515	425
	95	590	490
	99	685	565
	99.9	710	590
Whole Field Buffer Distances			
Minimum Stack (4 xch/hr)	90	0	0
	95	25	20
	99	195	165
	99.9	555	460

8.0 AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION

As per FQPA, when there are potential residential exposures to the pesticide, aggregate risk assessment must consider exposures from residues in food commodities and drinking water as well as exposures arising from non-dietary sources (e.g., incidental oral, dermal and inhalation routes). The residue from drinking water is expected to be negligible since PPO is used only indoors. PPO has no direct residential uses; however residential

bystanders may be exposed to emissions from fumigation facilities or structures. Dietary and bystander exposure cannot be combined for this assessment, however, because the endpoints selected for these exposures are not based on a common effect. Therefore, risk from dietary and inhalation routes are not aggregated for this assessment.

9.0 CUMULATIVE RISK CHARACTERIZATION/ASSESSMENT

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 propylene oxide and any other substances and propylene oxide does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that propylene 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 Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

10.0 OCCUPATIONAL EXPOSURE/RISK

Occupational exposures and risks are assessed for propylene oxide and propylene chlorohydrin (M. Crowley, D316545, 7/31/06). PPO exposures occur only after PPO application and thus are considered post application exposures. The "post application" activities can be broken down into "sterilization activities", including loading/unloading the sterilization chambers (opening chamber and chamber re-entry) and replacing/installing drums, and "post-sterilization activities", including transporting boxes/drums/bags and bagging/containerizing treated commodities. A target level of concern or margin of exposure (MOE) of 30 is considered adequate for short-, intermediate- and long-term occupational inhalation exposure to PPO, the primary exposure route of concern. OPP's goal is to reduce occupational exposures to reflect cancer risks no greater than $1x10^{-6}$. If the proposed cancer MOA is accepted by the Agency, inhalation exposure to PPO will not be regulated using a q* approach. Rather, a MOE analysis will be conducted. If the Agency concurs with the proposed MOA, then cancer and long-term non-cancer risks would be regulated at the same level, since the long-term non-cancer endpoint is based on nasal lesions that are considered precursors to the development of tumors.

10.1 Exposure Scenarios

HED anticipates the following activities to result in potential worker exposure to PPO.

- Inhalation exposure to PPO during sterilization activities.
- Dermal exposure to PPO during sterilization activities.
- Inhalation exposure to off-gassed PPO from treated commodities during post-sterilization activities.

- Dermal exposure to PPO residues during post-sterilization activities.

10.2 Established Exposure Levels

The regulatory levels or recommendations for exposure to propylene oxide from various organizations and the precautionary exposure limit levels mentioned in the EPA label are used for the estimation of exposure levels.

10.2.1 Regulatory/Recommended Exposure Levels

Table 13 lists various organizations and their regulatory levels or recommendations for exposure to propylene oxide.

Table 13: Propylene Oxide Regulatory Levels

Organization	Concentration (ppm)	Nomenclature
Occupational Safety and Health Administration (OSHA)	100	PEL[1]
National Institute for Occupational Safety and Health (NIOSH)	LFC[2]	REL[3]
American Conference of Governmental Industrial Hygienists (ACGIH)	2	TLV-TWA[4]
California Division of Occupational Safety and Health (Cal/OSHA)	20[5]	PEL

[1] Permissible Exposure Limit (PEL): The employer shall ensure that no employee is exposed to an airborne concentration of PPO in excess of the PEL as an 8-hour time-weighted average (8-hour TWA). 100 ppm PEL from 29 CFR 1910.1000 Z-1 Table.
[2] LFC = Lowest Feasible Concentration. NIOSH policy recommends potential occupational carcinogens without a quantitative REL to be at the lowest feasible concentrations. (Appendix A to NIOSH Pocket Guide to Chemical Hazards).
[3] Recommended Exposure Limit (REL): NIOSH-recommended exposure limit for an 8- or 10-h TWA and/or ceiling.
[4] Threshold Limit Value – Time Weighted Average (TLV-TWA): Expressed as a TWA for a conventional 8-hour workday and a 40-hour workweek, to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. This is a recommended level and is not enforceable. 2 ppm TLV adopted in 2001.
[5] From Table AC-1 of California Code of Regulations Title 8, Chapter 4, Subchapter 7, Group 16, Article 107, Section 5155 Airborne Contaminants. Note: The Cal/OSHA Standards Board had proposed lowering this level to 1.0 ppm, however the proposal was not adopted due to further review requirements under Executive Order S-2-03 (Cal/OSHA, 2004).

10.2.2 Label Requirements

The current end-use label (EPA Reg. No. 47870-1) requires the following regarding exposure and worker protection.

- Where there is potential for dermal contact, full body personal protective equipment (PPE) must be worn. This includes solvent-proof gloves, clothing, hat, apron, and boots. Vapor-proof goggles are also required.
- Where PPO air concentrations are 20 ppm or greater a full face self-contained breathing apparatus (SCBA) is required. This is for all work areas including the chambers and off-gassing holding areas.
- Areas where PPO air concentrations are 20 ppm or greater must be placarded to indicate the presence of PPO.

10.3 Exposure Monitoring Data

PPO inhalation worker exposure data reflecting outdoor fumigation activities was submitted during Phase III of the RED process. The majority of monitoring data, measured using personal badges, was submitted as daily time weighted averages (TWAs), although some "task-specific" data for unloading sterilization chambers was submitted as well. For risk assessment purposes, task-specific data was adjusted to represent a daily average.

The Almond Board of California and the California Walnut Commission submitted exposure data for workers exposed to PPO while fumigating almonds and walnuts. PPO concentrations in air (all reported as time-weighted averages) were measured using Propylene Oxide Vapor Monitor badges analyzed by gas chromatography with flame ionization detection (GC FID). The reference analysis method was NIOSH Method 1612. The analysis laboratory indicated the limit of quantification is 0.1 ppm for an 8-hour sample. Most of the data collected represent entire workdays (i.e., approximately 8 hours), although some samples document exposure during specific activities of shorter duration (i.e., chamber unloading and transportation of commodity to degassing room). Additional "area" concentrations were submitted for non-work areas and degassing rooms. Newly submitted worker exposure monitoring data is summarized in Table 13.

Table 14: Combined Almond and Walnut Fumigation Worker Exposure Data Summary

Data Source	Activity	# Samples	Avg Hrs Sampled	TWA (ppm)			
				Mean	Median	Geometric Mean	Max
All Data	Non-Specific (Daily TWA)	19	8.1	0.94	0.55	0.58	6.6
	Combined Non-Specific & Adjusted Chamber Unloading TWA	22	8.1	1.2	0.64	0.71	6.6

It is important to reiterate that all of the newly submitted data represent outdoor fumigations i.e., situations in which natural ventilation is provided by outdoor air. It is reasonable to assume that the daily exposure profile indicated by the newly submitted data are representative of all outdoor sterilization/fumigation operations i.e., that for outdoor fumigations, daily average exposure comprises sporadic, peak PPO exposures during certain sterilization/fumigation activities and negligible exposure for the remainder of the day.

However, the data cannot be assumed to be representative of fumigations conducted in indoor commercial sterilization facilities. An exposure survey performed for fumigations done using chambers housed inside large warehouses which are not open to the outside air could potentially exhibit a different exposure profile. It is reasonable to assume that, for indoor facilities, shortened periods of heightened PPO exposure would be similar to the outdoor facilities, however background PPO concentrations and exposure could be different due to differences in ventilation. Therefore, this data set and any risk estimates and recommendations should be considered only relevant to outdoor fumigation facilities.

10.4 Exposure Assumptions

It is assumed that there is potential for PPO exposure for short- (1-30 days)/intermediate- (1-6 months)/ and long- (> 6 months) term durations. For cancer risk calculations, exposure frequency (the amount of days per year workers are exposed to propylene oxide) is assumed to be 240 days per year and occupational exposure to be 35 years over a 70 year lifespan – both standard HED assumptions.

10.5 Exposure and Risk Estimates

10.5.1 Inhalation Exposure and Risk

The cancer and non-cancer risks from exposure to PPO were determined based on currently recommended or regulatory concentration levels. Concentrations at which risks are not of concern for cancer and non-cancer effects are provided in Table 14. Non-cancer and cancer risk estimates at regulatory and or recommended levels established by various organizations and regulatory agencies are provided in Table 15. HED also estimated risks based on recently submitted PPO inhalation worker exposure monitoring data. Task-specific monitoring data was adjusted to represent a daily average for risk assessment purposes. Results of that assessment are provided in Table 16. The short- (1-30 days), intermediate- (1-6 months), and long-term (greater than 6 months) inhalation non-cancer and cancer risks from the use of PPO in commodity sterilization/fumigation are of concern at 20 ppm the exposure limit value established by Cal/OSHA and included in current EPA PPO label. The acute, short-, intermediate- and long-term non-cancer risks are not of concern at the ACGIH recommended worker exposure concentration of 2 ppm. As previously noted, EPA has concluded that a proposed MOA is highly plausible, and EPA will review the proposed MOA in more depth, both within OPP and in conjunction other Agency offices. If the Agency concurs with the proposed MOA, then cancer and long-term non-cancer risks would be regulated at the same level, since the long-term non-cancer endpoint is based on nasal lesions that are considered precursors to the development of tumors.

Table 15: Exposure Levels at which Cancer and Non-Cancer Risks are Not of Concern

Cancer Risk		
Exposure Frequency (days/year)	**Cancer Risk**	**Exposure Concentration (ppm)**
240	1.0×10^{-4}	0.11
240	1.0×10^{-6}	0.0011
Non-Cancer Risk		
Exposure Duration	**LOC for MOE**	**Exposure Concentration (ppm)**
Acute	300	1.7
Short/Intermed- term	30	2.5
Long-term	30	3

$Q_1^* = 3.5 \times 10^{-6}$ $(\mu g/m^3)^{-1}$ or 0.0084 ppm^{-1}; Short-/Intermediate-term NOAEL = 75 ppm; Long-term $BMDL_{10}$ = 90 ppm (HEC)

Table 16: Non-Cancer and Cancer Risk Estimates at Regulatory Levels				
Organization	Concentration (ppm)	Non-Cancer MOE		Cancer Risk
		ST/IT	LT	
		LOC for MOE = 30		
OSHA (PEL)	100	0.8	0.9	9.2×10^{-2}
Cal/OSHA & EPA Label Levels (8-hour TWA)	20	3.8	4.5	1.8×10^{-2}
ACGIH (TLV-TWA)	2	38	45	1.8×10^{-3}

Short-/Intermediate-term NOAEL = 75 ppm; Long-term $BMDL_{10}$ = 90 ppm (HEC); $Q_1^* = 3.5 \times 10^{-6} (\mu g/m^3)^{-1}$ or 0.0084 ppm^{-1}

MOE = Inhalation NOAEL or BMDL ÷ Inhalation dose at regulatory level

Table 17: Non-Cancer and Cancer Risk Estimates – Almond/Walnut Exposure Monitoring Data					
Combined Data	Activity	Daily TWA[1] (ppm)	Non-Cancer MOE		Cancer Risk[4]
			ST/IT[2]	LT[3]	
			LOC for MOE = 30		
Mean	Non-Specific (Daily TWA)	0.94	80	96	8.7E-04
	Combined Non-Specific & Adjusted Chamber Unloading TWA	1.21	62	74	1.1E-03

[1] All almond and walnut fumigation data are combined. "Combined Non-Specific & Adjusted Chamber Unloading TWA" refers to the combination of all almond/walnut "non-specific" daily TWAs with the daily adjusted TWAs for chamber unloading during walnut fumigations.

[2] Short-/Intermediate-term NOAEL = 75 ppm

[3] Long-term $BMDL_{10}$ = 90 ppm (HEC)

[4] $Q_1^* = 3.5 \times 10^{-6} (\mu g/m^3)^{-1}$ or 0.0084 ppm^{-1}

10.5.2 Dermal Exposure and Risk

Dermal exposure to liquid PPO while changing drums is negligible as the exposure pattern is likely episodic and changing drums typically involves disconnecting and re-connecting valves while wearing full body protection including gloves, face shield, and goggles as required by the product labels. The registrant has indicated that commodities are fumigated in packaging which is sealed prior to shipping, and commodity processing is largely automated (Brooks, 2005). Therefore, dermal exposure to the treated commodities themselves is also likely negligible. Therefore a quantitative dermal exposure assessment is not considered necessary.

10.5.3 Risk Characterization

Because of a scarcity of monitoring data, HED has indirectly characterized inhalation risks for PPO by comparison to the OSHA PEL of 100 ppm, or to recommended air concentration limits, such as ACGIH's TLV of 2 ppm. During Phase III of the RED process, HED received data associated with the outdoor use of PPO on almonds and walnuts. The submissions provide exposure monitoring data (i.e., air concentrations), and descriptions of daily activities, including duration and, in some instances, PPE (i.e., respiratory protection) worn. Due to data limitations, primarily lack of data associating peak concentrations with specific tasks, HED could not use this information to quantitatively adjust daily average exposure based on PPE usage. Nevertheless, the submitted information and data clearly suggests that daily average PPO exposure is influenced by sporadic instances of peak PPO concentrations during certain activities during the day. Given this likely exposure pattern, HED believes that steps can be taken to mitigate risks. For example, respiratory protection during peak PPO exposures could

reduce the daily average exposure to levels that would not be of concern. Additional monitoring data and/or an exposure survey that "breaks down" activities throughout the day using separate monitoring badges for each activity or one that uses direct read instrumentation to obtain measurements throughout the course of the workday is expected from the registrant and industry representatives.

It is important to reiterate that the submitted data for outdoor fumigation facilities cannot be assumed to be representative of fumigations conducted in indoor commercial sterilization facilities. It is reasonable to assume that, for indoor facilities, shortened periods of heightened PPO exposure would be similar to the outdoor facilities, however background PPO concentrations and exposure could be different due to differences in ventilation. Therefore, additional monitoring data specific to indoor activities would be necessary to determine an appropriate mitigation strategy for indoor uses of PPO.

11.0 DATA NEEDS

11.1 Toxicology

Outstanding toxicology data requirements for PPO are reserved. The requirement for a nonrodent oral chronic toxicity study (870.4100b) is reserved pending further consideration of PPO's mode of action.

The toxicology database for PCH is considered complete.

11.2 Residue Chemistry and Label Requirements

Directions for use must be clearly defined on all labels that are allowed for the fumigation of cocoa bean, nutmeats (except peanut) and spices. Labels of all PPO formulations that are used to treat these commodities must include postharvest directions stating exposure time, temperature and percent humidity, amount of active ingredient PPO, aeration time in treatment chamber, additional storage conditions before treated commodities 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 parameters are needed so the established tolerances will always adequately cover potential residues of concern from PPO fumigation of the listed commodities. According to the registrant, items such as dried onions, dried garlic, and dehydrated vegetables are included in ASTA definition of spices. As these foods are in other crops groups as defined by the Agency, tolerances have to be established for these items.

The existing 300 ppm tolerance for vegetable gums should be revoked based on the registrant's request for voluntary cancellation of PPO use on all edible gums pursuant to FIFRA Section 6(f)(1)(A).

Labels of all PPO formulations that are used to treat tree nuts must mimic the application conditions used (one rate if for all tree nuts, and list of all rates if slightly different within the tree nut group) in the residue data trials to include postharvest directions stating

exposure time, temperature and percent humidity, maximum amount of active ingredient PPO allowed for treatment, aeration time in treatment chamber, additional storage conditions before treated commodities are released to market for consumption, and any other parameters (i.e., equipment type, capacity, etc.) that are necessary to insure consistency in each treatment. These parameters are needed so the established tolerances will always adequately cover potential residues of concern from the PPO fumigation of nutmeats.

Analytical reference standards for PPO and PCH are not currently available in the EPA National Pesticide Standards Repository. Analytical reference standards of PPO and PCH must be supplied and supplies replenished by the Repository.

Presently in 40 CFR §180.491 application directions are listed including time and temperature conditions. Sections listing application directions should be removed. All treatment parameters should be on the label only, and not in the tolerance expression. Recommended changes to the tolerance expression in 40 CFR §180.491 are provided in Appendix 8.0.

Newly submitted residue data clearly show that PPO residue are much lower than the existing 300 ppm tolerance much sooner that the label 28-day limitation. The newly submitted data is considered preliminary, however. Therefore, HED will require additional and adequate confirmatory residue data (with adequate sampling) to support any change to the existing 300 ppm tolerance. Any study submitted must be run under GLP conditions. Currently, the tolerance should remain at 300 ppm, but if the maximum label rate is lowered for treatment of tree nuts, and adequate confirmatory data is submitted, the tolerance may be decreased.

11.3 Occupational and Residential Exposure

Additional information regarding the sterilization activities and exposure monitoring data from the sterilization and commodity processing industries would help refine the assessment.

APPENDICES

1.0 GUIDELINE TOXICOLOGY DATA SUMMARY

Data requirements (40 CFR 158.340) for propylene 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 Propylene Oxide		
Test	**Technical**	
	Required	**Satisfied**
870.1100 Acute Oral Toxicity	yes	yes*
870.1200 Acute Dermal Toxicity	no¶	-
870.1300 Acute Inhalation Toxicity	yes	yes*
870.2400 Primary Eye Irritation	no¶	-
870.2500 Primary Dermal Irritation	no¶	-
870.2600 Dermal Sensitization	no¶	-
870.3100 Oral Subchronic (rodent)	yes	yes
870.3150 Oral Subchronic (nonrodent)	yes	yes
870.3200 21-Day Dermal	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	yes
870.3800 Reproduction	yes	yes
870.4100a Chronic Toxicity (rodent)	yes	yes
870.4100b Chronic Toxicity (nonrodent)	yes	reserved#
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 Neurotoxicity. (hen)	no	-
870.6100b 90-Day Neurotoxicity (hen)	no	-
870.6200a Acute Neurotoxicity. Screening Battery (rat)	no	no
870.6200b 90 Day Neurotoxicity. Screening Battery (rat)	no	no
870.6300 Develop. Neurotoxicity	no	-
870.7485 General Metabolism	yes	yes
870.7600 Dermal Penetration	no¶	-
Special Studies for Ocular Effects		
Acute Oral (rat)	no	-
Subchronic Oral (rat)	no	-
Six-month Oral (dog)	yes	yes

†Data gap exists for the metabolite of propylene oxide, propylene chlorohydrin; Refer to the Data Needs Section
¶Study not required based on the severe irritant properties of the compound.
#Study reserved pending consideration of PPO mode of action.
* No study submitted but information from the open literature is sufficient to satisfy the guideline studies

2.0 NON-CRITICAl TOXICOLOGY STUDIES

Subchronic Neurotoxicity Study - Propylene Oxide

Subchronic Neurotoxicity Study (MRID 45292801)

In a subchronic inhalation neurotoxicity study (MRID 45292801), groups of 30 Fisher-344 male rats were exposed to 0, 30, 100, or 300 ppm of propylene oxide (Lot No. 30215 III; >99% active ingredient) for 24 weeks. Exposures were for 6 hr/day, 5 days/week for the first 14 weeks and 7 days/week for the remainder of the study. Functional observational battery (FOB) testing was performed after 8, 16, and 24 weeks of exposure; motor activity measurements were assessed once for each animal at the end of the study. Body weights were recorded weekly for each animal. Neuropathologic examinations were performed on 10 animals from each of the control and high-concentration groups; brain weights were not reported.

No treatment-related mortalities or clinical signs of toxicity were observed in any rat. Gross necropsy and neuropathology were unremarkable.

Absolute body weights were significantly ($p \leq 0.05$) less than the control group levels beginning on day 11 for the high-concentration group (90-96% of controls) and on day 39 for the mid-concentration group (92-97% of controls). Body weights of the low-concentration group were consistently less (96-97% of controls) than those of the controls after the third week of treatment, but statistical significance was only attained occasionally and the magnitude was not considered to be biologically significant.

No treatment-related or statistically significant differences in mean hindlimb grip strengths were found for the treated groups as compared to the controls. No treatment-related abnormalities were observed during handling and no gait or locomotor abnormalities were noted in the open field. Reflex and sensorimotor responses were similar between the treated and control groups. Motor activity was not affected by treatment.

This study is classified as **Acceptable/Non-Guideline** and does not satisfy the requirements for a subchronic inhalation neurotoxicity study [OPPTS 870.6200 (§82-7)] in rats. The LOAEL for neurotoxic effects are not established. Validation of the laboratory neurotoxicity testing methods was not included and females were not tested. However, the study is sufficient for the purposes for which it was intended to assess the potential of propylene oxide to induce neurotoxicity in male rats following subchronic inhalation exposure.

COMPLIANCE: A signed and dated Quality Assurance statement was included. Data Confidentiality, Good Laboratory Practice Compliance, and Flagging statements were not provided.

Subchronic Toxicity Studies –Propylene oxide

Oral Exposure

There were two subchronic reports identified in the literature examining the toxic effects of PPO by oral route and these are either old (Rowe et al., 1956) or in a foreign journal (Antonova et al., 1981) and original information could not be verified. The studies cited below are not from original sources, and provide limited data and are cited as they are the only subchronic studies identified for the oral exposure. Therefore, these studies were not considered for the end point selection.

PPO was administered in drinking water to rats (strain unspecified, number of animals per group not known) at 0, 0.00052, 0.0052, 0.052 and 0.52 mg/kg/day for 26 weeks. At the highest dose level, polyuria, hematological abnormalities, decreased serum albumin, increased serum-beta globulin and increased activities of gastrointestinal mucosal enzymes were reported. Mild hematological abnormalities were reported at 0.052 mg/kg/day. **The NOAEL was identified as 0.0052 mg/kg/day and the LOAEL was identified as 0.052 mg/kg/day** (Antonova et al., 1981 as cited in WHO, 1985).

The study is classified as **Unacceptable /Non-Guideline**.

In a subchronic oral toxicity study, females rats (strain not specified, number of animals per treatment not known) were administered 0, 100, 200 or 300 mg/kg for 5d/week for 24 days (18 doses). It is assumed these doses were administered by gavage. The HDT has slightly lowered body weight, evidence of gastric irritation and slight liver damage. **The NOAEL was identified as 200 mg/kg/day and the LOAEL was identified as 300 mg/kg/day based on decreased body weight, liver damage, and gastric irritation.** (Rowe et al., 1956, as cited in Meylan et al., 1986).

The study is classified as **Unacceptable/Non-Guideline**.

Inhalation Exposure

In a range-finding test for a carcinogenicity study (NTP, 1985), groups of 5 male and 5 female Fischer 344/N rats were exposed to 0, 47, 99, 196, 487, 1433 ppm propylene oxide for 5 days per week, and 6 h per day, for two weeks. No gross or pathological effects were observed. Dyspnea, hypoactivity, gasping, ataxia, and diarrhea were observed at the HDT. Also, one male died at the HDT. Both males and females at the HDT had decreased body weight gain as compared to controls. **The NOAEL is determined as 487 ppm and LOAEL is determined as 1433 ppm based on mortality, decreased body weight gain, dyspnea, hypoactivity, gasping, ataxia, and diarrhea.**

In range-finding test for a carcinogenicity study (NTP, 1985), groups of 5 male and 5 female B6C3F1 mice were exposed to 0, 20, 47, 99, 196, 487 ppm propylene oxide for 5 days per week, and 6 h per day, for two weeks. No pathological effects were observed. Dyspnea was noticed at 196 and 487 ppm and mice at 487 ppm were also less active. No

significant changes in body weights were reported. **The NOAEL is determined as 99 ppm and LOAEL is determined as 196 ppm based on dyspnea effects.**

In range-finding test for a carcinogenicity study (NTP, 1985), groups of 5 male and 5 female Fischer 344/N rats were exposed to 0, 31, 63, 125, 250, 500 ppm propylene oxide for 5 days per week, and 6 h per day, for 13 weeks. No rats died. Final mean body weights relative to those of controls were 7.4% lower in males and 5.3% lower in females exposed to air containing 500 ppm propylene oxide. The changes in body weights were not considered as toxicologically significant. T**he NOAEL is determined as 500 ppm and LOAEL is not established.**

In range-finding test for a carcinogenicity study (NTP, 1985), groups of 5 male and 5 female B6C3F1 mice were exposed to 0, 31, 63, 125, 250, 500 ppm propylene oxide for 5 days per week, and 6 h per day, for 13 weeks. Decreased body weights (↓12.9% in males and ↓14.6% in females) were reported at HDT as compared to controls. No gross or microscopic changes were observed. **The NOAEL is determined as 250 ppm and LOAEL is determined as 500 ppm based on decreased body weights.**

Propylene Chlorohydrin

Subchronic Toxicity Studies

Rats

In a sub chronic study (NTP, 1988), designed as a range finding study for chronic carcinogenicity study, groups of 10 male and 10 female F344/N rats were administered 1-chloro-2-propanol (75% 1-chloro-2-propanol and 25% 2-chloro-1-propanol) in drinking water at concentrations of 0, 100, 330, 1,000, 3,300, or 10,000 ppm for 14 days. The daily doses determined by study authors correspond to 0, 15, 45, 140, 260, 265 mg/kg/day, respectively. Two 10,000 ppm females died before the end of the study (20% mortality). The final mean body weights and body weight gains and water consumption of 3,300 and 10,000 ppm rats were significantly less than those of the controls. The absolute thymus weight and relative thymus weight to body weight of 10,000 ppm rats were significantly less compared to controls. Exposure to 1-chloro-2-propanol at 3300 and 10000 ppm caused cytoplasmic alteration and degeneration of the acinar cells in pancreas, atrophy of the bone marrow in both sexes compared to respective controls. The females at 1000 ppm, also exhibited cytoplasmic alteration and degeneration of the acinar cells in pancreas, and atrophy of the bone marrow. Diffuse atrophy of the spleen was reported in both sexes at 10,000 ppm. **The LOAEL is determined as 1000 ppm (140 mg/kg/day) based on the histopathological changes in pancreas and bone marrow of females. The NOAEL is determined as 330 ppm (45 mg/kg/day).**

In a sub chronic study designed as a range finding study for the chronic carcinogenicity study (NTP, 1998), groups of 10 male and 10 female F344/N rats were administered 1-chloro-2-propanol (75% 1-chloro-2-propanol and 25% 2-chloro-1-propanol) at concentrations of 0, 33, 100, 330, 1,000, or 3,300 ppm in

drinking water for 14 weeks. The average daily doses as determined by study authors correspond to 0, 5, 10, 35, 100, or 220 mg/kg, respectively. All rats survived to the end of the study. Mean body weight gains of 3,300 ppm rats were significantly less than those of the controls. Water consumption by the 3,300 ppm male and female rats was significantly less than that by the controls. A minimal to mild anemia was observed in exposed female rats at 3300 ppm. The cauda epididymis and epididymis weights of 3,300 ppm males were significantly less than those of the controls. The percentage of abnormal sperm in 3,300 ppm males were significantly increased compared to the controls. The incidences of acinar cell degeneration and fatty change of the pancreas in 1,000 and 3,300 ppm rats, focal metaplasia of the pancreatic islets in 3,300 ppm females, cytoplasmic vacuolization of the liver in 3,300 ppm males, and renal tubule epithelium regeneration in 3,300 ppm females were increased compared to the controls. The LOAEL is determined as 1000 ppm (100 mg/kg/day) based on increased incidences of the acinar cell degeneration, fatty change in the pancreas of both sexes. The NOAEL is determined as 330 ppm (35 mg/kg/day).

In a subchronic oral toxicity study (USFDA, 1969 as cited in TNO BIBRA International, 1994), groups of rats (strain not specified; 10/sex/group) were given PCH in diets at 0, 1000, 2500, 5000 and 10,000 ppm for 25 weeks. Analysis of the 10,000 ppm diet revealed 3568 ppm (73% 1-chloro-2-propanol and 27% 2-chloro-1-propanol) immediately after mixing and 838 ppm (68% 1-chloro-2-propanol and 32% 2-chloro-1-propanol) after 7 days. The reviewer determined the daily doses as 0, 100, 250, 500, 1000 mg/kg/day prior to the correction for the stability of the diet. There was no information how often the diets were prepared. There were no effects on survival, hematological and clinical parameters or gross or pathological changes. At 5000 ppm and above body weights were decreased. **The LOAEL is determined as 5000 ppm (500 mg/kg/day) based on decreased body weight. The NOAEL is determined as 2500 ppm (250 mg/kg/day).**

In a subchronic oral toxicity study (USFDA, 1969 as cited in TNO BIBRA International, 1994), groups of rats (strain not specified; 10/sex/group) were administered PCH by gavage at 0, 25, 50, or 75 mg/kg/day for 22 weeks. Increased liver weights were seen in males at 25 mg/kg/day and in both sexes at 75 mg/kg/day. No effects on survival, the clinical parameters, organ weights, gross or microscopic changes. A fifth group was given doses increasing from 100 to 250 mg/kg/day over a 19 week period. Decreased body weights were reported at 200 mg/kg/day and 100% mortality was reported at 250 mg/kg/day within 3 weeks of treatment. **The LOAEL is determined as 25 mg/kg/day based on increased liver weight in males. The NOAEL is not established.**

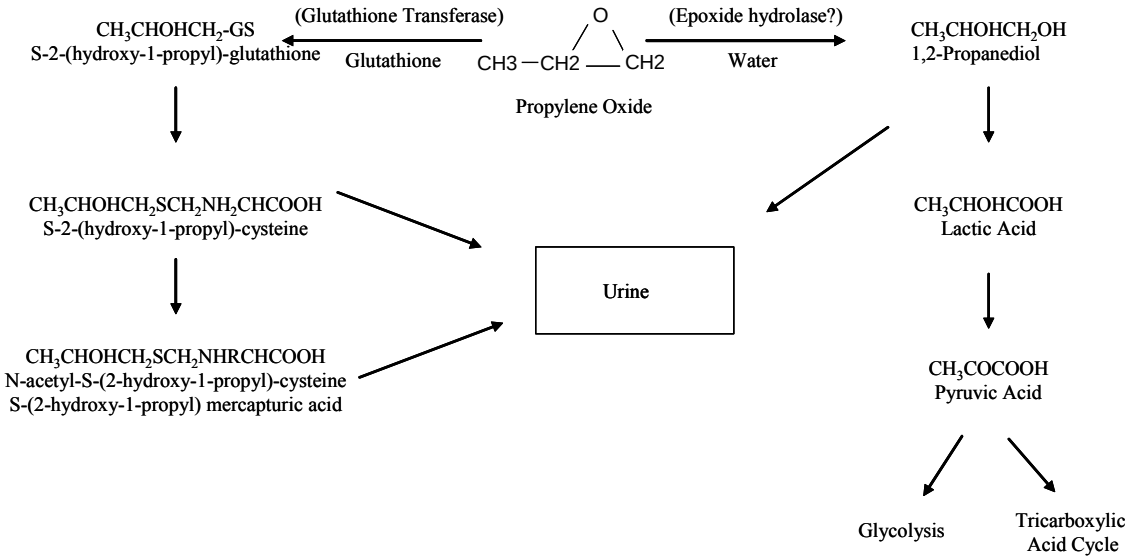
<u>Mice</u>

In a subchronic study designed as a range finding study for the carcinogenicity study (NTP, 1998), groups of 10 male and 10 female $B6C3F_1$ mice were administered 1-chloro-2-propanol (75% 1-chloro-2-propanol and 25% 2-chloro-1-propanol) in drinking water at concentrations of 0, 100, 330, 1,000, 3,300, or 10,000 ppm for 14 days. The average

daily doses determined by the study authors correspond to 0, 20, 60, 175, 430 or 630 mg/kg/day in males and 0, 25, 95, 290, 640 or 940 mg/kg/day in females. One male mouse in the 10,000 ppm group died before the end of the study. Mean body weight gains of 10,000 ppm mice were significantly less than those of the controls. Water consumption by 3,300 and 10,000 ppm males and females was significantly less than that by the controls throughout the study. Liver weights of 1,000, 3,300, or 10,000 ppm males and females were significantly greater and thymus weights of 10,000 ppm mice were significantly less than those of the controls. Exposure to 1-chloro-2-propanol caused hepatocellular vacuolization in males and females at 1000 ppm and above, cytoplasmic alteration and degeneration of the pancreas acinar cells at 3300 ppm and above, and atrophy of the spleen at 10000 ppm in both sexes. **The LOAEL is determined as 1000 ppm (175 mg/kg/day) based on increased liver weight relative to body weight and increased vacuolization of cytoplasm of hepatocytes in both males and females. The NOAEL is determined as 330 ppm (60 mg/kg/day).**

In a subchronic study designed as a range finding study for a carcinogenicity study (NTP, 1998), groups of 10 male and 10 female B6C3F_1 mice were administered 1-chloro-2-propanol (75% 1-chloro-2-propanol and 25% 2-chloro-1-propanol) in drinking water at concentrations of 0, 33, 100, 330, 1,000, or 3,300 ppm for 14 weeks. The average daily doses were determined by the study authors as 0, 5, 15, 50, 170, or 340 mg/kg in males and 7, 20, 70, 260, or 420 mg/kg in females. One 330 ppm male died before the end of the study. Mean body weight gains of exposed groups were similar to those of the controls. A minimal anemia was observed in 3,300 ppm males. The right epididymis weight of 3,300 ppm males was significantly greater than that of the controls. Kidney weights of 3,300 ppm mice, liver weights of 1,000 ppm males and of all exposed groups of females, and thymus weights of 1,000 and 3,300 ppm females were greater than those of the controls. The changes in liver weights in females of all treatment groups did not exhibit a clear dose response effect. The incidences of acinar cell degeneration and fatty change in the pancreas increased in 3,300 ppm males and females as compared to controls. The cytoplasmic vacuolization of the liver were increased in all groups of exposed females but the incidences were not dose dependent. The severities of renal tubule cytoplasmic vacuolization were greater in 1,000 and 3,300 ppm males than in the controls. **The LOAEL is determined as 1000 ppm (170 mg/kg/day) based on increased organ weights and increased incidence of the renal tubule cytoplasmic vacuolization in males. The NOAEL is determined as 330 ppm (50 mg/kg/day).**

3.0 Propylene Oxide Metabolism



Propylene Oxide Metabolism (WHO, 1985)

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5.0 ALTERNATE ORAL CANCER SLOPE FACTOR DERIVATION

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

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

ATTACHMENT 5

MEMORANDUM

June 27, 2006

SUBJECT: Propylene Oxide (PPO)**:** Qualitative/Quantitative Evaluation of Dietary Risk Assessment; PC Code 042501; D329650; Decision#:360739; RED-2560-1921

FROM: William Dykstra, Ph.D.
Toxicologist
Reregistration Branch 4
Health Effects Division (7509C)

THROUGH: Susan Hummel
Branch Senior Scientist
Reregistration Branch 4
Health Effects Division (7509C)

TO: Susan Bartow
Chemical Review Manager
Special Review Branch
Special Review and Reregistration Division (7509C)

Rebecca Daiss
Risk Assessor
Reregistration Branch 4
Health Effects Division (7509C)

Based on the submitted registrant's risk assessments, plus supporting documentation, HED has evaluated the qualitative/quantitative rationale for the further toxicological analysis of dietary risks from consumption of PPO residues in the diet.

REVIEW:

In the Dunkelberg Gavage study (1982), treated groups of 50 female Sprague-Dawley rats were orally gavaged with 0, 15, or 60 mg/kg of PPO in one mL volumes of 'Livio" salad oil twice weekly for 150 weeks (a total of 219 treatments). Controls consisted of

both vehicle-treated and untreated groups. Fore-stomach tumors, primarily squamous cell carcinomas, were observed in treated animals for PPO. For PPO, the incidence of squamous cell carcinomas was 2/50 (low dose) and 19/50 (high dose). No other tumors were produced at biologically significant levels.

As to the question of what becomes of PPO in the stomach, the stomach juice degradation rates for PPO were measured and it was found that PPO is hydrolyzed in the rat and human gastric compartments exclusively to PPG (propylene glycol). Even though there is a reasonable amount of chloride ion in the stomach (from the stomach acid) propylene chlorohydrin has been shown not to form as a degradation product in either the human stomach or the rat stomach .

In humans, in contrast to rodents, PPO which is ingested in the diet is rapidly detoxified by three mechanisms. The first of these three mechanisms is acid catalyzed hydrolysis. This operates effectively in the human stomach but not in the rat fore-stomach or glandular stomach due to the higher gastric acidity in humans in comparison to rodents. The second mechanism is enzyme catalyzed ring opening (via epoxide hydratase) This mechanism functions both in rats and humans. While this enzyme is typically more concentrated in the liver, studies have shown its active presence in other tissues such as the nasal and lung epithelium. The net effect of these first two mechanisms in the human is expected to be that PPO consumed in the diet will be functionally equivalent to propylene glycol (PPG), a substance which is GRAS for many uses. The third mechanism is the glutathione conjugation of PPO by GSH-S-transferase and excretion via the kidneys.

The net effect of all three of these mechanisms working together in humans is that gastric exposures to PPO consumed in the diet are essentially converted to PPG.

It is seen from an analysis of the PPO rodent studies that an increased tumor incidence is not seen at PPO doses/exposures which do not also cause an increase in inflammatory changes/restorative hyperplasia at the local site of administration in response to local tissue toxicity produced by high local concentrations of PPO.

However, in view of the fact that a gavage dose not resulting in a tumor response was not identified in the Dunkelberg study, a potential oral carcinogenic risk assessment is needed to be performed for PPO. Although the Dunkelberg gavage study can be extrapolated to calculate an oral NOAEL, the present reviewer cannot concur with this speculative method presented by the registrant's consultant, Dr. John Todhunter. In contrast, the present reviewer considers the use of the identified modifying factors and underlying scientific principles which help to characterize the possible, if any, carcinogenic risks of ingested PPO to be more justified than an RfD approach.

Experimentally Determined Constants for the Conversion of PPO to PPG in Human Gastric Juice and in Rat Fore-stomach Juice

Parameter	Human Gastric Juice	Rat Fore-stomach Juice
pH	1.46	4.8
Overall hydrolysis Rate for PPO	0.364 min -1	0.0020 min-1

Half-life of PPO	1.90 min	347 min

A Concentration-based Approach for Oral Cancer Risk Assessment

Fore stomach tumors in the rat treated by gavage may be considered a portal of entry response. By analogy to the RfC methodology which considers the concentration of test material to be the most important determinant of response in portal of entry tumors, PPO dosage may be expressed as a concentration.

The oral Q*, determined in the usual way, is 0.15 (mg/kg bw/day)-^{1}. Doses in the Dunkelberg study were 0, 15 and 60 mg/kg bw/day. There were 219 administrations of the test material over the 150 week duration of the study. For a standard 0.35 kg rat, the administered doses in mg/rat were 0, 5.25, and 21 mg. (e.g., 15 mg/kg bw/day x 0.35 kg = 5.25 mg/rat). Since the volume of administration was 1 mL/rat, the administered concentrations were 0, 5.25, and 21 mg/mL in the gavage study. To adjust the concentration to a continuous basis, the mg/mL concentrations are multiplied by 219 ÷ (150 weeks x 7days/week). The adjusted concentrations are 0, 1.10 and 4.38 mg/mL (e.g., 5.25 mg/mL x 219 ÷ (150 week x 7 days/week) = 1.10 mg/mL).

The administered PPO was dissolved in salad oil which has a density of 0.92 g/cc. The adjusted dosage in terms of mg PPO/g salad oil (dosing solution) is 1.19 and 4.76 mg/g or 0, 1190, and 4760 mg/kg dosing solution (e.g., 1.10 mg/mL ÷ 0.92 g/cc. = 1.19 mg PPO/g salad oil or dosing solution).

The BMD/BMDL$_{10}$ for the cancer dose-response in terms of mg/kg administered gavage solutions is 2,080/1,160 mg/kg dosing solution. **The slope factor using the BMDL$_{10}$ is 0.1/1160 mg/kg salad oil= 0.000086 (mg/kg dosing solution)$^{-1}$ (Attached). EPA assumes that kg dosing solution is a measurable surrogate for kg diet.**

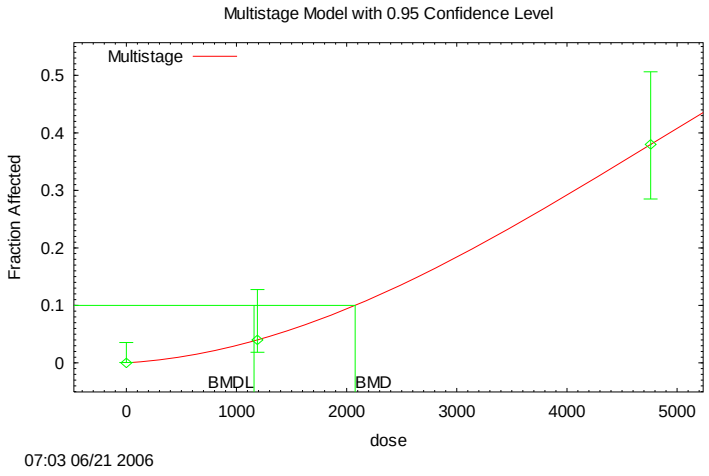
The chronic dietary exposure to PPO in the general population is estimated to be 0.0001 mg PPO/kg body weight. Since a 70 kg person eats an average of 1.5 kg of food per day, the average concentration of PPO in the diet is 0.0001 mg/kg bw x 70 kg ÷ 1.5 kg diet = 0.0047 mg PPO/kg diet.

Multiplying the slope factor of 0.000086 (mg/kg dosing solution) -^{1} by the PPO chronic dietary exposure in the general population (0.0047 mg/kg diet) results in a risk estimate of **4 x 10^{-7}.**

Quantitative cancer assessments using the RfC methodology include an adjustment for interspecies differences (the RGDR). In this example of alternative assessment for PPO using concentrations instead of doses in mg/kg bw, no interspecies adjustments have been made. If they were made, the adjustment would result in an even lower risk estimate, since the retention time of material in the rat fore-stomach is far greater than the residence time of food in the human esophagus.

```
================================================================================
======
        Multistage Model. $Revision: 2.1 $ $Date: 2000/08/21 03:38:21 $
        Input Data File: C:\BMDS\DATA\PPO_ADJUSTED_DIETARY.(d)
        Gnuplot Plotting File:  C:\BMDS\DATA\PPO_ADJUSTED_DIETARY.plt
                                          Wed Jun 21 07:03:24 2006
 ================================================================================
 Gavage conc (mg/L) x 0.92 x 219 /(150 wk x 7 d/w)
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
-beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive

   Dependent variable = Incidence
   Independent variable = Dose

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2

 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008

                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) =  1.2263e-005
                        Beta(2) =  1.8522e-008

           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                Beta(1)      Beta(2)

   Beta(1)            1        -0.98

   Beta(2)        -0.98            1

                          Parameter Estimates

       Variable           Estimate             Std. Err.
     Background                  0                   NA
        Beta(1)         1.2263e-005          0.000162211
        Beta(2)         1.8522e-008         3.55814e-008

NA - Indicates that this parameter has hit a bound
```

```
     implied by some inequality constraint and thus
     has no standard error.

                        Analysis of Deviance Table

       Model      Log(likelihood)  Deviance  Test DF     P-value
     Full model         -41.6004
   Fitted model         -41.6004   3.7943e-012      1           1
  Reduced model         -67.1864       51.1721      2      <.0001

           AIC:          87.2008

                      Goodness  of  Fit

     Dose     Est._Prob.    Expected    Observed     Size     Chi^2
res.
  ------------------------------------------------------------------------
--
i: 1
    0.0000     0.0000         0.000         0         100       0.000
i: 2
 1190.0000     0.0400         2.000         2          50      -0.000
i: 3
 4760.0000     0.3800        19.000        19          50      -0.000

 Chi-square =       0.00     DF = 1        P-value = 1.0000

   Benchmark Dose Computation

Specified effect =           0.1

Risk Type        =      Extra risk

Confidence level =          0.95

             BMD =       2076.86

            BMDL =       1159.24
```



6.0 MODE OF ACTION SUMMARY

The registrant and consultants to the registrant have submitted a large amount of information relevant to the carcinogenic mode of action (MOA) of PPO. Much of the submitted data are journal articles concerning formation of DNA or hemoglobin adducts of PPO. Other submissions focus on the genotoxic response of PPO in various mutagenicity test systems, and still others study the association between PPO concentration and cytotoxicity and cell proliferation at the site of tumor formation. Particularly informative articles compare the pattern of adduct formation with cytotoxicity, regenerative cell proliferation and tumor response. In addition to the journal articles, we have received a number of presentations that summarize the published information, and lay out the proposed MOA.

Briefly summarizing the key points of the proposed MOA, exposure to PPO in animals via the inhalation route results in a linear response with respect to blood concentration of PPO and the formation of hemoglobin and DNA adducts, but a highly sublinear response with respect to cytotoxicity and regenerative cell proliferation and tumor formation. The cytotoxicity/cell proliferation response appears to precede tumor response with respect to PPO concentration.

After an initial analysis, EPA concludes that the proposed MOA is plausible, and will review the proposed MOA in more depth, both within OPP and in conjunction other Agency offices.

If the proposed MOA is accepted by the Agency, propylene oxide will not be regulated using a q* approach. Rather, a Margin of Exposure analysis will be done. Currently, the long-term inhalation endpoint for propylene oxide is derived from the Kuper et al. (1988) (submitted as MRID 42039901) study with a point of departure of 5.2 ppm for nasal lesions (calculated from the NOAEC of 30 ppm – 30 ppm x 6 hr toxicity study/8 hr workday x 0.23 (RGDR)). This study and point of departure are reasonable choices to use to assess PPO cancer risks using an MOE approach, since they are based on basal cell hyperplasia and nest-like infolds of the nasal epithelium, effects that are likely to be among the continuum of events leading to cancer.

7.0 BMD ANALYSES

7.1 BMD Analysis Memo – Dunkelberg 1982

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

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

June 28, 2005

SUBJECT: Benchmark Dose Analysis of Propylene Oxide - Combined Incidences of Papillomas, Hyperplasia and Hyperkeratosis in Rat Forestomach

FROM: Becky Daiss
Environmental Health Scientist
Reregistration Branch 4
Health Effects Division (7509C)

TO: Santhini Ramasamy
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Reregistration Branch 4
Health Effects Division (7509C)

This memorandum provides benchmark dose analyses of combined incidences of papillomas, hyperplasia and hyperkeratosis carcinogenicity study of intragastric administration of ethylene oxide and 1,2-propylene oxide to rats.

BMD Analysis

A benchmark dose (BMD) approach was used to estimate a toxicity endpoint (as a basis for deriving an RfD) for combined incidences of papillomas, hyperplasia and hyperkeratosis in rats from chronic exposure to propylene oxide. A BMD is defined as

an exposure due to a dose of a substance associated with a specified low incidence of risk, generally in the range of 1% to 10%, of a health effect; or the dose associated with a specified measure or change of a biological effect. This dose is estimated using statistical methods for fitting curves to experimental data.

EPA's Benchmark Dose Software (BMDS version 1.3.2) was used for the BMD analyses of propylene oxide incidence data. Since the data are quantal (i.e., incidences of papillomas, hyperplasia and hyperkeratosis), the BMDS dichotomous models were used to derive estimated BMDs. Models used for the BMD analyses include gamma, log logistic, multistage, log probit, quantal linear, quantal quadratic, and Weibull. Model formulas are provided in the attached table.

BMDS dichotomous models were used to derive the BMD_{10}, the dose estimated to produce an excess risk of 10% (from incidences of papillomas, hyperplasia and hyperkeratosis), and the BMDL, the lower limit of a one-sided 95% confidence interval on the BMD_{10} (i.e., the lower confidence limit on the dose that would result in a 10% response). The following default initial parameters were used for the BMDS dichotomous model runs for this analysis: risk type = extra risk; benchmark response (BMR) = 0.1; power and/or slope restrictions ≥ 1; beta restriction ≥ 0.

Study Selected for BMD Analysis

The following study was selected for BMD analysis. The study was selected based on relevance, quality, potential for quantification, and significance of the dose-response results.

Dunkelberg, H. Carcinogenicity of Ethylene Oxide and 1,2-Propylene Oxide Upon Intragastric Administration to Rats; Br. J Cancer, 46, 924-933, 1982

Dose/Response Input Data

Incidence of Papillomas, Hyperplasia and Hyperkeratosis in Rat Forestomach		
Dose (mg/kg/day)	N	Incidences
0	100	0
2.58	50	7
10.28	50	50

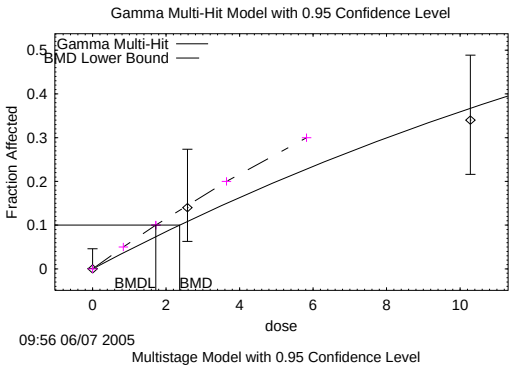
Summary of Results

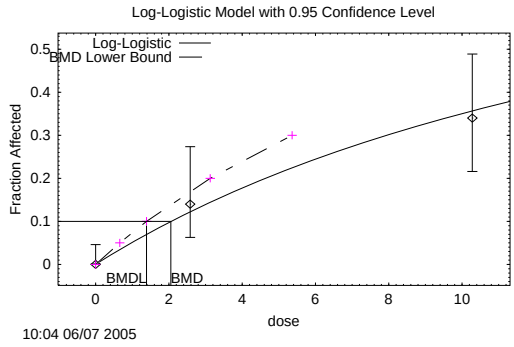
Results of the BMD analysis and representative dose-response graphs are provided below. Since it is particularly important that the data be adequately modeled for BMD calculation, it is recommended that p=0.1 be used to compute the value of goodness of fit.

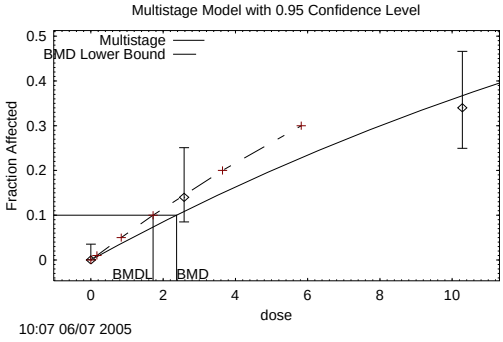
PPO - Rat Carcinogenicity - Combined Incidence - Papillomas, Hyperplasia, Hyperkeratosis						
Model (95% CL)	BMD Extra Risk	BMD	BMDL	x^2	P-Value	AIC

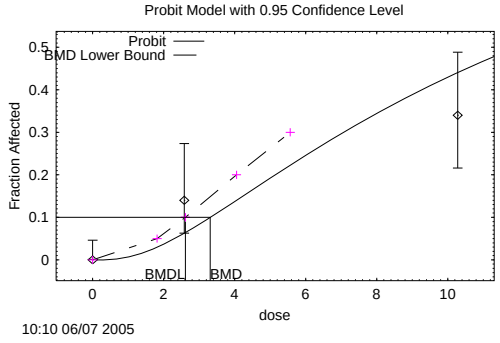
PPO - Rat Carcinogenicity - Combined Incidence - Papillomas, Hyperplasia, Hyperkeratosis						
Model (95% CL)	BMD Extra Risk	BMD	BMDL	x^2	P-Value	AIC
Gamma [1]	10%	2.4	1.7	0.7	0.7	107.2
Log Logistic [2]		2.0	1.4	0.2	0.9	106.8
Multistage2 [3]		2.4	1.7	0.7	0.4	107.2
Log Probit [2]		NA	NA	7	<0.05	112
Quantal Linear [1]		2.4	1.7	0.7	0.7	107.2
Quantal Quadratic [4]		NA	NA	13	<0.005	119
Weibull [1]		2.4	1.7	0.7	0.7	107.2

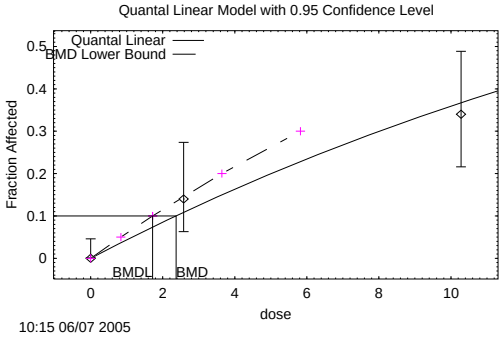
[1] The model parameter(s) Background and Power have been estimated at a boundary point and do not appear in the correlation matrix
[2] The model parameter(s) Background and Slope have been estimated at a boundary point and do not appear in the correlation matrix
[3] The model parameter(s) Background and Beta 2 have been estimated at a boundary point and do not appear in the correlation matrix
[4] The model parameter(s) Power have been estimated at a boundary point and do not appear in the correlation matrix.[4] The model parameter(s) Power have been estimated at a boundary point and do not appear in the correlation matrix

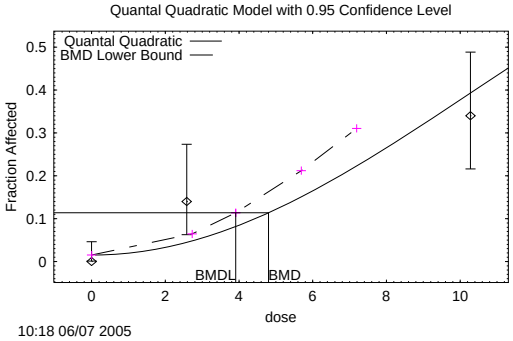


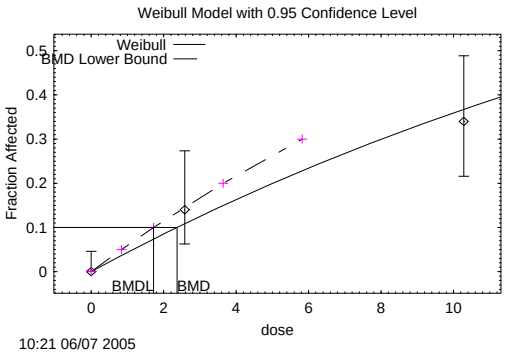












Attachment

BMDS Model	Model Formula
Gamma	$P(d) = \gamma + (1-\gamma) \times \frac{1}{\Gamma(\alpha)} \int_0^{\beta dose} t^{\alpha-1} e^{-t} dt$
Log Logistic	$P(d) = \frac{1}{1 + e^{-(\alpha + \beta \ln(dose))}}$
Multistage	$P(d) = \gamma + (1-\gamma) \times (1 - e^{\sum_{j=1}^{n} \beta_j dose^j})$
Probit	$P(d) = \gamma + (\gamma - 1)\Phi(\alpha + \beta \ln(dose))$
Quantal Linear	$P(d) = \gamma + (1-\gamma)(1 - e^{-\beta dose^{\alpha}})$ $\forall=1$
Quantal Quadratic	$P(d) = \gamma + (1-\gamma)(1 - e^{-\beta dose^{\alpha}})$ $\forall=2$
Weibull	$P(d) = \gamma + (1-\gamma)(1 - e^{-\beta dose^{\alpha}})$

(- background; ∀ - power; ∃ - slope;

7.2 BMD Analysis Memo – Kuper et al. (1988)

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

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

July 30, 2006

SUBJECT: Benchmark Dose Analysis of Propylene Oxide – Nasal Lesions Associated with Long-Term Inhalation Exposure

FROM: Ray Kent, Chief
Reregistration Branch 4
Health Effects Division

TO: Becky Daiss
Environmental Health Scientist
Reregistration Branch 4
Health Effects Division (7509C)

This memorandum provides benchmark dose analyses of nasal lesions associated with long-term administration of 1,2-propylene oxide (PPO) to rats.

Background

A benchmark dose (BMD) approach was used to select an endpoint for assessing long-term non-cancer occupational risks. The study selected for analysis had been used in a prior version of the PPO risk assessment, but because of the complexity of the study, the risk assessment team for PPO decided that a BMD analysis should be considered for establishing a point of departure for long-term scenario. EPA's Benchmark Dose Software (BMDS version 1.3.2) was used for the BMD analysis of propylene oxide incidence data. Since the data are quantal (i.e., incidences of various nasal lesions) the BMDS dichotomous models were used to derive estimated BMDs. Models used for the BMD analyses include gamma, log logistic, multistage, log probit, quantal quadratic, and Weibull. The models are listed in a table attached to the end of this assessment.

Study Selected for BMD Analysis

The following study was selected for BMD analysis.

MRID 42039901
Reuzel, P. and C. Kuper 1983. 1,2-Propylene Oxide: Chronic (28-month) Inhalation Toxicity/Carcinogenicity Study of 1,2-Propylene Oxide. TNO Netherlands Organization for Applied Scientific Research, P.O. Box 360, 3700 AJ Zeist, Netherlands. Laboratory project study identification V 82.215/280853, March 2, 1983.

This study was subsequently published as:

Kuper, C.F., P.G.J. Reuzel, V.J. Feron et al. 1988. Chronic inhalation toxicity and carcinogenicity study of propylene oxide in Wistar rats. Food Chem. Toxicol. 26: 159-167.

A NOAEL of 30 ppm from the study based on increased incidence of basal cell hyperplasia, and nest-like infolds of the respiratory epithelium was initially selected as the point of departure for assessment of long-term non-cancer inhalation risks to workers. The study is complex. There were a number of nasal lesions observed in the study and the responses were graded with respect to severity. There were a number of intermediate sacrifices in addition to the terminal sacrifice at 28 months. The NOAEL inadequately captures the variety of effects and the range of responses of the study whereas a benchmark analysis of the various nasal lesion was expected to provide more useful information for selection of endpoints and assessment of risk.

The executive summary of the Data Evaluation Record for the study may be found in Section **4.4.9.1 (study 1)** of this risk assessment.

Selection of Endpoints to be Modeled

The study describes three nasal lesions that were associated with long-term exposure to PPO: atrophy of the olfactory epithelium, basal-cell hyperplasia of the olfactory epithelium and nest-like infolds of the respiratory epithelium. This latter lesion is considered a hyperplastic response of the respiratory epithelium. The lesions were graded as slight, moderate or marked, although for reporting purposes, the moderate and marked categories were sometimes combined.

Two options were considered for combining the data on the nasal lesions for analysis: The first approach is to sum all rats exhibiting a nasal lesion. This is the more conservative approach and involves summing all rats with any particular lesion, slight, moderate or marked. The second approach is to sum the moderate and marked responses for each lesion. Because the lesions did not progress over the course of the 28-month study (4 months longer than the usual chronic study in rats), the second approach was selected. The incidence data for the three lesions under consideration are shown in Table 1.

Table 1. Incidence of Nasal Lesions* in Male and Female Rats Exposed to Propylene Oxide

	Nasal Lesions in Male Rats				Nasal Lesions in Female Rats			
Dose (ppm)	**0**	**30**	**100**	**300**	**0**	**30**	**100**	**300**
Animals Examined	**66**	**61**	**62**	**63**	**64**	**64**	**62**	**65**
Atrophy of the olfactory epithelium								
Slight response	5	8	7	10	7	9	6	21
Moderate response	**0**	**0**	**3**	**11**	**0**	**0**	**1**	**5**
Total (slight + moderate)	5	8	10	21	7	9	7	26
Basal-cell hyperplasia of the olfactory epithelium								
Slight response	3	1	5	10	0	0	8	17
Moderate response	1	1	5	9	0	0	1	8
Marked response	0	0	0	5	0	0	0	8
Moderate + marked response	**1**	**1**	**5**	**14**	**0**	**0**	**1**	**16**
Total responders	4	2	10	24	0	0	9	33
Nest-like infolds of the respiratory epithelium								
Slight response	4	11	27	21	4	7	19	29
Moderate response	1	0	2	17				
Marked response	0	0	0	9				
Moderate + marked response	**1**	**0**	**2**	**26**	**0**	**1**	**1**	**14**
Total responders	5	11	29	47	4	8	20	43

* the bold response rows indicate the datasets that were modeled.

Selection of the Benchmark Response

The default BMR for dichotomous data is 10% response. In addition, for the study under consideration, with 61 –66 animals examined for potential responses, 10% is approximately the level of statistical significance at the $p<.05$ level, and therefore 10% was chosen as the BMR.

Summary of Results

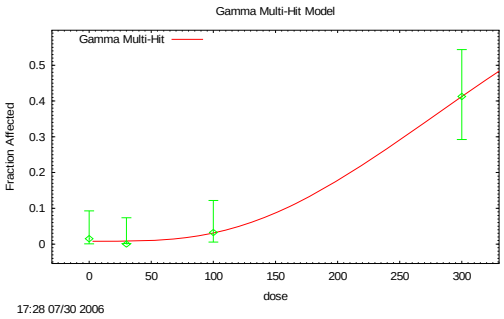
Six dichotomous models were fit to the incidence data for each of the three lesions in both male and female rats. For each set of models, the results were ordered (Table 2) by increasing AIC (Akaike's Information Critierion, a measure of model fit particularly useful for selecting among competing models.). When the models were ordered in this way, the endpoint with the lowest $BMDL_{10}$ was selected – 120 ppm for male rats exhibiting a moderate to marked response of nest-like infolds of the respiratory epithelium. There was one other reasonable endpoint that could have been selected – atrophy of the olfactory epithelium in male rats. The $BMDL_{10}$ associated with the model with the lowest AIC is 131 ppm, but the AIC's for the six models analyzed for this lesion did not differ by much (127.3 to 128.6), and the mean of the model $BMDL_{10}$s is 112 ppm, which is lower than the endpoint and model selected. The difference between the $BMDL_{10}$s is not considered meaningful. The **$BMDL_{10}$ of 120 ppm** was chosen as the point of departure for long-term noncancer risk assessment.

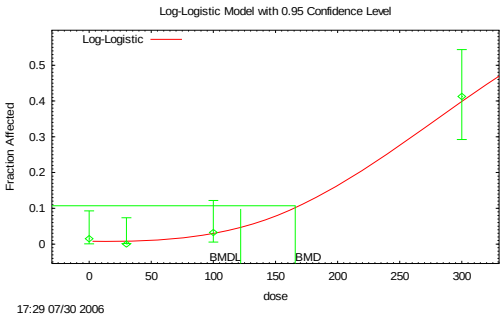
Table 2 summarizes the benchmark dose analysis and Figure 1 shows graphically all of the model runs for nest-like infolds of the respiratory epithelium in male rats. The model printouts and graphs are available as appendices to this document.

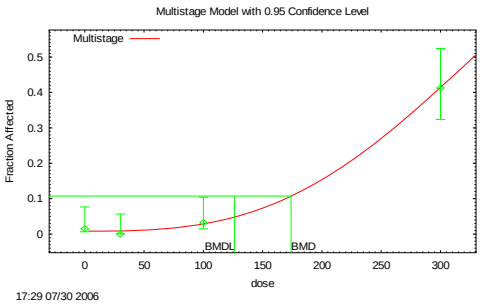
Table 2. Results of Benchmark Dose Modeling of Nasal Lesions in Rats

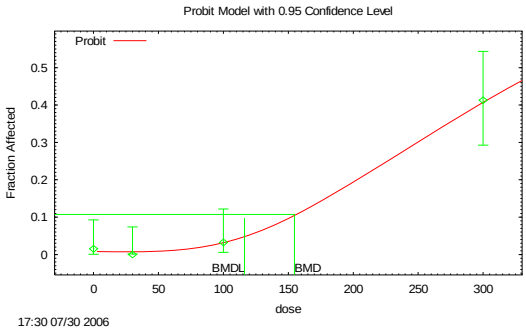
Model	AIC	P	BMD_{10}	$BMDL_{10}$
Atrophy of olfactory epithelium - females				
Quantal quadratic	47.87	0.95	332	246
Probit	48.14	0.85	321	234
Gamma	49.75	0.92	350	242
Logistic	49.76	0.92	350	242
Weibull	49.76	0.92	348	244
Multistage	49.83	0.89	340	246
Atrophy of olfactory epithelium - males				
Probit	85.70	0.69	192	149
Quantal quadratic	86.06	0.59	209	170
Gamma	87.27	0.74	196	139
Logistic	87.29	0.74	195	136
Weibull	87.34	0.73	198	139
Multistage	87.60	0.67	204	136
Basal-cell hyperplasia - olfactory epithelium - females				
Quantal quadratic	85.62	0.90	189	157
Probit	86.80	1.00	192	146
Gamma	86.84	0.99	200	154
Logistic	86.86	0.98	204	154
Weibull	86.87	0.98	207	157
Multistage	86.90	0.97	210	161
Basal-cell hyperplasia - olfactory epithelium - males				
Probit	127.28	0.52	173	131
Quantal quadratic	127.65	0.41	194	156
Logistic	128.40	0.58	153	94
Gamma	128.41	0.57	155	99
Weibull	128.44	0.56	156	98
Multistage	128.57	0.50	160	98
Nest-like infolds - respiratory epithelium - females				
Multistage	93.01	0.65	223	148
Quantal quadratic	93.87	0.47	203	165
Weibull	95.63	0.31	226	137
Logistic	95.63	0.31	224	136
Gamma	95.65	0.31	222	136
Probit	95.66	0.31	216	154
Nest-like infolds - respiratory epithelium - males				
Quantal quadratic	120.47	0.30	140	120
Probit	120.76	0.33	155	116
Gamma	120.80	0.33	162	122
Logistic	120.83	0.33	166	122
Weibull	120.85	0.33	171	125
Multistage	120.87	0.33	174	126

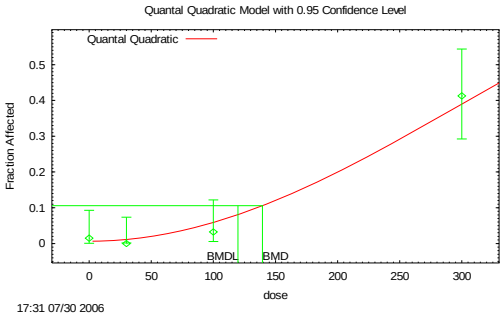
Figure 1. Nest-like infolds of the respiratory epithelium in male rats - "moderate+marked" response

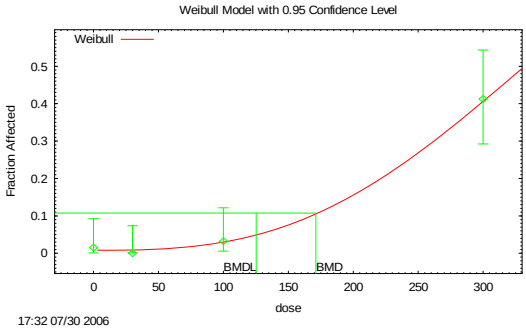












Attachment

BMDS Model	Model Formula
Gamma	$P(d) = \gamma + (1-\gamma) \times \frac{1}{\Gamma(\alpha)} \int_0^{\beta dose} t^{\alpha-1} e^{-t} dt$
Log Logistic	$P(d) = \frac{1}{1 + e^{-(\alpha + \beta \ln(dose))}}$
Multistage	$P(d) = \gamma + (1-\gamma) \times (1 - e^{\sum_{j=1}^{n} \beta_j dose^j})$
Probit	$P(d) = \gamma + (\gamma - 1)\Phi(\alpha + \beta \ln(dose))$
Quantal Linear	$P(d) = \gamma + (1-\gamma)(1 - e^{-\beta dose^{\alpha}})$ $\alpha = 1$
Quantal Quadratic	$P(d) = \gamma + (1-\gamma)(1 - e^{-\beta dose^{\alpha}})$ $\alpha = 2$
Weibull	$P(d) = \gamma + (1-\gamma)(1 - e^{-\beta dose^{\alpha}})$

. γ- background; α - power;. β - slope;

8.0 TOLERANCE REASSESSMENT TABLE

Tolerance Reassessment Summary for Propylene oxide				
Commodity	**Current Tolerance (ppm)**	**Residues (ppm)**	**Tolerance Reassessment (ppm)[1]**	**Comment/[Correct Commodity Definition]**
Tolerances Listed Under 40 CFR §180.491 For Propylene Oxide				
Cacao bean, bean	300	<137	200	change to Cacao bean, dried bean
Gum, edible	300	NA	revoke	Use has been voluntarily cancelled
Nutmeat, processed (except peanut)	300	<300	300	change to Nut, tree, group 14
Spices, processed	300	<164	300	[Herbs and spices, group 19, dried]
Tolerances to Be Recommended under 40 CFR 180.491 For Propylene Oxide				
Cacao bean, cocoa powder	none	<137	200	
Garlic, dried	none	none	300[2]	
Onion, dried	none	none	300[2]	
Grape, raisin	none	<1.0	1.0	
Fig	none	<3.0	3.0	
Plum, prune, dried	none	<2.0	2.0	
Tolerances to Be Recommended under 40 CFR 180.491 For Propylene chlorohydrins:				
Cacao bean, dried bean	none	<13	20	
Cacao bean, cocoa powder	none	<20	20	
Nut, tree, group 14	none	<6	10	
[Herbs and spices, group 19, dried], except basil	none	<1500	1500[3]	
Basil, dried leaves	none	<6000	6000	
Garlic, dried	none	NA	6000[2]	
Onion, dried	none	NA	6000[2]	
Grape, raisin	none	<4.0	4.0	
Fig	none	<3.0	3.0	
Plum, prune, dried	none	<2.0	2.0	

[1] Reassessed tolerances are based on residues measured or estimated at 2 days (spices and cacao bean), 27/28 days (nutmeats), and 0 days (grape, fig, and prune) after treatment.
[2]Tolerance based on data given for basil. Data were not given for dried onion or dried garlic.
[3] Tolerance based on spice. Data not given for herbs other than basil.
NA: not available

Tolerance Expression in 40 CFR §180.491

The tolerance expression in the CFR should be revised to reflect the following changes:

180.491 Propylene oxide; tolerances for residues.

Remove all of current Section (a) (1),

Add a new Section (a)(1),

(a) General (1) Tolerances are established for the residues of propylene oxide when used as a postharvest fumigant in or on the following food commodities:

Commodity	Parts per million
Tolerances to be Listed Under 40 CFR 180.491(a)(1) for propylene oxide	
Cacao bean, bean	200
Gum, edible	revoke
Nutmeat, processed (except peanut)	300
Spices, processed	300
Tolerances to be Proposed Under 40 CFR 180.491(a)(1) for propylene oxide	
Cacao bean, cocoa powder	200
Garlic, dried	300
Onion, dried	300
Grape, raisin	1.0
Fig	3.0
Plum, prune, dried	2.0

Remove all of current Section (a)(2), (a)(3), (a)(4), and (a)(5)

Add a new Section (a)(2):

Tolerances are also established for residues of the propylene oxide reaction products 1-chloro-2-propanol and 2-chloro-1-propanol, commonly referred to as propylene chlorohydrin, when propylene oxide is used as a post-harvest fumigant in or on the following food commodities.

Commodity	Parts per million
Tolerances to be Proposed Under 40 CFR 180.491(a)(2) for propylene chlorohydrin	
Cacao bean, dried bean	20
Cacao bean, cocoa powder	20
Nut, tree, group 14	10
[Herbs and spices, group 19, dried], except basil	1500
Basil, dried leaves	6000
Garlic, dried	6000
Onion, dried	6000
Grape, raisin	4.0
Fig	3.0
Plum, prune, dried	2.0

Appendix K. Environmental Fate and Effects Risk Assessment

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

OFFICE OF PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

May 16, 2006

MEMORANDUM

SUBJECT: EFED RED Chapter for Propylene Oxide (042501)
DP Barcode D263366

TO: Susan Bartow
Special Review and Reregistration Division (7508W)

FROM: Edward Odenkirchen, Ph.D., Senior Biologist
Environmental Risk Branch I
Environmental Fate and Effects Division (7507P)

THROUGH: Nancy Andrews, Ph.D., Chief
Environmental Risk Branch I
Environmental Fate and Effects Division (7507P)

The following document comprises the Environmental Fate and Ecological Effects Division's (EFED) Science Chapter for the Reregistration Eligibility Document for propylene oxide. This risk assessment has not changed from the previous draft with respect to risk conclusions for indoor uses. Indoor uses are not of concern with respect to risks to non-target terrestrial and aquatic organisms. However, as requested by the Special Review and Reregistration Division, this version of the assessment also includes labeled uses associated with the Propoxide 892 product. This label has a number of uses which do not entirely fall within the indoor uses category. These uses include rail cars, tented areas, tarped materials, and in-field treatment chambers. The bulk of the ecological risk assessment addresses risks associated with the Propoxide 892 uses. It should be noted that the entire suite of fate and effects studies described under the 40 *CFR* data requirements have not been submitted by the registrant.

Conclusions of the Risk Assessment

Indoor Uses of propylene Oxide

Indoor uses of propylene oxide are not of concern with respect to risks to non-target terrestrial and aquatic organisms because environmental exposure is assumed to be insignificant.

Taxonomic Groups for Which Risks are Not a Concern for Propoxide 892

The results of the risk assessment indicate that there are likely no concerns for acute lethality or reproduction impairment in terrestrial mammals. This no-concern finding for acute risk to mammals can be extended to birds and reptiles because of other lines of evidence, including relative inhalation rates for birds, reptiles and terrestrial phase amphibians, suggests that gas exposure and thus acute lethal risks for birds and reptiles would not be any greater than those predicted for mammals. Extrapolating the no concern finding for reproduction effects in mammals to other terrestrial vertebrates (e.g. birds) is not without uncertainty. There are physiological differences between mammalian reproduction and other terrestrial vertebrates. The avian reproduction data gap evident for propylene oxide represents a possible significant source of uncertainty. Similarly, the reactive alkylating nature of propylene oxide, the potential for tissue damage from this alkylation, and the importance of amphibian skin as a respiratory organ not encountered in other terrestrial vertebrates, suggests that extrapolation of mammalian and avian risk conclusions to terrestrial phase amphibians for propylene oxide is uncertain.

The Agency has not established levels of concern for interpreting risk quotients for terrestrial invertebrate risk assessment. However, the exposure modeling conducted in the risk assessment shows air concentrations of propylene oxide to be well below effects levels determined for terrestrial arthropods. Consequently, the risk assessment concludes no risks of concern for terrestrial invertebrates.

Acute risks to fish and aquatic invertebrates do not appear to be of concern based on a first approximation analysis of possible water concentrations compared with available acute toxicity data. Estimations of propylene oxide concentrations in water used in the risk assessment are based on very conservative exposure assumptions. The conservative nature of these exposure predictions enhances the confidence of the no risk conclusion. There is a lack of chronic effects data for propylene oxide to aquatic animals. However, the physical/chemical properties of the gas suggest that little opportunity of anything but short term exposures exist in the aquatic environment. Therefore, chronic effects to fish and aquatic invertebrates are not expected.

Taxonomic Groups for which Risk is Assumed to be of Concern from Propoxide 892 Because of a Lack of Information

Propylene oxide is a highly reactive compound with the potential to alkylate bio-molecules on contact. Little can be said for risk conclusions regarding acute effects to aquatic and terrestrial plants beyond this statement, because no data are available to establish effects measures for these taxa. In the absence of such data, and given the reactivity of propylene oxide with a variety of bio-molecules, risks to plants cannot be precluded. The data gaps regarding effects of propylene oxide on terrestrial and aquatic are therefore significant from a risk assessment standpoint.

Environmental Fate and Effects Data Requirements

It should be noted that the entire suite of fate and effects studies described under the 40 *CFR* data requirements have not been submitted by the registrant (see tables below). This was presumably the result of consideration of only the indoor use patterns. To bring the risk assessment to its present state of completion, EFED has turned to publicly available physical/chemical property and effects information. The result of the lack of this environmental fate and effects information is a diminished confidence in the conclusions of the ecological risk assessment for propylene oxide as labeled for the Propoxide 892 product. The significance of a lack of reproduction effects testing with birds and any effects testing with terrestrial and aquatic plants is noted in the risk assessment.

Environmental Fate Data Requirements

835.2120	161-1	Hydrolysis	No	No Data	No Data
835.2240	161-2	Photodegradation - Water	No	No Data	No Data
835.2410	161-3	Photodegradation - Soil	No	No Data	No Data
835.4100	162-1	Aerobic Soil Metabolism	No	No Data	No Data
835.4200	162-2	Anaerobic Soil Metabolism	No	No Data	No Data
835.4400	162-3	Anaerobic Aquatic Metabolism	No	No Data	No Data
835.4300	162-4	Aerobic Aquatic Metabolism	No	No Data	No Data
835.1240	163-1	Leaching & Adsorption/ Desorption	No	No Data	No Data
835.1410	163-2	Laboratory Volatilization	No	No Data	No Data
835.6100	164-1	Terrestrial Field Dissipation	No	No Data	No Data
--	165-4	Bioaccumulation in Fish	No	No Data	No Data

Ecological Effects Data Requirements

850.2100	71-1	Avian Acute Oral Toxicity	No	No Data	No Data
850.2200	71-2	Avian Dietary Toxicity	No	No Data	No Data
	71-3	Wild Mammal Toxicity	No	No Data	No Data
850.2300	71-4	Avian Reproduction	No	No Data	No Data
850.1075	72-1	Fish Toxicity	No	No Data	No Data
850.1010	72-2	Invertebrate Acute Daphnid Toxicity	No	No Data	No Data
850.1075	72-3	Estuarine/Marine Toxicity	No	No data	No Data
850.1400	72-4	Aquatic Organism Early Life Stage	No	No Data	No Data
850.1400	72-5	Life Cycle Fish	No	No Data	No Data
850.4100	122-1a	Seedling Emergence	No	No Data	No Data
850.4150	122-1b	Vegetative Vigor	No	No Data	No Data
850.4400	122-2	Aquatic Plant Growth	No	No Data	No Data
850.3020	141-1	Honey Bee Acute Contact	No	No Data	No Data

United States Environmental Protection Agency

Office of Prevention, Pesticides, and Toxic Substances

Environmental Fate and Ecological Risk Assessment for the Reregistration of Propylene Oxide

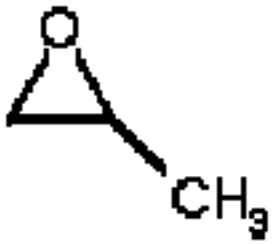


Table of Contents

I. **EXECUTIVE SUMMARY**

A. Stressors and Use Characterization

This risk assessment comprises the Environmental Fate and Ecological Effects Division's science chapter for the Reregistration Eligibility Document for Propylene Oxide. Propylene oxide, a gas, is commonly used as a fumigant for the control of microbial and arthropod pests in stored commodities. The majority of use sites are considered to be indoors such as large warehouses. For these indoor uses, propylene oxide exposure to the environment has been considered to be inconsequential and no environmental fate or effects data have been required. **There is no concern for adverse effects to terrestrial or aquatic organisms from these indoor uses.**

The Special Review and Reregistration Division requested that the risk assessment include a consideration of the Propoxide 892 labeled product. Propoxide 892 is an 8 percent propylene oxide product that includes a number of commodity uses on cosmetic articles, gums, ores, packaging, pigments, pharmaceutical materials, discarded nut shells prior to disposal, shipping containers, processed species, cocoa, cocoa beans, and in shell processed nutmeats (excluding peanuts). Dried fruit (figs, prunes, and raisins) are potential new uses for the product as well and though not currently on the label, they have been included as part the overall assessment of risks for propylene oxide. The label for Propoxide 892 indicates that application may be made to trailers, containers, rail cars, tarped materials and tents. These uses as described on the Propoxide 892 label, unlike those traditionally associated with propylene oxide use, do not involve permanent structures and are not "indoor" in the usual interpretation for pesticide uses. It is believed that fugitive emissions of propylene oxide from these non-indoor uses of Propoxide 892 may potentially be of environmental significance and the analysis of the potential risks of these releases is the principal subject of the risk assessment.

B. Fate

As late as 1990, environmental fate and effects data were not required for propylene oxide because the uses of the gas at that time were considered to be indoor uses. However, in light of the Propoxide 892 label and its indicated non-indoor use sites, a re-evaluation of available information suggests a number of environmental fate and effects data gaps. For example, no registrant submitted data are available for any of the 40 CFR Section 158 requirements for environmental fate and effects. The limited information on propylene oxide suggests that the gas is highly soluble in water, is of low affinity for organic carbon, and is not likely to bioconcentrate in biota. While substantial environmental fate data gaps exist, the physical chemical properties of the gas that are available from other information sources have been useful in evaluating, to a limited extent, the exposure of terrestrial and aquatic organisms to release of the gas to the atmosphere.

C. Effects

Available propylene oxide effects data are limited for many taxa. Adequate effects data are available for non-target mammals and that information has been applied to the evaluation of acute effects to other terrestrial vertebrates (birds, reptiles and terrestrial amphibians). ECOTOX has provided additional information on acute effects to fish and terrestrial invertebrates. There is a complete lack of effects data for aquatic invertebrates, though data are available for the close chemical analog, ethylene oxide (data used as a surrogate for propylene oxide). No data are available for aquatic and terrestrial plants. The strong alkylating nature of propylene oxide suggests that exposure to the gas can produce effects at the bio-molecular level and this may be as applicable to plants as well as other organisms. Available data cannot preclude the potential concern that propylene oxide may pose risks to terrestrial and aquatic plants.

D. Risk Conclusions

Taxonomic Groups for Which Risks are Not a Concern for Propoxide 892

The results of the risk assessment indicate that there are likely no concerns for acute lethality or reproduction impairment in terrestrial mammals. Fugitive emissions of propylene oxide to air surrounding a treated area, as predicted using the Health Effects Division modeling tool PERFUM, are well below acute lethal and reproduction concern levels for mammals. Analysis of other lines of evidence, including relative inhalation rates for birds and reptiles, suggest that gas exposure and so acute lethal inhalation risks for birds, reptiles, and terrestrial phase amphibians would not be any greater than those predicted for mammals. While the risk assessment has used mammalian risk results to conclude no risks for other terrestrial vertebrates (birds and reptiles), this conclusion is made with considerable uncertainty because of obvious differences between reproduction in mammals and other terrestrial vertebrates. The avian reproduction data gap evident for propylene oxide represents a possible significant source of uncertainty. Similarly, given the reactive alkylating nature of propylene oxide, the potential for tissue damage from this alkylation, and the importance of amphibian skin as a respiratory organ not encountered in other terrestrial vertebrates, suggests that extrapolation of mammalian and avian risk conclusions to terrestrial phase amphibians in this particular situation is uncertain.

No Agency-established level of concern for interpretation of risk quotients is available for terrestrial invertebrate risk assessment. However, the exposure modeling conducted in the risk assessment shows air concentrations of propylene oxide to be well below effects levels measured in terrestrial arthropods.

Acute risks to fish and aquatic invertebrates do not appear to be of concern based on a first approximation analysis of possible water concentrations compared with available acute toxicity data. The fact that estimations of propylene oxide in water are based on very conservative exposure assumptions enhances the confidence of this conclusion. Although there is a lack of chronic effects data for propylene oxide, the

physical/chemical properties of the gas suggest that little opportunity for anything but short term exposures exist in the aquatic environment. Therefore, chronic effects to fish and aquatic invertebrates are not expected.

Taxonomic Groups for which Risk is Assumed to be of Concern from Propoxide 892 Because of a Lack of Information

Propylene oxide is a highly reactive compound with the potential to alkylate bio-molecules on contact. Little can be said for risk conclusions regarding acute effects to aquatic and terrestrial plants beyond this statement. No effects data are available to establish effects measures for the taxa. There is insufficient information to preclude a presumption of acute risk to these organisms. The data gaps associated with propylene oxide effects on terrestrial and aquatic plants is significant in this regard.

Endangered Species Conclusions for Propoxide 892

The following table summarizes the potential concerns for direct and indirect adverse effects to federally-listed threatened or endangered plants and animals (listed species).

Listed Taxon	Direct Effects	Indirect Effects
Terrestrial and semi-aquatic plants - monocots	Yes[1]	No
Terrestrial and semi-aquatic plants - dicots	Yes[1]	No
Terrestrial invertebrates	No[2]	Yes[3]
Birds	No[2]	Yes[3,4]
Terrestrial phase amphibians	No[2]	Yes[3,4]
Reptiles	No[2]	Yes[3]
Mammals	No[2]	Yes[3,4]
Aquatic vascular plants	Yes[1]	No
Freshwater fish	No[2]	Yes[3,4]
Aquatic phase amphibians	No[2]	Yes[3,4]
Freshwater crustaceans	No[2]	Yes[3,4]
Mollusks	No[2]	Yes[3,4]
Marine/estuarine fish	No[2]	Yes[4]
Marine/estuarine invertebrates	No[2]	Yes[3,4]

[1] The alkylating nature of propylene oxide suggests that adverse effects to organism tissues are possible. No data are available to quantify at what level of exposure such effects would be expressed. Therefore this conclusion is the product of a data limitation and could change if effects data were made available.
[2] Environmental releases of propylene oxide are expected to be below levels known to cause adverse effects.
[3] There is a potential for direct effects on terrestrial plants (conclusion based on data limitations), which is a concern for indirect effects on animal species dependent upon plants.
[4] There is a potential for direct effects on aquatic plants (conclusion based on data limitations), which is a concern for indirect effects on animal species dependent upon these plants.

Unlike crop applications of pesticides, there is a paucity of information available to the risk assessor concerning locations of propylene use consistent with the Propoxide 892 label. Rail cars, infield chambers, tarped materials, and treatment tents may be located

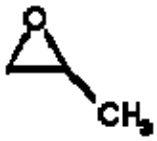
anywhere. Before a list of potentially affected listed species can be assembled, additional information regarding potential locations of Propoxide 892 use would be necessary.

II. PROBLEM FORMULATION

A. Chemical Stressors Considered in the Risk Assessment

This risk assessment considers propylene oxide gas. Propylene oxide is a highly reactive alkylating agent and electrophilic substance. The epoxide moiety reacts with cellular macromolecules such as RNA, DNA and proteins.

The structure of propylene oxide is as follows:



B. Use Characterization

In accordance with Office of Pesticide Programs Policy (40 *CFR* Sections158.290, 490, and 540), indoor pesticides involving substances of a gaseous, highly volatile liquid or highly reactive solid do not require submission of environmental fate data, or data on effects to non-target terrestrial wildlife, aquatic organisms, or plants. Presumably these data requirement exclusions are based on an assumption that exposures to non-target wildlife, aquatic organisms, and plants from such labeled indoor uses of such materials are negligible. Propylene Oxide is a gaseous material. The Agency has maintained that exposure to wildlife and water resources from the exclusive registration of propylene oxide for indoor food and nonfood uses would be negligible. Up to now, the Agency has not required or received environmental fate and ecological effects data for propylene oxide. In the November 28, 1990 "List B Review for Propylene Oxide," EFED wrote of environmental fate data that "(t)here are no significant issues at this time. The only required information, chemical identity (160-5), will be submitted sometime in the future and reviewed during Phase V." The chemical identity study is not reviewed by EFED. In regard to the ecological effects data, EFED wrote in 1990 that "(d)ata is (*sic*) not required for this chemical because it is a highly volatile liquid used indoors." These uses are not considered to have complete exposure pathways to ecological receptors and are not analyzed in this risk assessment

Propoxide 892 is a propylene oxide product for which a label has been submitted to the Agency for consideration. This product has proposed uses that potentially are not consistent with indoor permanent structures. This product can be used on cosmetic articles, gums, ores, packaging, pigments, pharmaceutical materials, discarded nut shells prior to disposal, shipping containers, processed species, cocoa, cocoa beans, and in shell processed nutmeats (excluding peanuts). Dried fruit (figs, prunes, and raisins) are potential new uses for the produce and though not currently on the label, they have been included as part the overall assessment of risks for propylene oxide. Importantly, many of these uses involve application of up to 2.8 lbs of propylene oxide per100 ft^3 to trailers,

containers, rail cars, tarped materials and tents. These uses, unlike those traditionally ascribed to propylene oxide use, do not involve permanent structures and are not "indoor" in the classical interpretation for pesticide use. Consequently, fugitive emissions of propylene from these non-permanent structure uses may potentially be significant and are the primary subject of this risk assessment.

One final use appearing on the Propoxide 892 label is a birdseed use. This use would appear to present a possible exposure to wildlife through propylene oxide resides in the birdseed. However, the Special Review and Reregistration Division (SRRD) has indicated that this will no longer be a supported use (personal communication Susan Bartow, SRRD, January 27, 2006). Therefore the birdseed use is not a subject of this risk assessment.

C. Ecological Receptors Considered in this Risk Assessment

The screening level risk assessment approaches the analysis for adverse effects through the use of broad plant and animal taxonomic groups including:

- Birds (also used as surrogate for terrestrial-phase amphibians and reptiles),
- Mammals,
- Terrestrial plants,
- Freshwater fish (also used as a surrogate for aquatic phase amphibians),
- Freshwater invertebrates (including sediment-dwelling species),
- Algae and vascular aquatic plants

Because of known effects of propylene oxide to arthropods pests, the risks of the gas to non-target terrestrial invertebrates will also be evaluated, but without the benefit of Agency established concern thresholds to aid in interpretation of assessment results. It should be noted that data limitations in this risk assessment preclude a fully quantitative analysis of fish and aquatic invertebrates, and prevent quantitative analysis of risks to plants.

D. Exposure Pathways Considered for Terrestrial Organisms

For the purposes of this risk assessment, terrestrial non-target organisms are assumed to occupy areas immediately adjacent to treatment sites. For a gaseous pesticide released from a treatment chamber, tarped material, or rail car the terrestrial animal exposure pathways considered most likely to occur include inhalation of gas and dermal absorption of the gas. Given the low octanol/water partitioning coefficient of propylene oxide (K_{ow} 0.03 from Hazardous Substances Databank, HSDB 2005, http://toxnet.nlm.nih.gov) it is unlikely that dermal absorption is a significant pathway for most terrestrial animals (possible exceptions are amphibians, see Risk Characterization). Similarly, the low octanol water partitioning coefficient and high vapor pressure (538 mm Hg HSDB 2005, http://toxnet.nlm.nih.gov) suggest that propylene oxide contamination of dietary materials for terrestrial wildlife is very unlikely. On that basis this risk assessment for terrestrial animals will focus on the inhalation pathway.

For terrestrial plants, contact with propylene oxide gas is assumed to be capable of producing effects to the external layer of plant tissues, to react with the cuticle, and, through penetration of the plant through the spiracles, produce effects to internal plant tissues. Because there are no quantitative effects data available to the Agency, quantification of exposure levels of propylene oxide to plants are not included in this risk assessment.

E. Exposure Pathways Considered for Aquatic Organisms

The most likely pathways for propylene oxide to enter aquatic systems may include gas in solution as it contacts surface waters and introduction of propylene oxide to surface waters during precipitation events where the gas dissolves in the precipitation. The estimated Henry's Law constant for propylene oxide is 6.96 X 10^{-5} atm-cu m/mole (HSDB 2005, http://toxnet.nlm.nih.gov) suggesting that the gas may dissolve in water from the atmospheric phase.

The low octanol water partitioning coefficient and high vapor pressure suggest that adsorption to soil surfaces and subsequent transport to surface waters with runoff would be very limited.

F. Conceptual Model

Risk Hypothesis

The risk hypothesis for this screening-level risk assessment is as follows:

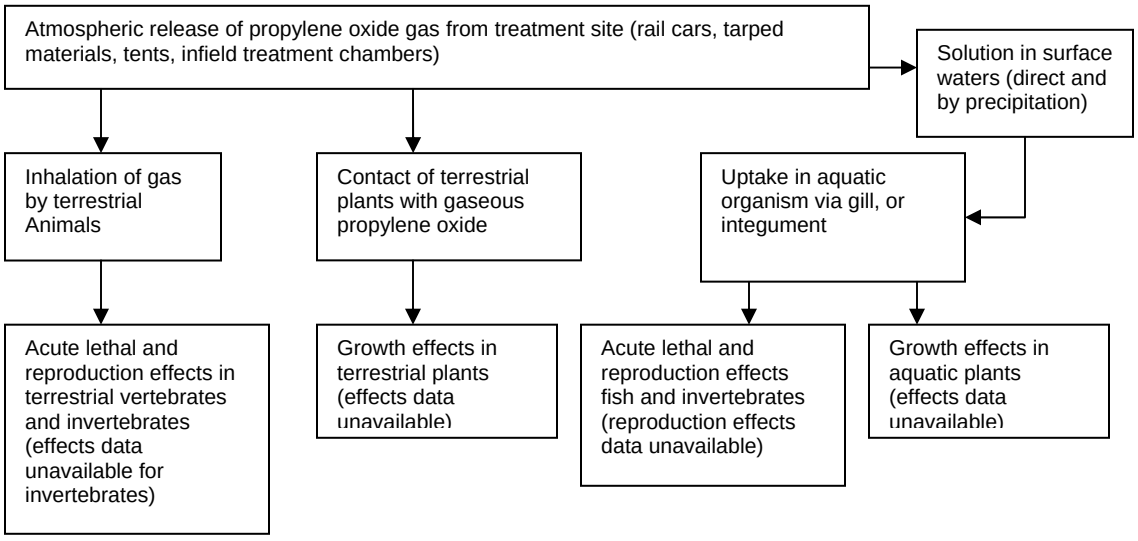
Propylene oxide, used in accordance with the Propoxide 892 label, results in adverse effects upon survival and reproduction of non-target terrestrial and aquatic organisms.

Testable elements of this hypothesis are confined by effects data and exposure methods to inhalation risks to terrestrial vertebrates (quantitatively evaluated), terrestrial invertebrates (quantitatively evaluated but without the aid of Agency policy concern levels) and fish (qualitatively evaluated).

Because of a lack of effects data, it is not possible to use available techniques to evaluate the risk potential of propylene oxide to plants or aquatic invertebrates. Therefore, available methods and information cannot be used to refute the above hypothesis for these taxa.

Conceptual Diagram

The following is a conceptual plan diagram depicting sources of exposure, potential receptors and adverse effects from the supported uses of propylene associated with Propoxide 892



G. Analysis Plan

Preliminary Identification of Data Gaps and Methods

No environmental fate or effects data consistent with studies outlined in 40 CFR have been submitted for propylene oxide.

The Agency has conducted an ECOTOX search, which yielded effects data for terrestrial arthropods and fish. Effects data for mammals are available through submissions in compliance with human health risk assessment data requirements. For the purposes of this risk assessment and the exposure routes evaluated, available effects data for propylene oxide in mammals are used as a surrogate for all terrestrial vertebrates. Risks to terrestrial invertebrates are assessed using the target arthropod pest effects data, though the Agency has no policy for establishing thresholds of concern at this time. Available fish effects data address acute lethal responses and are used to assess risk to fish and aquatic phase amphibians. The gaseous nature of propylene oxide, coupled with its potential to rapidly volatilize from water, suggests that chronic effects would not be an issue for aquatic systems. The lack of any effects data on aquatic invertebrates and plants precludes even a qualitative discussion of risks to these taxa.

The Agency has turned to other sources of physical chemical data to obtain information on likely properties important to an analysis of propylene oxide gas environmental fate and transport.

Assessment Endpoints

Assessment endpoints for this screening-level ecological risk assessment are reduced survival, reproductive output, and growth of individual organisms. These assessment endpoints, while measured at the individual level, provide insight about risks at higher

levels of biological organization (e.g., populations). It is assumed that toxicants do not affect populations or communities except through the impact on the individuals comprising the population or community and the demographics of birth, growth, and death that govern population dynamics. The number of individuals within a population change (intrinsic rate of increase) primarily because of births (fecundity) and deaths (survival) and secondarily from migration in and out of a specific area. If effects on the survival and reproduction of individuals are limited, it is assumed that risks at the population level from such effects will be of minor consequence. However, as the risk of reductions in survival and/or reproduction rates increases, so does the potential risk to populations.

Exposure Measures

Exposures estimated in the screening-level risk assessment for non-target organisms are not species specific.. Because of the inhalation pathway of concern for this risk assessment and the lack of a standard peer reviewed gaseous exposure model in EFED, inhalation exposure for terrestrial animals was evaluated using a method developed by the Health Effects Division (HED). The HED approach for evaluating the human by-stander risks of fugitive emissions of propylene oxide makes use of the PERFUM model. OPP is coordinating with EPA's Office of Air, the CDPR, and others to evaluate and implement the PERFUM modeling approach based on Industrial Source Complex Short Term model (ISCST3), which incorporates actual meteorological data and refined flux inputs that are based on available data and other information. PERFUM allows users to develop an understanding of the distributions of potential exposures around the perimeter of a treatment facility or structure and thus more fully characterize the range of risks impacting organisms from commodity treatments. PERFUM V2.1.2 is available at http://www.sciences.com/perfum/index.html. For comparative purposes, PERFUM V1.1 is available at http://www.epa.gov/opphed01/models/fumigant/ . ISCST3 is an integral part of the PERFUM model (for further details see http://www.epa.gov/scipoly/sap/2004/index.htm). The basic physics and code of ISCST3 remain unchanged. PERFUM essentially provides ISCST3 with daily meteorological data over the selected 5 years as well as user defined flux inputs. PERFUM then uses this information to create distributional outputs for receptor locations around the treated structure. For the purposes of this risk assessment, EFED relied on the conservative 99.9 percentile estimate of propylene concentration with distance over a four hour averaging time. Further discussion of the PERFUM model inputs and scenario are described in the Exposure Assessment portion of this document.

The Agency does not have a standard peer-reviewed method to estimate aquatic exposures for gaseous materials released to the atmosphere. or a model to estimate such water concentrations with any certainty. Instead, the risk assessment makes use of available physical/chemical data for propylene oxide and estimates a maximum theoretical dissolved water concentration of the gas based on assumptions of a two equal compartment equilibrium model. The 99.9 percentile four hour averaged air emissions information from PERFUM serve as the source of air concentration in this approach.

Effects Measures

The screening-level risk assessment typically relies on a suite of toxicity studies performed on a limited number of organisms from broad taxonomic groups. As indicated earlier, effects data were only available for mammals, some terrestrial invertebrates, and fish. Mammalian inhalation toxicity endpoints were available and applicable to the performance of an inhalation exposure pathway risk assessment for mammals. Also indicated earlier, mammalian effects endpoints (acute lethality and chronic reproduction impairment) are being used as surrogates for all terrestrial vertebrates because there are no effects data (confirmed by a search of the ECOTOX database) for other forms of terrestrial vertebrate wildlife (e.g., birds, reptiles, and terrestrial phase amphibians). The effects measures employed for terrestrial vertebrates for this risk assessment include the most sensitive acute inhalation median lethal concentration (LC_{50}) and the rat no observed adverse effect concentration (NOAEC) for reproduction effects.

The ECOTOX database provides a number of studies of propylene oxide effects on terrestrial invertebrates. While these data are for target arthropod pests, the lowest four hour LC_{50} from these species is used as the effect measurement endpoint for terrestrial invertebrates.

Limited data are available for propylene oxide effects on aquatic organisms and are confined to effects data on fish as confirmed from a search of the ECOTOX database. The acute effects measure for fish, and as a surrogate for aquatic phase amphibians, is the median lethal concentration (LC_{50}) for the most sensitive fish species tested.

Measures of effects have not been quantified for plants and aquatic invertebrates and are not included in this risk assessment because there are no effects data available to the Agency. Given the potential for propylene oxide to react with bio-molecules, the potential for propylene oxide to produce adverse effects in these taxa cannot be dismissed.

IV. ANALYSIS

A. Environmental Fate and Transport Assessment

No guideline data have been submitted to the Agency that allow for an assessment of the biotic and abiotic degradation processes for propylene oxide. Available data from the Hazardous Substances Databank (HSDB 2005, http://toxnet.nlm.nih.gov) include water solubility (590g/l), vapor pressure (538 mm Hg), octanol/water partitioning coefficient (K_{ow} 0.03), and Henry's Law constant (estimated 6.96 X 10^{-5} atm-cu m/mole). The data suggest that propylene oxide predominates in a gaseous state and is highly soluble in water. The low octanol/water partition coefficient suggests little affinity for organic carbon in soils or sediment and a low potential for bioconcentration in organisms. HSDB (2005, http://toxnet.nlm.nih.gov) also reports that propylene oxide, present at 100 mg/l,

reached 95% of its theoretical BOD in 3 weeks using an activated sludge at 30 mg/l by the Japanese MITI test, suggesting that biodegradation is possible.

B. Terrestrial Exposure Assessment

Terrestrial wildlife exposure estimates, in terms of air concentration associated with fugitive emissions for treated rail cars, in-field treatment chambers, and tarped materials were calculated using the HED PERFUM Model. HED maintains that the PERFUM provides the most refined, scientifically defensible approach for calculating and characterizing risks associated with bystanders to commodity fumigation operations because it incorporates actual weather data and links flux profiles to the appropriate time of day. It also uses as its core processor the proven technology of ISCST3.

The PERFUM model was run for a 5000 ft^3 treatment chamber (the maximum size considered in the HED risk assessment and believed consistent with the in-field chambers, rail cars and tarped operations specified on the Propoxide 892 label). Propylene treatment rate was modeled as 2.8 lbs/100 ft^3. One hundred percent of the treatment material was conservatively assumed available for release from the treatment enclosure, and that release was conservatively assumed to occur without an emission stack, essentially a simple open door. Three meteorological files encompassing 5 years of data provided the necessary wind inputs for the model runs. These included Ventura, California (1995-1999); Flint, Michigan (1987-1991); and Tallahassee, Florida (1988-1992). The model was run to simulate six release periods each modeling day with the air concentration estimate being a four-hour average for each period based on a highly conservative assumption of a release occurring each hour of each release period.

The PERFUM model calculates a distribution of daily isopleths of air concentration radiating out from the propylene oxide treatment source for each of the six daily treatment periods. These are then compared with effects thresholds expressed in terms of air concentration ("air concentrations of concern"). The model output is the percentile distances at which air concentrations reach the defined effects thresholds. As a consequence, PERFUM model outputs for air concentration are not specifically presented in this section of the risk assessment but are internal to the computations of the PERFUM model.

C. Effects Assessment

An ECOTOX database search has been conducted for propylene oxide. No toxicity data are available from either this database search or from registrant submissions for birds, aquatic invertebrates, and aquatic and terrestrial plants. Data are available for mammals, terrestrial invertebrates and fish. These are summarized below.

Mammalian Effects

Data on inhalation exposure effects to mammals are available from HED. These include a rat 4-hour acute LD50 (7697 mg/m^3) and a mouse 4-hour acute LD50 (2420 mg/m^3). In

keeping with the screening-level risk assessment approach to use the most sensitive species tested, the mouse LD_{50} serves as the acute toxicity threshold for terrestrial vertebrates in this risk assessment.

In a two-generation reproduction study (MRID 45292701), propylene oxide (30215 III, >99%, a.i.) vapor was administered to groups of 30 male and 30 female F0 and F1 Fischer 344 rats by inhalation at chamber concentrations of 0, 30, 100, or 300 ppm. Each group was exposed to room air (controls) or propylene oxide vapor for 6 hours/day, 5 days/week for 14 weeks (F0) or 17 weeks (F1) during the pre-mating period and for 6 hour/day, 7 days/week during the mating, gestation, and lactation periods. The F1 pups selected to parent the F2 generation were exposed to room air or the same concentrations of propylene oxide vapor as their parents. No treatment-related deaths, clinical signs, or gross lesions were observed in rats exposed to any concentration of propylene oxide vapor during pre-mating and post-mating periods for adult F0 or F1 males or during the pre-mating period for adult F0 or F1 females. Exposure to concentrations up to 300 ppm had no exposure-related effect on reproductive performance (mating, fertility or gestation indices) of the adults or on offspring parameters [clinical signs, mean liter size at any time during lactation, survival indices (live birth, viability, or lactation), pup weights or gross and microscopic findings in weanlings. The reproductive NOAEL is 300 ppm or 720 mg/m^3. The reproductive LOAEL is not established. The NOAEL from this study served as the reproduction effects threshold for terrestrial vertebrates for this risk assessment.

Terrestrial Invertebrate Effects

The ECOTOX database provides information on a number of propylene oxide acute lethal endpoints for arthropod pest species. The toxicity data are available for the four hour exposure interval modeled in this risk assessment.

Species	4-hour LD50 (mg/m3 air)	Reference
Rust-red flour beetle *Tribolium castaneum*	44055	Navarro et al (2004)
Flat bark beetle *Oryzaephilus surinamensis*	2100-5700*	Isikber et al. (2004)
Rust-red flour beetle *Tribolium castaneum*	5100-9800*	Isikber et al. (2004)
Indian meal moth *Plodia interpunctella*	1900-7700*	Isikber et al. (2004)
Almond moth *Ephistia cautella*	1600-7200*	Isikber et al. (2004)

* The range of values is based on test organism life stages

The most sensitive LC50 from the list (1600 mg/m^3) serves as the effects measure for terrestrial invertebrates for the risk assessment.

Terrestrial Plant Effects

No data for airborne propylene oxide effects associated with terrestrial plants are available.

Fish Effects

No data are available for propylene oxide from registrant submissions. However, the following data for acute effects are available from a search of the ECOTOX database.

Species	96-hour LC_{50} (mg/L)	Reference
bluegill *Lepomis macrochirus*	215	Crews 1974
mosquitofish *Gambusia affinis*	141	Crews 1974
striped mullet *Mugil cephalus*	89	Crews 1974

The most sensitive freshwater fish (mosquitofish) and estuarine/marine fish (striped mullet) yield the most sensitive effects endpoints for these taxa. Because there is no established screening-level risk assessment method to derive estimated environmental concentrations from atmospheric releases of gases, risks to fish are discussed in qualitative terms in the risk characterization based on first approximations of exposure.

Aquatic Invertebrate Effects

No data for propylene oxide are available for aquatic invertebrates. However, ECOTOX does have data for the close chemical analogue ethylene oxide. These are summarized below.

Species	48-hour LC_{50} (mg/L)	Reference
Brine shrimp *Artemia sp.*	490-1000	Conway et al.(1983)
Daphnia magna	137 – 300	Conway et al.(1983)

In the absence of other available data, the lowest values for the above endpoints are the effects measures for acute effects to freshwater (*Daphnia magna* 137 mg/L) and estuarine/marine invertebrates (Brine shrimp 490 mg/L)

V. RISK CHARACTERIZATION

A. Terrestrial Vertebrate Risk Estimation

Normally, the exposure assessment conducted for the screening-level risk assessment produces a suite of expected environmental concentrations (EECs, the exposure measurement endpoint). The ratio of EECs to the acute and chronic effects thresholds constitute the risk quotients. These risk quotients serve as the integration of exposure and effects measurement endpoints and are then compared to the Agency's stated levels of concern (LOCs), which are the policy interpretation of risk quotients.

Contrary to this normal risk quotient process for risk estimation routinely performed in screening-level risk assessments, this risk assessment uses a modified approach dictated by the computational environment associated with the PERFUM model. In this modified approach, "air concentrations of concern" serve as in input to the PERFUM model. The model then compares these concentrations of concern to the calculated distributions of estimated air concentrations to estimate a distance from the pesticide release source where estimated air concentrations are equal to the "air concentration of concern".

To establish the "air concentrations of concern", this risk assessment uses the effects measurement endpoints (acute and chronic) established for terrestrial vertebrate wildlife and modifies them by multiplying the endpoints by the acute and chronic LOCs established by the Agency for non-listed and Federally-listed threatened and endangered species (listed species). In this manner, the PERFUM model can be run to establish the distance for propylene oxide use to which estimated propylene oxide concentrations in air meet or exceed concentrations of concern. The following table presents the acute and chronic air concentrations of concern for the PERFUM model.

Establishing Propylene Oxide Air Concentrations of Concern for Use in PERFUM Model

Risk Concern Level	Toxicity endpoint (mg/m^3)	LOC	Air Concentration of Concern (mg/m^3)*
Acute non-listed species	2420	0.5	1210
Acute listed species	2420	0.1	242
Chronic all species	720	1	720

*air concentration of concern = (toxicity endpoint)(LOC)

Because the acute listed species air concentration of concern is much lower than non-listed species acute concentration of concern and the chronic effects concentration of concern for all species, it was assumed that screening with the PERFUM model for the acute listed species air concentration of concern would provide a protective initial evaluation. If the PERFUM model predicted that air concentrations above this concern

level extended beyond the point of propylene oxide treatment, further analysis for the other air concentration concern levels would be performed.

Results of the PERFUM Model for Terrestrial Vertebrates

Results of the PERFUM model runs are presented in Appendix A for comparisons with the 242 mg/m^3 air concentration of concern. Because the model output for all scenarios predicts that 4-hour average air concentrations will be below 242 mg/m^3 at all distances from the point of release , all other air concentration of concern (720 and 1210 mg/m^3) will not be exceeded either. Therefore, no air concentrations beyond the treatment point are expected to exceed levels of concern for inhalation by any listed or non-listed terrestrial vertebrates.

B. Qualitative Discussion of Risks to Terrestrial Invertebrates

The PERFUM modeling conducted for terrestrial vertebrate exposure indicated that air concentrations at the release point of propylene oxide use will not exceed 242 mg/m^3**.** Although the Agency has not established RQ levels of concern for terrestrial invertebrates, it is reasonable to expect that all air concentrations are well below the most sensitive terrestrial invertebrate LC_{50} (1600 mg/m^3) by close to if not more than an order of magnitude.

C. Qualitative Discussion of Risks to Aquatic Organisms

While toxicity data are available for freshwater and estuarine/marine fish, no other effects data are available for aquatic invertebrates or plants. Additionally, a reviewed method for quantitatively estimating water concentrations of gases associated with atmospheric relies is unavailable. Consequently, definitive calculations of risk quotients for aquatic organisms cannot be made at this time. However, using a simplifying assumption of equal environmental compartment volumes (air and water) and a condition of equilibrium, it is possible to make some inferences on the likelihood that propylene oxide would be of toxicological concern.

Using the Henry's Law constant, vapor pressure, and water solubility of propylene oxide it is possible to provide a coarse approximation of a water concentration for any given estimate of air concentration. To do so, it is necessary to assume that water and air compartments are in equilibrium and those compartments are finite and equivalent in volume. To investigate how such estimates inform conclusions regarding aquatic risk, EFED used the lowest air concentration of concern (242 mg/m^3) used in the PERFUM model predictions for wildlife inhalation exposure as follows:

(1) (242 mg/m^3)(m^3/1000 L) = 0.242 mg/L
(2) (0.242 mg/L)(22.4 L molar volume of atmosphere at standard temperature and pressure)= 5.4208 mg

(3) 5.4208 mg/58,058 mg/mole MW of propylene oxide = 9.33687E-05 moles

(4) P = nRT/V = ((9.33687 E-05 moles)(0.08314 bars L/moles K)(298 K))/22.4 L
= 1.0327128 E-04 bars
= 1.01928 E-04 atmospheres

(5) Estimated Water Concentration = Vapor Pressure/Henry's constant
= 1.01928 E-04 atm/6.96E-03 atm-m^3/mole
= 0.0146448 mole/m^3
= (0.0146448 mole/m^3)(m^3/1000L)
= 1.46448 E-5 moles/L
= (1.46448E-5 moles/L)(58,058 mg/mole)
= **0.8502 mg/L**

The resulting water concentration pf 0.8502 mg/L would be below both the lowest freshwater and estuarine/marine fish LC_{50} values available (141 mg/L for mosquitofish and 89 mg/L for striped mullet). The same water concentration would also be well (two or more orders of magnitude) below the lowest freshwater and estuarine/marine LC50 values available (*Daphnia magna* 137 mg/L, Brine shrimp 490 mg/L). Given that **all** the available PERFUM model run scenarios predict that air concentrations fall well below 242 mg/m^3 at any distance from the propylene oxide release point, it is reasonable to expect that propylene oxide use will not produce associated water concentrations adjacent to treatment areas in excess of the most sensitive fish and invertebrate acute toxicity endpoints. Furthermore, the water concentration estimate is very conservatively based on assumptions of equilibrium (a condition not likely to occur given the finite sources of propylene oxide and the changing wind conditions modeled in PERFUM) and finite/equivalent environmental compartments (in reality the atmosphere is effectively an infinite compartment). It is reasonable to expect that water concentrations will likely be orders of magnitude lower than predicted, suggesting no concern for effects on listed or non-listed fish.

Propylene oxide is a highly reactive compound with the potential to alkylate bio-molecules on contact. Little beyond this statement can be said for conclusions regarding the risk for effects to aquatic plants. No effects data are available to establish effects measures for this taxa. Therefore no comparisons of even first approximations of water concentrations of propylene oxide to effects measures can be made. There is insufficient information to preclude a presumption of acute risk to aquatic plants.

The physical/chemical properties of propylene oxide suggest that residence times in water will be short. Consequently, it is not likely that propylene oxide will remain in water long enough to raise concerns for chronic effects in aquatic organisms.

D. Uncertainties and Limitations in the Risk Assessment

Avian and Other Non-Mammalian Terrestrial Vertebrate Risks

The risk assessment for terrestrial mammals is used as a surrogate for assessing risks to birds, reptiles and terrestrial phase amphibians. It is likely that the risk assessment is

adequate to describe the external exposure (i.e., air concentrations) of each of these taxa to atmospheric propylene oxide. However reliance on mammalian toxicity endpoints for the effects portion of the assessment is not without uncertainty. Because respiration rates for each of the untested taxa differ from mammals, this may be manifested in differing patterns of sensitivity to a given air concentration of propylene oxide.

An allometric equation is available to estimate inhalation rates of non-passerine birds (USEPA 1993):

$$\text{Inhalation Rate (ml/min)} = 284(\text{body weight kg})^{0.77}$$

This equation can be compared to the allometric rate for inhalation in mammals (USEPA 1993):

$$\text{Inhalation Rate (ml/min)} = 379(\text{body weight kg})^{0.80}$$

The results of such a comparison is summarized in the table below for body weights of 20 50 500 and 1000 g animals.

Comparison of Inhalation Rates for Birds and Mammals

Body weight g	Avian Inhalation ml/min	Mammal Inhalation ml/min	Ratio of Birds to Mammals
20	13.97	16.58	0.84
50	28.28	34.50	0.82
500	166.5	217.68	0.76
1000	284	379	0.75

The comparison indicates that avian inhalation rates are lower than corresponding size mammals. This would suggest that for any given air concentration of propylene oxide, the amount inhaled over any given time would be greater for mammals than for birds. It is likely that propylene oxide, a strong alkylating agent, exerts acute through respiratory epithelium damage. If one assumes that the amount of damage is related to the mass of propylene oxide gas available for reaction with the epithelium then it would follow that mammals may be at a slightly greater risk for acute damage than birds. Therefore the mammal risk assessment for inhalation would be protective of acute effects in birds as well. A similar argument can be made for reptile inhalation risks as it is highly likely that the lower metabolic rates of cold-blooded taxa correspond to lower inhalation rates and therefore lower exposures at modeled air concentrations. The mechanism of action associated with reproduction effects in mammals is not likely linked to respiratory epithelium damage. It is likely a result of actual testing of avian species for either acute or reproduction effects would provide additional lines of evidence to address the uncertainty regarding equivalent propylene oxide sensitivity between mammals and birds.

Assumptions of Significance for Dermal Exposure to Terrestrial Wildlife

This risk assessment has assumed that dermal contact with gaseous propylene oxide does not constitute a significant source of exposure in birds and mammals. The logic for this

assumption is that the low K_{ow} suggests limited penetration across the skin of these organisms. For amphibians, this assumption is highly uncertain. The skin of amphibians is gas permeable and serves as a adjunct respiratory organ. The extent to which propylene oxide will either penetrate or adversely impact amphibian skin function for gaseous exchange is unknown.

E. Conclusions of Risk Assessment

Terrestrial Vertebrate Risks

As indicated in the results of the PERFUM model runs, no estimated air concentrations exceed the most sensitive air concentration of concern established for terrestrial vertebrates. Because this air concentration of concern was selected to be below acute and chronic LOCs for both listed and non-listed terrestrial vertebrates, it is concluded that risks to terrestrial vertebrates, from fugitive air emissions of propylene oxide from the non-indoor use sites of commodity treatment will not be of concern for either acute or chronic effects. There are adequate lines of evidence to refute the hypothesis that propylene oxide poses acute and chronic risk concerns to terrestrial mammals.

The risk assessment has relied upon toxicity endpoints derived from mammal testing as a surrogate for effects in other terrestrial vertebrates (birds, reptiles, and terrestrial phase amphibians). Analysis of other lines of evidence, including relative inhalation rates for birds and reptiles, suggest that a conclusion of no acute risk to mammals would be protective of birds and reptiles. There is a potential for propylene oxide to produce tissue damage from alkylation upon chemical contact with amphibian skin. Amphibian skin is an important respiratory organ not encountered in other terrestrial vertebrates. This suggests that extrapolation of mammal, bird, and reptile risk conclusions to terrestrial phase amphibians, is not without some uncertainty in this particular situation,.

It is uncertain whether risk findings for reproduction effects in mammals are applicable to other terrestrial vertebrates with any certainty because of differences between the mammalian reproduction and other terrestrial vertebrates. The avian reproduction data gap evident for propylene oxide represents a possible significant source of uncertainty.

Terrestrial Invertebrate Risks

The Agency currently does not have a policy tool such as an LOC for interpreting exposure/effects ratios for terrestrial invertebrates. Because the PERFUM modeling performed for vertebrate risk assessment shows that release concentrations of propylene oxide from Propoxide 892 use are well below the most sensitive toxicity value for terrestrial invertebrates by at least a factor of 8x and more likely at least an order of magnitude it is reasonable to expect that terrestrial invertebrate risks are not a concern. If one were to use the terrestrial animal LOCs already established for wildlife taxa, it is likely that the comparisons of estimated air concentrations with terrestrial invertebrate effects thresholds (the RQ) would be below the accepted 0.1 value for listed species.

Fish and Aquatic Invertebrate Risks

There appears to be adequate information to refute the hypothesis of propylene oxide risks to fish.

Available information suggests that risks to freshwater and estuarine/marine fish and invertebrates are not of concern. The first approximation water concentration, associated with the limits of estimated air concentrations at the point of release from the propylene oxide use site are below the most sensitive effects endpoints for fish. Furthermore, the modeled water concentrations are very conservative, perhaps by orders of magnitude, because they are based on assumptions of equilibrium and equal volume for all environmental compartments. Considering all lines of information, propylene oxide concentrations in water from the Propoxide 892 use are not expected to be of acute or chronic concern for listed and non-listed fish and aquatic phase amphibians.

Chronic risks to fish and invertebrates, though not quantitatively assessed in this risk assessment, are not likely to be of concern. The physical/chemical properties of propylene oxide suggest that water concentrations of the gas will quickly decline after the four hour release period modeled. This decline is assumed not to afford adequate exposure periods to elicit chronic effects.

F. Risks to Federally Listed Threatened and Endangered Species

Action Area

For listed species assessment purposes, the action area is considered to be the area affected directly or indirectly by the Federal action and not merely the immediate area involved in the action. At the initial screening-level, the risk assessment considers broadly described taxonomic groups and conservatively assumes that listed species within those broad groups are located on or adjacent to the treated site and aquatic organisms are assumed to be located in a surface water body adjacent to the treated site. The assessment also assumes that the listed species are located within an assumed area which has the relatively highest potential exposure to the pesticide, and that exposures are likely to decrease with distance from the treatment area.

If the assumptions associated with the screening-level action area result in RQs that are below the listed species LOCs, a "no effect" determination conclusion is made with respect to listed species in that taxa, and no further refinement of the action area is necessary. Furthermore, RQs below the listed species LOCs for a given taxonomic group indicate no concern for indirect effects upon listed species that depend upon the taxonomic group covered by the RQ as a resource. However, in situations where the screening assumptions lead to RQs in excess of the listed species LOCs for a given taxonomic group, a potential for a "may affect" conclusion exists and may be associated with direct effects on listed species belonging to that taxonomic group or may extend to indirect effects upon listed species that depend upon that taxonomic group as a resource.

In such cases, additional information on the biology of listed species, the locations of these species, and the locations of use sites could be considered to determine the extent to which screening assumptions regarding an action area apply to a particular listed organism. These subsequent refinement steps could consider how this information would impact the action area for a particular listed organism and may potentially include areas of exposure that are downwind and downstream of the pesticide use site.

Taxonomic Groups Potentially at Risk

The Level I screening assessment process for listed species uses the generic taxonomic group-based process to make inferences on direct effect concerns for listed species. The first iteration of reporting the results of the Level I screening is a listing of pesticide use sites and taxonomic groups for which RQ calculations reveal values that meet or exceed the listed species LOCs. An evaluation of risk conclusions for each taxonomic group is presented below.

Listed Taxon	**Direct Effects**	**Indirect Effects**
Terrestrial and semi-aquatic plants - monocots	Yes[1]	No
Terrestrial and semi-aquatic plants - dicots	Yes[1]	No
Terrestrial invertebrates	No[2]	Yes[3]
Birds	No[2]	Yes[3,4]
Terrestrial phase amphibians	No[2]	Yes[3,4]
Reptiles	No[2]	Yes[3]
Mammals	No[2]	Yes[3,4]
Aquatic vascular plants	Yes[1]	No
Freshwater fish	No[2]	Yes[3,4]
Aquatic phase amphibians	No[2]	Yes[3,4]
Freshwater crustaceans	No[2]	Yes[3,4]
Mollusks	Yes[1]	Yes[3,4]
Marine/estuarine fish	No[2]	Yes[4]
Marine/estuarine invertebrates	No[2]	Yes[3,4]

[1] The alkylating nature of propylene oxide suggests that adverse effects to organism tissues are possible. No data are available to quantify at what level of exposure such effects would be expressed. Therefore this conclusion is the product of a data limitation and could change if effects data were made available.
[2] Environmental releases of propylene oxide are expected to be below levels known to cause adverse effects.
[3] There is a potential for direct effects on terrestrial plants (conclusion based on data limitations), which is a concern for indirect effects on animal species dependent upon plants.
[4] There is a potential for direct effects on aquatic plants (conclusion based on data limitations), which is a concern for indirect effects on animal species dependent upon these plants.

VII. REFERENCES

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Appendix A
Propylene Oxide PERFUM Model Runs

README File from Contractor Regarding Propylene Oxide Modeling Runs

This CD contains the results of the PERFUM2 runs that were done for propylene oxide for three meteorological areas: Ventura, CA, Tallahassee, FL, and Flint, MI.

Under each met region, you will find two directories, one for each endpoint EFED desired analyzed: 1,210 mg/m3 and 242 mg/m3.

Under each of these directories, you will find two directories, one for 4-hour estimates where an emission occurred once every 4 hours and one for 4-hour estimates where an emission occurred every hour.

Under each of these directories, you will find 10 directories, one for each scenario modeled. These directories include: treatment and aeration from a building w/o a stack (treatment aeration no stack); aeration from a building with a stack 10 feet above the roof top (aeration min stack @ full exit velocity, ½ exit velocity, and 5% exit velocity); aeration from a building w/ a 50 foot portable stack attached (aeration portable stack @ full exit velocity, ½ exit velocity, and 5% exit velocity); and aeration from a building w/ a ventilation hose hooked to it (aeration ppq @ full exit velocity, ½ exit velocity, and 5% exit velocity). These are the same scenarios we used in prior modeling commodity fumigations for PPO.*(EFED comment: building w/o stack represents the most conservative scenario)*

Under each of these directories you will find 44 PERFUM2 files and 1 batch file that was used to automate the process. Each PERFUM2 run consists of 4 files with the following extensions:

.per is the input file for PERFUM2
.out is the output file from PERFUM2 (this will be the file you'll focus on mostly)
.ctr is a contour file generated by PERFUM2 (nice for making figures)
.plt is a file that has the same results as in the output file, but can imported easily into Excel or Lotus

PERFUM2 runs were done for the following building volumes: 1000, 2000, 5000, 10000, 25000, 50000, 100000, 250000, 500000, 750000, and 1000000 cu ft. (*EFED comment: 5000 cu ft was selected as maximum for Propoxide 892 label applications for the ecological and human health risk assessments)*

In each output file (.out) you will find results for different release rates (labeled application rates in the output file) for whole field and maximum distance analysis. The results are profiles of distances to the concentration of concern. Do not be alarmed by the application rates that are depicted in the output files; these are values that were used to make it easier for someone to visualize the percent applied that is being released; it does not actually indicate the amount applied or released - this information is reflected as the hourly flux values. The amount applied values should appear as: 100, 99, 95, 90, 75, 50, 25, 10, 5, and 1 lbs/1000 cu ft. For the portable stack and PPQ, because we are

minimizing the effects of the buildings, we had to use the following values: 100,000, 990,000, 95,000, 90,000, 75,000, 50,000, 25,000, 10,000, 5,000, and 1,000 lbs/1000 cu ft.

Tallahassee Florida PERFUM Model run for 5000 cubic foot chamber treated with 2.8 lb propylene oxide/ 100 cubic feet. Model assumes a conservative no-stack emission scenario. The run is for hourly emissions, with 4 hour averaging times. Air concentration of Concern is 242 mg/m3 (the lowest/most conservative endpoint evaluated)

```
*****************************************************
** PERFUM Output File
*****************************************************

 Version 2.1.1 - compiled on 12/19/2005
 Run finished on: 03/09/2006 at 01:23

*****************************************************
** Basic information about the model run
*****************************************************
 Scenario Type: GRN

 Source of flux data: CDPR Commodity Permit Conditions
 Source of meteorological data: Tallahassee, FL
 ISCST3 meteorological file:         ..\PERFUM2\MET\tl.MET
 Field size (acres):    0.007
 Length in x-direction (m):     5.20
 Length in y-direction (m):     5.20
 Grid density: FINE


*****************************************************
** Toxicity Inputs
*****************************************************

 Human Equivalent Conc (ug/m3) :  242000.0 (EFED Note; This is the Mammalian
Acute LC%) multiplied by the Endangered Species LOC of 0.1)
 Uncertainty factor:     1.0
 Threshold (ug/m3): *******


*****************************************************
** Exposure Assumptions
*****************************************************

 Exposure averaging period (hours):   4
 Distribution averaging time (hours):   4


*****************************************************
** Time Assumptions
*****************************************************

 Starting year: 1988
 Ending year: 1992
 Application Start Hour:   3


*****************************************************
** Additional assumptions for greenhouse scenario
*****************************************************
 Greenhouse source type: Area
```

Height of greenhouse (m): 5.2
Adjusted greenhouse height (m): 0.9
Source of flux data: Manually entered by user (EFED Note treatment was 2.8 lb/100 cubic feet)

****

** Fumigant Flux Profiles
****
Flux rates for day number: 1

HOUR	Flux Rate
1	64558.000
2	64558.000
3	64558.000
4	64558.000
5	64558.000
6	64558.000
7	64558.000
8	64558.000
9	64558.000
10	64558.000
11	64558.000
12	64558.000
13	64558.000
14	64558.000
15	64558.000
16	64558.000
17	64558.000
18	64558.000
19	64558.000
20	64558.000
21	64558.000
22	64558.000
23	64558.000
24	64558.000

** All flux rates in micrograms per meter squared per second

----- Number of Periods with Buffer Length Estimates -----

Period	Valid Periods	Calm Periods
1	1186	640
2	1802	24
3	1826	0
4	1826	0
5	1626	200
6	1281	545

------- Definition of Flux Averaging Periods ----------
Period 1: Hours 3 to 6
Period 2: Hours 7 to 10
Period 3: Hours 11 to 14
Period 4: Hours 15 to 18
Period 5: Hours 19 to 22
Period 6: Hours 23 to 2

--------- PERFUM Model Results -----------
Whole field buffer percentiles for an application rate of 100.0 for Flux Profile Day No. 1

Percentile	Per1	Per2	Per3	Per4	Per5	Per6
5	0	0	0	0	0	0
10	0	0	0	0	0	0
15	0	0	0	0	0	0
20	0	0	0	0	0	0
25	0	0	0	0	0	0
30	0	0	0	0	0	0
35	0	0	0	0	0	0
40	0	0	0	0	0	0
45	0	0	0	0	0	0
50	0	0	0	0	0	0
55	0	0	0	0	0	0
60	0	0	0	0	0	0
65	0	0	0	0	0	0
70	0	0	0	0	0	0
75	0	0	0	0	0	0
80	0	0	0	0	0	0
85	0	0	0	0	0	0
90	0	0	0	0	0	0
95	0	0	0	0	0	0
97	0	0	0	0	0	0
99	0	0	0	0	0	0
99.9	0	0	0	0	0	0
99.99	0	0	0	0	0	0

Maximum concentration buffer percentiles for an application rate of 100.0 for Flux Profile Day No. 1

Percentile	Per1	Per2	Per3	Per4	Per5	Per6
5	0	0	0	0	0	0
10	0	0	0	0	0	0
15	0	0	0	0	0	0
20	0	0	0	0	0	0
25	0	0	0	0	0	0
30	0	0	0	0	0	0
35	0	0	0	0	0	0
40	0	0	0	0	0	0
45	0	0	0	0	0	0
50	0	0	0	0	0	0
55	0	0	0	0	0	0
60	0	0	0	0	0	0
65	0	0	0	0	0	0
70	0	0	0	0	0	0
75	0	0	0	0	0	0
80	0	0	0	0	0	0
85	0	0	0	0	0	0
90	0	0	0	0	0	0
95	0	0	0	0	0	0
97	0	0	0	0	0	0

99	0	0	0	0	0	0
99.9	0	0	0	0	0	0
99.99	0	0	0	0	0	0

Flint Michigan PERFUM Model run for 5000 cubic foot chamber treated with 2.8 lb propylene oxide/ 100 cubic feet. Model assumes a conservative no-stack emission scenario. The run is for hourly emissions, with 4 hour averaging times. Air concentration of Concern is 242 mg/m3(the lowest/most conservative endpoint evaluated)

```
*****************************************************
** PERFUM Output File
*****************************************************
 Version 2.1.1 - compiled on 12/19/2005
 Run finished on: 03/09/2006 at 04:37

*****************************************************
** Basic information about the model run
*****************************************************
 Scenario Type: GRN
 Source of flux data: CDPR Commodity Permit Conditions
 Source of meteorological data: Flint, MI
 ISCST3 meterological file:         ..\PERFUM2\MET\flint.MET
 Field size (acres):    0.007
 Length in x-direction (m):     5.20
 Length in y-direction (m):     5.20
 Grid density: FINE

*****************************************************
** Toxicity Inputs
*****************************************************
 Human Equivalent Conc (ug/m3) :  242000.0(EFED Note; This is the Mammalian
Acute LC%) multiplied by the Endangered Species LOC of 0.1)
 Uncertainty factor:     1.0
 Threshold (ug/m3): *******

*****************************************************
** Exposure Assumptions
*****************************************************
 Exposure averaging period (hours):   4
 Distribution averaging time (hours):   4

*****************************************************
** Time Assumptions
*****************************************************
 Starting year: 1987
 Ending year: 1991
 Application Start Hour:   3

*****************************************************
** Additional assumptions for greenhouse scenario
*****************************************************
 Greenhouse source type: Area
 Height of greenhouse (m):    5.2
 Adjusted greenhouse height (m):    0.9
 Source of flux data: Manually entered by user(EFED Note treatment was 2.8
lb/100 cubic feet)

*****************************************************

** Fumigant Flux Profiles
*****************************************************
```

Flux rates for day number: 1

HOUR	Flux Rate
1	64558.000
2	64558.000
3	64558.000
4	64558.000
5	64558.000
6	64558.000
7	64558.000
8	64558.000
9	64558.000
10	64558.000
11	64558.000
12	64558.000
13	64558.000
14	64558.000
15	64558.000
16	64558.000
17	64558.000
18	64558.000
19	64558.000
20	64558.000
21	64558.000
22	64558.000
23	64558.000
24	64558.000

** All flux rates in micrograms per meter squared per second

----- Number of Periods with Buffer Length Estimates -----

Period	Valid Periods	Calm Periods
1	1786	39
2	1821	4
3	1824	1
4	1822	3
5	1822	3
6	1809	16

------- Definition of Flux Averaging Periods ----------
Period 1: Hours 3 to 6
Period 2: Hours 7 to 10
Period 3: Hours 11 to 14
Period 4: Hours 15 to 18
Period 5: Hours 19 to 22
Period 6: Hours 23 to 2

--------- PERFUM Model Results -----------

Whole field buffer percentiles for an application rate of 100.0 for Flux Profile Day No. 1

Percentile	Per1	Per2	Per3	Per4	Per5	Per6
5	0	0	0	0	0	0

10	0	0	0	0	0	0
15	0	0	0	0	0	0
20	0	0	0	0	0	0
25	0	0	0	0	0	0
30	0	0	0	0	0	0
35	0	0	0	0	0	0
40	0	0	0	0	0	0
45	0	0	0	0	0	0
50	0	0	0	0	0	0
55	0	0	0	0	0	0
60	0	0	0	0	0	0
65	0	0	0	0	0	0
70	0	0	0	0	0	0
75	0	0	0	0	0	0
80	0	0	0	0	0	0
85	0	0	0	0	0	0
90	0	0	0	0	0	0
95	0	0	0	0	0	0
97	0	0	0	0	0	0
99	0	0	0	0	0	0
99.9	0	0	0	0	0	0
99.99	0	0	0	0	0	0

Maximum concentration buffer percentiles for an application rate of 100.0 for Flux Profile Day No. 1

Percentile	Per1	Per2	Per3	Per4	Per5	Per6
5	0	0	0	0	0	0
10	0	0	0	0	0	0
15	0	0	0	0	0	0
20	0	0	0	0	0	0
25	0	0	0	0	0	0
30	0	0	0	0	0	0
35	0	0	0	0	0	0
40	0	0	0	0	0	0
45	0	0	0	0	0	0
50	0	0	0	0	0	0
55	0	0	0	0	0	0
60	0	0	0	0	0	0
65	0	0	0	0	0	0
70	0	0	0	0	0	0
75	0	0	0	0	0	0
80	0	0	0	0	0	0
85	0	0	0	0	0	0
90	0	0	0	0	0	0
95	0	0	0	0	0	0
97	0	0	0	0	0	0
99	0	0	0	0	0	0
99.9	0	0	0	0	0	0
99.99	0	0	0	0	0	0

Ventura California PERFUM Model run for 5000 cubic foot chamber treated with 2.8 lb propylene oxide/ 100 cubic feet. Model assumes a conservative no-stack emission scenario. The run is for hourly emissions, with 4 hour averaging times. Air concentration of Concern is 242 mg/m3(the lowest/most conservative endpoint evaluated)

```
*****************************************************
** PERFUM Output File
*****************************************************
 Version 2.1.1 - compiled on 12/19/2005
 Run finished on: 03/09/2006 at 02:39

*****************************************************
** Basic information about the model run
*****************************************************
 Scenario Type: GRN
 Source of flux data: CDPR Commodity Permit Conditions
 Source of meteorological data: Ventura, California
 ISCST3 meterological file:         ..\PERFUM2\MET\vt.MET
 Field size (acres):    0.007
 Length in x-direction (m):     5.20
 Length in y-direction (m):     5.20
 Grid density: FINE

*****************************************************
** Toxicity Inputs
*****************************************************
 Human Equivalent Conc (ug/m3) :  242000.0
 Uncertainty factor:     1.0
 Threshold (ug/m3): *******

*****************************************************
** Exposure Assumptions
*****************************************************
 Exposure averaging period (hours):   4
 Distribution averaging time (hours):   4

*****************************************************
** Time Assumptions
*****************************************************
 Starting year: 1995
 Ending year: 1999
 Application Start Hour:   3

*****************************************************
** Additional assumptions for greenhouse scenario
*****************************************************
 Greenhouse source type: Area
 Height of greenhouse (m):    5.2
 Adjusted greenhouse height (m):    0.9
 Source of flux data: Manually entered by user(EFED Note treatment was 2.8
lb/100 cubic feet)


*****************************************************

** Fumigant Flux Profiles
*****************************************************
```

Flux rates for day number: 1

HOUR	Flux Rate
1	64558.000
2	64558.000
3	64558.000
4	64558.000
5	64558.000
6	64558.000
7	64558.000
8	64558.000
9	64558.000
10	64558.000
11	64558.000
12	64558.000
13	64558.000
14	64558.000
15	64558.000
16	64558.000
17	64558.000
18	64558.000
19	64558.000
20	64558.000
21	64558.000
22	64558.000
23	64558.000
24	64558.000

** All flux rates in micrograms per meter squared per second

----- Number of Periods with Buffer Length Estimates -----

Period	Valid Periods	Calm Periods
1	1438	357
2	1773	22
3	1792	3
4	1791	4
5	1717	78
6	1306	489

------- Definition of Flux Averaging Periods ----------
Period 1: Hours 3 to 6
Period 2: Hours 7 to 10
Period 3: Hours 11 to 14
Period 4: Hours 15 to 18
Period 5: Hours 19 to 22
Period 6: Hours 23 to 2

--------- PERFUM Model Results -----------
Whole field buffer percentiles for an application rate of   100.0 for Flux Profile Day No. 1

Percentile	Per1	Per2	Per3	Per4	Per5	Per6
5	0	0	0	0	0	0

10	0	0	0	0	0	0
15	0	0	0	0	0	0
20	0	0	0	0	0	0
25	0	0	0	0	0	0
30	0	0	0	0	0	0
35	0	0	0	0	0	0
40	0	0	0	0	0	0
45	0	0	0	0	0	0
50	0	0	0	0	0	0
55	0	0	0	0	0	0
60	0	0	0	0	0	0
65	0	0	0	0	0	0
70	0	0	0	0	0	0
75	0	0	0	0	0	0
80	0	0	0	0	0	0
85	0	0	0	0	0	0
90	0	0	0	0	0	0
95	0	0	0	0	0	0
97	0	0	0	0	0	0
99	0	0	0	0	0	0
99.9	0	0	0	0	0	0
99.99	0	0	0	0	0	0

Maximum concentration buffer percentiles for an application rate of 100.0 for Flux Profile Day No. 1

Percentile	Per1	Per2	Per3	Per4	Per5	Per6
5	0	0	0	0	0	0
10	0	0	0	0	0	0
15	0	0	0	0	0	0
20	0	0	0	0	0	0
25	0	0	0	0	0	0
30	0	0	0	0	0	0
35	0	0	0	0	0	0
40	0	0	0	0	0	0
45	0	0	0	0	0	0
50	0	0	0	0	0	0
55	0	0	0	0	0	0
60	0	0	0	0	0	0
65	0	0	0	0	0	0
70	0	0	0	0	0	0
75	0	0	0	0	0	0
80	0	0	0	0	0	0
85	0	0	0	0	0	0
90	0	0	0	0	0	0
95	0	0	0	0	0	0
97	0	0	0	0	0	0
99	0	0	0	0	0	0
99.9	0	0	0	0	0	0
99.99	0	0	0	0	0	0