UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460
OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

September 27, 2007

SUBJECT: **Acrolein** HED Risk Assessment for Reregistration Eligibility Decision (RED) Document PC Code No. 000701; DP Barcode No. 334662

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This document provides the Health Effects Division's (HED's) risk assessment of acrolein for purposes of issuing a Reregistration Eligibility Decision Document. The disciplinary science chapters and other supporting documentation for HED's acrolein risk assessment are incorporated into the risk assessment or included as attachments as follows.

Abdallah Khasawinah - Hazard Identification Assessment; Section 4 and Appendices.
Thurston Morton - Residue Chemistry Assessment; (D 334663, 9/27/07)
Thurston Morton - Dietary Risk and Exposure Estimate Through Subsistence Diets; (D334666, 7/26/07)
Becky Daiss - Occupational and Residential Exposure Assessment (D334664, 9/27/07)
R.David Jones - Assessment of Drinking Water Exposure and Acrolein Concentrations to which Fish May be Exposed (D334659, 7/16/07))
Monica Hawkins and Hans Allender - Review of Acrolein Incident Reports (D320992, 2/14/06)
William Phillips and Jenna Carter - Determination of Surface Water Overhead Application and Timing Relative to Harvest Timing for Selected Crops Irrigated with Acrolein Treated Water (D360044, 5/2/07)

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1.0 EXECUTIVE SUMMARY

This assessment provides information to support the issuance of a risk management decision document known as a Reregistration Eligibility Decision (RED) Document for acrolein. EPA's pesticide reregistration process provides for the review of older pesticides (those initially registered prior to November 1984) under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) to ensure that they meet current scientific and regulatory standards. This document addresses the exposures and risks associated with exposures to acrolein used as an aquatic herbicide and as a microbiocide for the control of bacteria and microorganisms in oil field production systems. These uses have been determined to be non-food uses and are not subject to Food Quality Protection Act (FQPA) requirements.

Use Profile

Acrolein has two use patterns: as an herbicide for control of vegetation in irrigation canals and as a biocide in water pumped into injection wells associated with petroleum production. As an aquatic herbicide, acrolein is used for control of submerged aquatic weeds and algae in irrigation canals and, in some states, irrigation reservoirs. It is injected directly below the surface of moving water and moves with the flow killing weeds on contact. Treated water may be used directly for irrigation. Currently, there is one active registration and six Special Local Needs (SLN) registrations for acrolein used as aquatic herbicide. The currently registered acrolein products MAGNACIDE H (aquatic herbicide) and MAGNACIDE B (biocide) are packaged as a liquid and stored under an inert gas blanket and contain 95% acrolein as the active ingredient. Acrolein is not directly applied to crops. However, water treated with the MAGNACIDE H herbicide is used for irrigation of a wide variety of crops. No tolerances have been established for residues of acrolein in/on plant or animal commodities. Both the herbicide and biocide products are applied through a closed system. Acrolein is a restricted use pesticide subject to strict use limitations. It can only be sold to and applied by trained and certified applicators or persons under their direct supervision. It can be used only for uses covered by the applicator's certification. There are no products available for residential application. OPP's Biological and Economical Analysis Division (BEAD) estimates that approximately 1 million pounds of acrolein are used annually.

Regulatory History

Acrolein is a FIFRA List B reregistration pesticide. The Agency completed its Phase IV Review of acrolein in October, 1990. EPA also issued several Data Call-In (DCI) notices in the late 1980s and early 1990s identifying outstanding data needs for acrolein. The DCIs included requests for plant and animal metabolism studies in order to determine the need for crop tolerances.

Hazard Identification

The acrolein toxicity data base is adequate for evaluating and characterizing toxicity. Acrolein is acutely toxic by inhalation, oral, and dermal exposures (Toxicity Category I for all routes). Its toxicity is exerted at the point of contact with tissues. It is a strong dermal irritant, causing skin burns in humans.

The major effects from chronic inhalation exposure to acrolein in humans are general respiratory congestion and eye, nose, and throat irritation. Animal studies also indicate that the respiratory system is the major target organ for acrolein inhalation toxicity. Oral acrolein exposure may result in gastrointestinal discomfort, vomiting, and stomach ulceration and/or hemorrhage. In addition, changes in body and organ weights, hematology, and serum biochemistry have been observed in animals exposed orally to acrolein, although some of these effects are believed to be secondary effects of gastrointestinal and/or respiratory tract irritation. The central nervous system does not appear to be a target of acrolein toxicity based on an Agency for Toxic Substances Disease Registry (ATSDR) 2005 review.

Based on developmental studies in rats and rabbits and a reproductive toxicity study in rats, fetal or neonatal toxicity from administration of acrolein does not occur at doses lower than doses causing effects in parental animals.

Available literature metabolism studies indicate that orally administered acrolein is excreted (as metabolites) in the urine, feces and as carbon dioxide. Inhaled acrolein is retained primarily in the upper respiratory tract because of its high solubility and reactivity.

In vitro studies have shown acrolein to be weakly mutagenic. The International Agency for Research on Cancer (IARC) and EPA have determined that the potential carcinogenicity of acrolein is not classifiable based on an inadequate database. While the potential carcinogenicity of acrolein cannot be determined definitively due to insufficient data, HED does not believe cancer studies are required for this assessment based on use patterns, anticipated exposure patterns, severe local toxicity, and available data on mutagenicity and carcinogenicity.

Glycidol, a metabolite of acrolein reported in a fish study, is considered a probable human carcinogen to humans by the International Agency for Research on Cancer. The National Toxicology Program Annual Report concludes that glycidol is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity in experimental animals.

Dose Response Assessment

Acrolein

Toxicological endpoints were selected only for potential or expected exposure routes. Acute and chronic RfDs were not established for acrolein for this RED because dietary exposure to acrolein is not expected based on the use pattern and the physical/chemical properties of the compound. Toxicological endpoints for dermal exposure were not required and not selected for

this RED because dermal exposure is not expected based on use patterns and required PPE for workers. Toxicological endpoints were selected for potential occupational exposure and exposure to residential bystanders to acrolein via the inhalation exposure pathway. A Short-term inhalation exposure endpoint based on eye irritation at 0.09 ppm was selected from a study on human volunteers exposed by inhalation for 1 hour. The target level of concern (LOC) or margin of exposure (MOE) for occupational and residential exposure via inhalation is 30 (10 for intraspecies variation and 3 for LOAEL to NOAEL based on minor eye irritation.

Glycidol

A cancer endpoint was selected for glycidol, a metabolite of acrolein in fish, for use in a dietary exposure assessment. To quantify the carcinogenic response of glycidol, a multistage model BMD analysis was performed to derive a point of departure or slope factor.

Exposure/Risk Assessment and Risk Characterization

Acrolein

Risk assessments were conducted for occupational and residential exposure pathways only based on label prescribed uses. A dietary risk assessment of acrolein was not conducted as dietary exposures to acrolein are not expected based on the use pattern, available data on metabolism, and post-irrigation reentry intervals. Risks from drinking water exposures were not assessed because OPP's Environmental Fate and Effects Division (EFED) did not establish quantitative estimated environmental concentrations (EECs) for use in risk assessment. Since there are no residential uses of acrolein, an assessment of residential handler and post-application exposure scenarios was not required. However, residential bystanders may be exposed due to application of acrolein (MAGNACIDE H) to irrigation canals. Exposures to acrolein from use of MAGNACIDE B are not expected based on the use pattern. Therefore, only potential occupational and residential exposures resulting from use of the herbicide MAGNACIDE H are assessed for the acrolein RED. Only short-term, intermittent exposures are expected and assessed based on use pattern and physical-chemical properties of the compound. Potential inhalation exposure was assessed using available air monitoring data collected during application of acrolein to canals.

The exposure level at which risks are not of concern is 3 ppb. Based on available air monitoring data, MOEs for both worker and residential bystander exposures to acrolein may present risks of concern.

Gylcidol

An assessment of dietary exposure of subsistence fishermen to glycidol, a metabolite of acrolein in fish, was conducted for this RED. Based on data provided by EFED on acrolein concentrations in fishable waters and data from EPA on the location and fishing habits of tribes living in areas proximate to treated canals, HED believes that a subsistence fisherman scenario is

plausible. HED's assessment of dietary exposure of subsistence fishermen to glycidol indicates cancer risks are not of concern.

Non-cancer effects from glycidol were not assessed separately for this RED because the cancer slope factor for glycidol is so high that protecting against cancer will protect against non-cancer toxicity. The nonneoplastic lesions in both rats and mice related to treatment with glycidol included hyperkeratosis and epithelial dysplasia of the forestomach. Fibrosis of the spleen was also present in rats of each sex, and cysts of the preputial gland and kidney were present in male mice.

Use of Human Studies

This risk assessment relies in part on data from a study in which adult human subjects were intentionally exposed to a pesticide or other chemical. This study, listed below, has been determined to require a review of its ethical conduct. It is also subject to review by the Human Studies Review Board (HSRB). The HSRB reviewed the study at a June 28, 2007 meeting and determined the study to be ethically and scientifically acceptable. The written report of the HSRB is not yet completed but will be made available once it has been finalized.

A. Weber Tschopp, T. Fischer, R. Gierer and E. Grandjean (1977) Experimentally Induced Irritating Effects of Acrolein on Man. Int. Arch. Occup. Environ. Hlth. 1977 (40): 117-130 Institute for Hygiene and Occupational Physiologe, Swill Federal Engineering College, Zurich (MRID 46769601)

Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf).

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas postapplication are evaluated. Further considerations are currently in development, as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

2.0 INGREDIENT PROFILE

2.1 Summary of Registered Uses

There are 8 active acrolein registrations, two Section 3s and six SLNs (24(c)s). Baker Petrolite produces the TGAI, and as the sole technical registrant, intends to support the two Section 3 registrations, MAGNACIDE H (10707-9) and MAGNACIDE B (10707-10). There are 6 Special Local Needs (24(c)) registrations. Baker Petrolite has indicated that they are interested in supporting all six of these SLNs. Three of these SLNs (WA0400017, ID900005, and NE030003) reduce the holding time specified on the Section 3 label for treated water. The other three SLNs (UT030001, OR910018 and CA780039) are for reservoir use. SLNs for use of acrolein in rodent burrows and burrow entrances have been cancelled.

Table 1. Summary Report of Supported Registered Products

Reg #	Name	Company Name	%Ai
10707-9	MAGNACIDE H HERBICIDE	Baker Petrolite Corporation	95
10707-10	MAGNACIDE B Microbiocide		95
Ca780039	MAGNACIDE H HERBICIDE		95
Id900005	MAGNACIDE H HERBICIDE		95
Ne030003	MAGNACIDE H HERBICIDE		95
Or910018	MAGNACIDE H HERBICIDE		95
Ut030001	MAGNACIDE H HERBICIDE		95
Wa040017	MAGNACIDE H HERBICIDE		95

For herbicidal use in irrigation canals, the maximum single application concentration of acrolein is 15 ppm. This application rate is used when there is high weed density in the treated canal. Applications can occur multiple times during a year. Neither the maximum number of applications, nor the minimum interval between applications is specified on the label. Based on application data provided by the registrant, Baker Petrolite Corporation (MRID 46976913), applications are made to irrigation systems in 15 states in the Great Plains or West: Arizona, California, Colorado, Idaho, Kansas, Montana, Nebraska, Nevada, New Mexico, North Dakota, Oregon, South Dakota, Utah, Washington, and Wyoming. The maximum single application rate used during the year at each irrigation system is most often 8 ppm but applications at 15 ppm commonly occur (reported in at least one irrigation district in 9 of 15 of these states). Acrolein is applied up to 26 times per year in some irrigation systems with an interval as short as 7 days, but 6 applications per year is the most common, with a two or three week interval between applications. In some irrigation systems applications are more frequent but at lower concentrations to control the lower weed density.

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2.2 Structure, Nomenclature, and Physical/Chemical Properties

The nomenclature and physicochemical properties of acrolein and glycidol are provided in Tables 2-4.

Table 2. Test Compound Nomenclature	
Compound	**Acrolein**

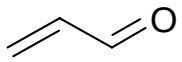
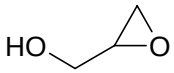
Table 2. Test Compound Nomenclature	
Compound	**Acrolein**
Chemical Structure	
Common Name	acrolein
Synonyms	2-propenal, acrylaldehyde, acraldehyde, acrylic aldehyde, allyl aldehyde, propenal, trans acrolein, acquinite, aqualin, aqualine, biocide, crolean, ethylene aldehyde, MAGNACIDE, MAGNACIDE H, NSC 8819, prop-2-en-1-al, 2-propene-1-one, slimicide, prop-2-enal
CAS #	107-02-8
PC Code	000701

Table 3. Physicochemical Properties of Acrolein	
Molecular Weight	56.1
Boiling Point	53°C
Melting Point	-81°C
Specific Gravity	0.0839
Vapor Density	1.94 (air = 1)
Vapor Pressure	220 torr 20° C
Flashpoint	-15ºF (-26.1ºC)
Solubility	208 g/L at 20ºC soluble in water, alcohol, ether, and acetone.
Description	Clear, colorless to yellow liquid

Table 4. Physicochemical Properties of Glycidol (CAS 556-52-5)	
Chemical Structure	
Synonyms	1,2-Epoxy-3-Hydroxy Propane; 2,3-Epoxy-1-propanol; 2,3-epoxypropanol; 2-hydroxymethyloxirane; 3-hydroxy-1,2-epoxypropane;; glycide; glycidyl alcohol; Glycidol;
Molecular Weight	74.1
Boiling Point	166° C (decomposes)
Melting Point	-45°C
Specific Gravity	0.0839
Vapor Density	2.15 (air = 1)
Vapor Pressure	120 Pa 25° C
Flashpoint	72 ºC)
Solubility	Miscible.
Octanol Water Partition Coefficient (Log p_{ow})	- 0.95
Description	Clear, colorless liquid

3.0 SUMMARY OF RESIDUES OF CONCERN FOR RISK ASSESSMENT

In addition to the parent compound, acrolein, compounds of potential concern include glycidol, a metabolite of acrolein found in fish, and 3-hydroxypropanal, a metabolite of acrolein found in acrolein treated water. There are currently no tolerances for residues of acrolein in/on plant or livestock commodities. Based on the available data, HED is not proposing to establish tolerances for acrolein on plant or animal commodities but is requesting a confirmatory nature of

the residue study in a root and tuber crop. Acrolein is not a residue of concern for risk assessment for either dietary or drinking water exposures based on use pattern and physical-chemical properties. Glycidol, a metabolite of acrolein in fish, has been identified as a residue of concern for risk assessment purposes. HED is not proposing to establish tolerances for glycidol in fish. However, given that the registrant is supporting SLN registrations for the application of acrolein to reservoirs and that existing label restrictions are inadequate to effectively prevent fishing in reservoirs, HED is requesting a fish magnitude of the residue study. Glycidol is not formed as a metabolite of acrolein in mammals based on available metabolism studies in livestock and rats. 3-hydroxypropanal is a metabolite of acrolein in water but is not considered a metabolite of concern for risk assessment purposes. While acrolein forms 3-hydroxypropanal spontaneously in solution, it is an equilibrium process and acrolein will be reformed from 3-hydroxypropanal as acrolein is dissipated by other processes.

Table 5. Parent, Metabolites and Degradates Considered for Risk Assessment

Matrix	Compound of Potential Concern	Residue included in Risk Assessment
Plant	Acrolein	No
Livestock	Acrolein	No
Fish	Glycidol	Yes
Drinking Water	Acrolein, 3-Hydroxypropanal	No

4.0 HAZARD CHARACTERIZATION/ASSESSMENT

4.1 Hazard Characterization

The acrolein toxicity database is adequate for evaluating and characterizing its toxicity. The toxicological evaluation of acrolein is based primarily on information provided in the Agency for Toxic Substance and Disease Registry's (ATSDR) 2005 Draft Toxicological Profile for Acrolein and the EPA Integrated Risk Information System (IRIS) 2003 review.

Acrolein is acutely toxic by inhalation, oral, and dermal exposures (Toxicity Category I for all routes). It is a potent irritant to the mucous membranes. Direct contact with liquid acrolein causes rapid and severe eye and skin irritation or burns. Dermal exposure to acrolein liquids or vapors may cause stinging of the eyes, lacrimation, and reddening, ulceration, or necrosis of the skin.

Oral acrolein exposure may result in gastrointestinal discomfort, vomiting, and stomach ulceration and/or hemorrhage. The stomach epithelium appears to be the most sensitive target for oral exposure. Higher concentrations of ingested acrolein have primarily resulted in increasingly severe irritation effects in the stomach (2 mg/kg and higher).

Signs and symptoms resulting from inhalation exposure to airborne acrolein may include irritation of the nose, throat and lungs, pulmonary edema, lung hemorrhage, and death. The nasal tissues appear to be the most sensitive target of inhalation exposure, with onset of noticeable irritation occurring in seconds (0.3 ppm). Higher airborne concentrations of acrolein (2– 5 ppm) result in increasingly severe manifestations of irritation over the entire respiratory

tract.

Histological changes in respiratory and gastrointestinal epithelium have been observed from both inhalation and oral exposures, respectively. Changes in body and organ weights, hematology, and serum biochemistry, as well as developmental effects such as skeletal malformations and reduced weight of offspring, have been observed in animals. Some of these effects are believed to be secondary effects of gastrointestinal and/or respiratory tract irritation (i.e., loss of appetite and weight loss due to gastrointestinal irritation).

Apart from rare cases of sensitization, no adverse effects in humans chronically exposed to low concentrations of acrolein have been reported.

Based on developmental studies in rats and rabbits and a reproductive toxicity study in rats, fetal or neonatal toxicity from administration of acrolein does not occur at doses lower than doses causing effects in parental animals.

Inhaled acrolein is retained primarily in the upper respiratory tract because of its high solubility and reactivity. Orally administered acrolein is excreted (as metabolites) in the urine, feces and as carbon dioxide. The main pathway of metabolism for acrolein is the addition of glutathione (GSH) to the activated double bond followed by conversion to mercapturic acid. A second pathway is that of epoxidation of the double bond followed by attack on the epoxide by glutathione. A third pathway is addition of water to acrolein to form 3-hydroxypropionaldehyde, which can be further metabolized and ultimately incorporated into normal metabolic pathways.

In vitro studies have shown acrolein to be weakly mutagenic. The evidence for the carcinogenicity of acrolein is equivocal, with a significant tumor incidence found in a single animal drinking water study. The findings of this study were challenged by an independent pathology working group. Another well-designed cancer bioassay in orally-gavaged rats failed to detect significant increases in cancer incidence. The International Agency for Research on Cancer (IARC) and EPA have determined that acrolein is not classifiable as to carcinogenicity in humans based on an inadequate data base.

Glycidol, a metabolite of acrolein reported in a fish study, is considered a probable carcinogen to humans (Group 2A) by the International Agency for Research on Cancer. The National Toxicology Program Annual Report states that, “Glycidol is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity in experimental animals.”

Tables 2 and 3 in Appendix 1.0 provide the toxicity profile for acrolein.

4.2 Toxicity Endpoint Selection

The toxicology database for acrolein is adequate for evaluating and characterizing acrolein toxicity and selecting endpoints for purposes of this risk assessment.

4.2.1 Acute and Chronic Reference Dose (RfD) – All Populations

Acute and chronic oral (dietary and drinking water) exposure to acrolein is not expected based on use patterns, physical-chemical properties, and plant metabolism data. Therefore, acute and chronic reference doses are not required and were not selected for this assessment.

4.2.2. Incidental Oral Exposure (short and intermediate durations: 1 day - 6 months)

There are no residential uses for acrolein. Therefore incidental oral exposure endpoints are not required and not selected for this assessment.

4.2.3 Dermal Absorption

There are no dermal absorption studies available with acrolein.

4.2.4 Dermal Exposure (All Durations)

Dermal exposures for workers are not expected based on use patterns and personal protective equipment requirements. There are no residential uses for acrolein and dermal exposures to residential bystanders are not expected based on use patterns and physical-chemical properties. Given that label requirements do not effectively prohibit swimming in acrolein treated waters, there is potential for exposure to dilute concentrations of acrolein in treated water. However, available dermal toxicity studies were conducted with concentrated technical acrolein and both acute and longer term toxic effects are due to the highly reactive and corrosive nature of the concentrate. There are no data available on dermal effects of exposure to dilute concentrations of acrolein found in treated water bodies. Therefore appropriate dermal exposure endpoints are not available and have not been selected for this assessment.

4.2.5 Inhalation Exposure (Short Term)

The inhalation endpoint was selected from a 1977 study in human volunteers (Weber-Tschopp et al. 1977; MRID 47060601) Healthy male and female college student volunteers were exposed to acrolein in a 30 cubic meter chamber at an 0.1 hourly air exchange rate in 3 trials: (1) A continuous exposure at constantly increasing acrolein concentrations, (2) Discontinuous short exposures to successively increasing concentrations, and (3) Constant concentration for one hour. Data from Trial 3 was evaluated as most appropriate for assessing toxicity based on the exposure profile for acrolein (i.e., short-term intermittent exposures). In that Trial, 46 students in groups of threes (21 males and 25 females) were exposed to a 0.3 ppm acrolein concentration for 60 minutes. Measurements of eye blinking frequency, breathing frequency and subjective symptoms of irritation were taken at the beginning of exposure and during exposure. Eye, nose and throat irritation reached a plateau after 20-30 minutes of exposure, while eye blinking frequency plateaued after 10 minutes. Respiratory rate decreased

20% after 40 minutes exposure ($p<0.01$). The severity of the annoyance significantly increased almost immediately after acrolein was introduced. Eye, nose and throat irritation and eye blink frequency increased with increasing exposure duration. After 40 minutes the subjective irritation reached a constant intensity while eye blink frequency reached a definite rate after almost 10 minutes. Throat irritation reached significance after only 10 minutes at this long exposure. There was a significant individual correlation (p between <0.05 and <0.01) between eye blink frequency and the subjective eye irritation. Every person with a sharp increase in eye blink frequency also had a sharp increase of eye irritation. The volunteers were asked about the air quality during the exposure if it was good, bad or for the desire to leave the chamber and the degree of irritation to the eyes, nose and throat. The effects to continuous exposure increased with acrolein concentration. Some indication of adaptation to the irritating effects of acrolein was suggested by the study investigators. The eyes were more sensitive than the nose to the irritating effects of acrolein. In the continuous exposure the irritation was significantly greater both in the eyes and nose than in the discontinuous short exposures. Throat irritation in continuous exposure increased significantly through 0.43 ppm. The eye blink frequency of 34 subjects in the continuous trial was a function of the acrolein concentration. It increased from 0.17 ppm to 0.26 ppm ($p<0.01$) and it doubled at about 0.3 ppm. The breathing frequency of 19 subjects in the continuous exposure trial decreased slightly with increasing acrolein concentration. This decrease was statistically significant at 0.6 ppm ($p<0.05$). At this concentration, the decrease in breathing frequency reached 4 breaths per minute - a decrease corresponding to about 25%. An increase in irregular breathing frequency in 11/19 subjects compared to controls was observed, very soon after the addition of acrolein but mostly in the second half or last third of the exposure time. Nearly half of the subjects displayed more or less pronounced tendency to lengthen the expiration cycle or more rarely the inspiration cycle holding the breath toward the end of the acrolein exposure.

Dose and Endpoint Selected - The LOAEL was determined to be 0.09 ppm for eye irritation effects. Because a human study is being used for the short-term intermittent inhalation exposure scenario for acrolein, an interspecies uncertainty factor is not necessary. To account for the individual variability, an intraspecies uncertainty factor of 10X is applied to the selected LOAEL of 0.09 ppm. Because a minimal (relatively non-severe) LOAEL threshold effect is used, a 3X uncertainty factor is sufficient. Therefore, a total of 30X uncertainty factor is applied to the endpoint. The LOAEL of 0.3 ppm (equivalent to 0.7 mg/M^3) for nasal and throat irritation and decreased respiratory rate in volunteers exposed for 60 minutes was selected by ATSDR as the basis for an acute-duration minimal risk level (MRL) of 0.003 ppm. The LOAEL of 0.3 ppm was divided by a factor of 100 (10 for using a LOAEL and 10 for human variability). The LOAEL for nasal and throat irritation and decreased respiratory rate is considered co-critical for establishment of an appropriate inhalation endpoint for acrolein. Based on both the LOAEL of 0.09 ppm for eye irritation and the LOAEL of 0.3 ppm for nasal and throat irritation, the concentration of concern for humans is determined to be 0.003 ppm when uncertainty factors are considered.

Comments about Study/Endpoint: The study selected is appropriate for the route of exposure and duration. The study provides the most comprehensive description available of

acute/short-term effects in humans and provides the best information available for establishing a Point of Departure (PoD) for short-term intermittent inhalation worker and residential bystander exposure scenarios.

4.2.6 Margins of Exposure

The LOC for short-term exposure to acrolein is 30 when applied to the LOAEL of 90 ppb (for eye irritation) (10x for intraspecies variation and 3x for lack of a NOAEL.)

4.2.7 Recommendation for Aggregate Exposure Risk Assessments

When there are potential residential exposures to the pesticide, aggregate risk assessment must consider exposures from three major sources: oral, dermal and inhalation exposures. Since there are no dietary/drinking water exposures to acrolein, an assessment of aggregate exposure from risk from food and non-food sources is not required.

4.2.8 Classification of Carcinogenic Potential

4.2.8.1 Acrolein

The IRIS 2003 Report states that under the Draft Revised Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1999), the potential carcinogenicity of acrolein cannot be determined because the existing "data are inadequate for an assessment of human carcinogenic potential for either the oral or inhalation route of exposure."

According to IRIS, there are no adequate human studies of the carcinogenic potential of acrolein. Collectively, experimental studies provide inadequate evidence that acrolein causes cancer in laboratory animals. Specifically, two inhalation bioassays in laboratory animals are inadequate to make a determination because of protocol limitations. Two gavage bioassays failed to show an acrolein-induced tumor response in two species of laboratory animals. The finding of suggestive evidence of an extra-thoracic tumorigenic response in a drinking water study in female rats was not supported in a reanalysis of the data by an independently-convened pathology working group. Questions were also raised about the accuracy of the reported levels of acrolein in the drinking water from this study. A skin tumor initiation-promotion study was negative, and the findings from an intraperitoneal injection study were of uncertain significance. Although acrolein has been shown to be capable of inducing sister chromatid exchange, DNA cross-linking and mutations under certain conditions, its highly reactive nature and the lack of tumor induction at portals of entry make it unlikely that acrolein reaches systemic sites at biologically-significant exposure levels. The observations of positive mutagenic results in bacterial systems occurred at high concentrations near the lethal dose.

The 2003 evaluation replaces the cancer assessment for acrolein added to the IRIS data base in 1988. Under the Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) applied at that time, acrolein was classified as a possible human carcinogen (Category C). The 1988

classification for acrolein was based on the increased incidence of adrenal cortical adenomas in female rats and carcinogenic potential of an acrolein metabolite, its mutagenicity in bacteria, and its structural relationship to probable or known human carcinogens. The updated cancer characterization considered new study results and reevaluated previous studies.

While the potential carcinogenicity of acrolein cannot be determined definitively due to insufficient data, HED does not believe cancer studies are required for this assessment based on use patterns, anticipated exposure patterns, and available data which does not indicate carcinogenity. Oral exposures to acrolein via dietary and drinking exposure are not expected or assessed based on use patterns and physical/chemical property data. Continuous chronic exposures via inhalation and dermal pathways are not expected based on established use patterns.

4.2.8.2 Glycidol

Glycidol is a metabolite of acrolein reported in a fish metabolism study. Glycidol is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity in experimental animals (NTP 1990, IARC 2000). Two-year studies were conducted with mice and rats that were administered glycidol by gavage. Male rats showed increased incidences of mesotheliomas of the tunica vaginalis, fibroadenomas of the mammary gland, gliomas of the brain, and neoplasms of the forestomach, intestine, skin, Zymbal gland, and thyroid gland. Female rats had increased incidences of fibroadenomas and adenocarcinomas of the mammary gland, gliomas of the brain, neoplasms of the oral mucosa, forestomach, clitoral gland, and thyroid gland, and leukemia. Male B6C3F1 mice had increased incidences of neoplasms of the harderian gland, forestomach, skin, liver, and lung. Female B6C3F1 mice had increased incidences of neoplasms of the harderian gland, mammary gland, uterus, subcutaneous tissue, and skin. Other neoplasms that may be related to the administration of glycidol were fibrosarcomas of the glandular stomach in female rats and carcinomas of the urinary bladder and sarcomas of the epididymis in male mice (NTP 1990). No adequate human studies of the relationship between exposure to glycidol and human cancer have been reported (IARC 2000).

To quantify the carcinogenic response of glycidol, a multistage model BMD analysis was performed to derive a slope factor of 0.16 $(mg/kg/day)^{-1}$. (See Appendix 4.0)

4.2.9 Summary of Endpoints Selected for Risk Assessment

Toxicological doses/endpoints selected for the acrolein risk assessment are provided in Table 6.

Table 6. Summary of Toxicological Doses and Endpoints for Acrolein for Use in Human Risk Assessments			
Exposure Scenario	**Dose Used in Risk Assessment**	**Uncertainty/Safety Factor**	**Study and Toxicological Effect**
Acute Dietary (General Population including infants and children)	Acute oral (dietary and drinking water) exposure to acrolein is not expected based on use patterns, physical-chemical properties, and plant metabolism data. Therefore, acute RfDs are not required and were not selected for this assessment.		
Chronic Dietary (All Populations)	Chronic oral (dietary and drinking water) exposure to acrolein is not expected based on use patterns, physical-chemical properties, and plant metabolism data. Therefore, chronic RfDs are not required and were not selected for this assessment.		
Incidental Oral (all durations)	There are no residential uses for acrolein. Therefore incidental oral exposure endpoints are not required and not selected for this assessment.		
Dermal (all durations)	Worker dermal exposures are not expected based on use patterns and personal protective equipment requirements. There are no residential uses for acrolein and dermal exposures to residential bystanders are not expected based on use patterns and physical-chemical properties. Therefore dermal exposure endpoints are not required and have not been selected for this assessment.		
Short –Term Inhalation (1-30 days)	Minimal LOAEL = 0.09 ppm (0.21 mg/m^3)	Occupational LOC=30 Residential LOC=30 LOC = 10x for intraspecies variation & 3x for lack of a NOAEL	Human volunteers exposed by inhalation for 60 minutes (Weber-Tschopp et al. 1977) based on a minimal effect LOAEL of 0.09 ppm for eye irritation. The LOAEL of 0.3 ppm for nasal and throat irritation and decreased respiratory rate is considered co-critical for endpoint selection.
Cancer (oral, dermal and inhalation)	"The potential carcinogenicity of acrolein cannot be determined because the existing "data are inadequate for an assessment of human carcinogenic potential for either the oral or inhalation route of exposure." (IRIS 2003). To quantify the carcinogenic response of glycidol, a multistage model analysis was performed to derive a cancer slope factor of 0.16 $mg^{-1}kg^{-1}day^{-1}$ at a 0.95 confidence level. (See Appendix)		

NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, MOE = margin of exposure, LOC = level of concern.

4.3 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).

5.0 PUBLIC HEALTH DATA

The following data bases were consulted for poisoning incident data on the active ingredient acrolein; OPP Incident Data System (IDS), Poison Control Centers, California Department of Pesticide Regulation, National Pesticide Telecommunications Network (NPTN), and National Institute of Occupational Safety and Health's (NIOSH) Sentinel Event Notification System for Occupational Risks (SENSOR) (M. Hawkins and H. Allender, D320992, 2/14/06).

Two incident reports in IDS were located related to acrolein. A pesticide incident occurred in 1999, when a man reported eye irritation, difficulty breathing, and chemical burns. A valve on a cylinder, that contained the product, was transported on a flatbed truck that was struck by an overhead obstacle while entering a service station. The collision ripped the valve off the cylinder that released three to five gallons of residual product. Two men were overwhelmed by the vapors and were taken to the hospital. One of the men was treated and later released and the other man was retained in the hospital. No further information on the disposition of the case was reported. A pesticide incident occurred in 1999, when a thirty-eight year old man, who was a high school teacher, was found unconscious by his wife in their home. He died the next day. The man was a certified applicator who worked for a canal company for the previous three years while on summer break from school. He was exposed to the product while pumping it into a irrigation canal southwest of a nearby city. The man moved his truck to allow a nearby resident access to the road and accidentally ran over and broke the plastic pipe and snapped the metal riser on the application delivery system, spilling about 1 to 3 gallons of the product. He climbed on the bed of the vehicle to close the cylinder valve, without personal protective equipment. The man washed himself off in the irrigation canal and went to the hospital where he was treated by a physician and later released. He was not observed for the recommended 24-hour time period after exposure to the product. Two police officers and a canal company employee were also exposed to the product after a pipe was cut that contained about a cup of the product. These individuals were hospitalized overnight and released the following day. Specific symptoms were not mentioned. No further information on the disposition of the case was reported.

Based on exposures reported to Poison Control Centers from 1993 through 2003, 47 cases were reported. A wide range of symptoms were reported including eye irritation/lacrimation (4 cases reported), headache (3 cases), nausea (2 cases), cough/choke (2 cases), superficial burns (2 cases), and one single event of throat irritation, vomiting, erythema skin irritation, pruritus, etc.

Detailed descriptions of 15 cases submitted to the California Pesticide Illness Surveillance Program (1982-2003) were reviewed. In 14 of these cases, acrolein was used alone or was judged to be responsible for the health effects. Only cases with a definite, probable or possible relationship were reviewed. A variety of worker activities were associated with exposure to acrolein including applicator, mechanical work, emergency response, mixer/loader, and coincidental exposure. Applicator and coincidental activities were associated with 8 of the

14 reported exposure related illnesses. These illnesses included symptoms of coughing, headache, nausea, and burns on the right arm.

On the list of the top 200 chemicals for which NPIC received calls from 1984-1991 inclusively, acrolein was not reported to be involved in human incidents. Out of 5,899 reported cases from 1998 to 2003, there was only one case reported in the NIOSH SENSOR database involving acrolein. The reported incident occurred in California and involved inhalation exposure to an engineering technician. Insufficient toxicological information was available to determine a causal relationship between exposure and health effect. Evidence of exposure was based solely upon written or verbal report by exposed individual. The exposed individual reported blurred vision and a feeling of warmth.

Poison Control Center Data generally support the finding that acrolein's main effect is due to its irritant properties. Incidents involving more severe effects resulted from accidental exposures that occurred due to misuse of the acrolein product.

6.0 DIETARY AND DRINKING WATER PROFILE

Dietary exposures to acrolein are not expected based on the use pattern, available data on metabolism, and post-irrigation reentry intervals. A lettuce metabolism study indicates that acrolein is readily decomposed/incorporated into natural products. The only residue of concern is acrolein on the day of application. BEAD has determined that other than in unusually high temperature circumstances for some apples grown in the Pacific Northwest, the duration between overhead irrigation and harvest is greater than or equal to two days. In fact, in most cases the duration is greater than seven days, while in a few cases the duration can be up to 30 days. Also, in the state of Washington, the minimum duration between overhead irrigation and harvest is between 2 and 5 days for wine and juice grapes, respectively (T. Morton, D320993, 7/27/07, W. Phillips and J. Carter, D360044, 5/2/07).

Risks from drinking water exposures were not assessed. There is currently no Maximum Contaminant Level (MCL) set for the protection of drinking water for acrolein under the Safe Drinking Water Act. Also, OPP's Environmental Fate and Effects Division (EFED) did not establish quantitative estimated environmental concentrations (EECs) for use in risk assessment. While uncertainties remain regarding the potential for drinking water exposure, such exposures are considered unlikely due to fact that most, if not all of the acrolein will volatilize before and during the aeration stages of drinking water treatment.

An assessment of dietary exposure of subsistence fishermen to glycidol, a metabolite of acrolein in fish, was conducted for this RED. Based on data provided by EFED on acrolein concentrations in fishable waters and data from EPA on the location and fishing habits of tribes living in areas proximate to treated canals, HED believes that a subsistence fisherman scenario is plausible. (R.D. Jones, D334659, 7/17/07)

6.1 Residue Chemistry

6.1.1 Plant Metabolism

Based on a lettuce metabolism study, acrolein is readily decomposed/incorporated into natural products in lettuce. The only residue of concern is acrolein on the day of application. An additional plant metabolism study must be conducted in a root and tuber crop (preferably radish) to demonstrate that the metabolism observed in lettuce is typical of general metabolism of acrolein in plants. The registrant's request for waiver from the requirement of an additional nature of the residue in plants study (GLN 860.1300) is not justified.

6.1.2 Metabolism in Livestock, Poultry, and Fish

Based on metabolism studies of acrolein in lactating goats and laying hens, the qualitative nature of the residue in ruminants and poultry is adequately understood. Acrolein was not found in any tissue sample in either study. Major metabolites (>3%) in milk and tissue from the goat study included glucose, glycogen, and lactic acid, aspartate, glutamate, alanine, glycine/serine, and glycerol. Major metabolites identified in the hen study included glycine, glutamate, alanine, oleic acid, stearic acid, glycerol, creatine, cholesterol, aspartate, ornithine, and lactic acid. Other amino acids and fatty acids were identified but were present at lower concentrations in both studies.

The qualitative nature of the residue in fish and shellfish is adequately understood based on a nature of the residue study of acrolein in fish. Concentrations of metabolites found at the 20X and 101X treatments ranged from 0.005 ppm to 1.2 ppm (glyceric acid in clams). The probable level of these metabolites in tissues at the 1X discharge level (1 - 5 ppb, after a 6 day holding) would not be quantifiable. With the exception of propiolic acid (15% TRR clam) and glycidol (48% TRR catfish), the identified residues are components of the various biochemical processes. Acrolein, allyl alcohol, and acrylic acid were NOT found in any tissue. The major metabolite in catfish (0.217 ppm) was glycidol (48% TRR); in sunfish (0.251 ppm), 1,3-propanediol (40% TRR) and glyceric acid (14% TRR); in clams (5.344 ppm), glyceric acid (22% TRR), propiolic acid (15% TRR), and carbohydrates (33% TRR); in crayfish (0.419 ppm), malonic acid (16% TRR) and glycerol (53% TRR). The proposed metabolic paths involve conversion to simple (2 -3 C) alcohols and acids. The proposed metabolic path for clams differs in that extensive carbohydrate incorporation of glycerol, glyceric acid, and propiolic acid is included. The Metabolism Committee (S. Funk, Memorandum of Meeting, 06/95) has determined that glycidol, a carcinogen, constitutes a residue of concern in fish.

6.1.3 Magnitude of the Residue in Livestock, Poultry and Fish

There are no direct applications of acrolein to crops except through irrigation. No magnitude of the residue studies have been submitted. The Metabolism Committee (S. Funk, Memorandum of Meeting, 06/95) determined that glycidol, a carcinogen, is a residue of concern in fish for risk assessment purposes. Therefore the MARC determined that the registrant’s request to waive fish/shellfish feeding studies is not appropriate. However, based on ChemSAC’s recommendation (6/27/07) a fish/shellfish feeding study should be required only for uses that

involve application of acrolein to reservoirs as proposed in the SLN registrations. Consequently, based on ChemSACs recommendations and those of HED's Risk Assessment Review Committee (RARC), if the SLN registrations for application of acrolein to reservoirs continue to be supported and labels for these uses are not revised to provide effective fishing prohibitions (e.g., posting, restricted entry, etc.), feeding studies (GLN 860.1400) must be conducted for a bottom feeder, a crustacean, a predator, and a mollusk. Each must be exposed at the maximum non-lethal level of acrolein in water and multiple applications of acrolein to the water must be made. Fish and shellfish should be exposed until periodic analysis of edible tissue reveals that residues of acrolein and glycidol have plateaued. The conditions of the water (pH, temperature, inorganic salt concentrations) should approximate the natural conditions for the species tested. Control fish must be spiked with acrolein and glycidol (2 - 5X LOQ) at the time of final fish/shellfish sampling and must be stored, processed, and analyzed under the same conditions as the test samples. The registrant is urged to submit a protocol before beginning any study.

6.1.4 Magnitude of the Residue in Potable Water

Potable drinking water monitoring studies were conducted in Arizona (MRID 41855401) and Washington (41933001). The studies were conducted in order to fulfill the data requirement for Magnitude of Residue in Potable Water (GLN 860.1400), which is required for aquatic food and non-food use crops. (T. Morton, D320993, 7/26/07 and R.D. Jones, D334659, 7/16/07).

For the Arizona study, the Main Canal in the Roosevelt Irrigation District was treated with a nominal rate 15 mg per L of acrolein and then monitored at nine sites along the 29 mi canal. The last site was 27.2 mi from the application point and not at the discharge point from the canal. The nominal application rate was in fact exceeded and the maximum concentration detected in the canal at the first monitoring site 0.28 mi downstream from the application site was 20.2 mg per L. Substantial concentrations of acrolein (1600 $\mu g \cdot L^{-1}$) were still being found in the canal at the last monitoring point 30 h after application. 3-hydroxypropanal was found starting at the 4^{th} site downstream, 8 mi from the application site and 7 h after application. The highest concentration of 3-hydroxypropanal (2900 $\mu g \cdot L^{-1}$) was found at 19 mi from the application site, 18 h after application and decreased somewhat downstream, but was still being found at 2.4 $\mu g \cdot L^{-1}$, 27 mi downstream 29 h after application. At this point the concentrations were higher than the parent which was 1.6 $\mu g \cdot L^{-1}$ at the same site and time.

The Washington study was conducted in the Wapato Irrigation District in Washington State. Two canals were treated, the pump canal, and a lateral, with lengths of 19.5 and 3 mi, respectively. There were six monitoring sites along the lateral canal and nine monitoring sites along the pump canal. As with the Arizona potable water study, the nominal concentration for application was 15 mg L^{-1}, but the measured concentration at the first site exceeded the nominal in the pump canal with 19 mg per L at the first monitoring site 0.1 mi downstream. The highest measured concentration in the lateral canal was at the second monitoring site which was 0.85 mi downstream from the application site and was 10 mg per L. Acrolein was detected at the last monitoring site on both canals with 5200 µg per L in the lateral and 1700 µg per L in the pump canal. Dissipation half-lives in these two water bodies were in the same range as those in the other

monitoring studies, at 7.9 h and 12.9 h in the lateral and pump canals respectively.

3-hydroxypropanal was found in both canals. In the pump canal, it was found starting at the fifth monitoring site, 4.5 h after application and 3 mi downstream at 310 µg per L. It was found at all subsequent sites with a peak concentration of 600 µg per L 15 mi downstream and 22 h after application. In the lateral canal, 3-hydroxypropanal was found only at the last two sites, starting at 2.65 mi downstream and 6.5 h after application at 230 µg per L. The maximum concentration was at the last site (3 mi) at 320 µg per L.

6.1.5 Residue Analytical Method

An analytical method for data collection must be developed and validated for the determination of acrolein and glycidol in fish and shellfish. An analytical reference standard for acrolein is not available at the EPA National Pesticide Standards Repository. Reference standards for all residues of concern should be submitted. An enforcement analytical method must be developed and validated, including validation by an independent laboratory, for the determination of glycidol and acrolein in fish and shellfish.

6.2 Environmental Fate and Transport

Based on the limited available laboratory fate data, and the available field study and monitoring study data, while it appears that acrolein dissipates from irrigation canals with a half-life of less than one day, it is sufficiently persistent and mobile that it may reach the drainage points of irrigation systems in concentrations frequently between 0.1 and 1 ppm and at distances up to 70 miles from the application point. This indicates that if water containing acrolein reaches the terminus of an irrigation system, and cannot be held back by containment or diversion structures, acrolein will enter natural waters. The concentrations at a drinking water facility downstream from a discharging irrigation system would depend upon the dilution due to the relative flow rates of the irrigation system (or volumes in the case of reservoirs) and of the receiving water body, and the travel time between the two points. Some reduction in acrolein concentration would be expected during the drinking water treatment process, as some volatilization would likely occur during treatment, but the magnitude of the reduction cannot be quantified. Air stripping is a particular drinking water treatment technology that can remove volatile compounds, but a preliminary assessment based on the Henry' s Law Constant indicates that standard air stripping would not completely remove acrolein from drinking water. It is possible that an air stripping system could be specifically designed for that purpose.

Acrolein forms 3-hydroxypropanal spontaneously in solution, but it is an equilibrium process and acrolein will be reformed from 3-hydroxypropanal as acrolein is dissipated by other processes. Other degradates (mostly 3-carbon acids and alcohols) are formed by microbial metabolism. (R.D. Jones, D334659, 7/16/07)

6.3 Drinking Water Treatment

There is currently no Maximum Contaminant Level set for the protection of drinking water for acrolein under the Safe Drinking Water Act. There are no direct studies indicating how drinking water treatment would impact acrolein during drinking water treatment if acrolein reaches the intake for a drinking water facility. It would be expected that volatilization would play a major role in dissipating acrolein from drinking water during treatment since aeration plays a significant role in several steps during treatment; however, it is unlikely to completely remove it. Air stripping is a method for removing volatile compounds from water (OPP, 2001). Based on a study by McCarty (1987), compounds with a Henry's Law Constant of 1×10^{-3} atm·m^3/mol were amenable to remediation by air stripping. While acrolein is very volatile, it also very soluble, so the Henry's Law Constant, which is related to both properties, is only 1.92×10^{-4} atm·m^3/mol, indicating that it may not be completely removed by air stripping unless stripping towers were specifically designed for that purpose (OPP, 2001). (R.D. Jones, D334659, 7/16/07)

6.4 Acrolein Concentrations to which Fish May Be Exposed

It is possible that there is exposure to acrolein or its metabolites through the consumption of fish which live in irrigation canals, or waters which receive drainage from treated canals. In order to assess this exposure, it is necessary to identify the concentrations of acrolein in which fish are living. These concentrations can then be used to estimate the body load of acrolein and its metabolites in consumed fish. Concentration ranges in canals can be as high as the application rate and concentrations over 1000 µg·L^{-1} have been measured at the discharge points from canals, as discussed above. If these canals discharge in rivers or streams during summer low-flow conditions, concentrations in the receiving water body could potentially be similar to those in the canal. However, fish are not likely to persist in an edible state in these concentrations. Since only living fish can be caught by angling, acute fish toxicity data can indicate what are the highest concentrations which are tolerated by fish, and hence the highest concentrations to which consumed fish may be exposed. Median lethal concentrations for fish species range from 14 µg·L^{-1} for fathead minnow to 69 µg·L^{-1} for coho salmon. The latter would serve as a good estimate of the maximum concentration to which fish may be exposed and still be caught as about half the fish will survive this concentration and coho salmon are commonly eaten fish species. (R.D. Jones, D334659, 7/16/07)

7.0 DIETARY EXPOSURE ASSESSMENT FOR GLYCIDOL IN FISH

An assessment of dietary exposure of subsistence fishermen to glycidol, a metabolite of acrolein in fish, was conducted for this RED. Based on data provided by EFED on acrolein concentrations in fishable waters and data from EPA on the location and fishing habits of tribes living in areas proximate to treated canals, HED believes that a subsistence fisherman scenario is plausible. Portions of the Columbia River Basin affected by tribal fishing in Washington, Oregon, and Idaho receive drainage from treated canals. Tribal fishing sites identified by EPA for a Columbia River Basin Fish Contaminant Survey were located in the following rivers: Clearwater River, Snake River, main stem Columbia River (lower Columbia below Bonneville, Bonneville pool, Dalles Pool, John Day Pool, Hanford Reach), Klickitat River, Deschutes River, Grande Ronde River, Fifteen Mile Creek, Umatilla River, Wenatchee River, Willamette River, and

Yakima River. Information provided by EFED on concentrations of acrolein in which fish are living can be used to estimate the body load of acrolein and its metabolites in consumed fish.

In the nature of the residue study in fish and shellfish, glycidol accounted for as much as 48% of the total radioactive residue in catfish in a study conducted at 20 ppb water concentration of acrolein. This amounts to 0.10 ppm radioactivity attributed to glycidol. (S. Funk, D204967, 5/25/95). According to EFED, the mean LC50 for a variety of fish ranged from 14 to 68 ppb (R.David Jones, D334659, 7/16/07). If an LC50 of 68 ppb is assumed, the nature of the residue in catfish study was conducted at a 0.3x rate and normalizing the study to 1X would give a glycidol residue concentration of 0.33 ppm or µg/g. Based on data provided in EPA's Exposure Factors Handbook Volume II dated August 1997, the mean Native American subsistence fish harvest is 70 g/day. Based on use information, an application rate of 26 times per year represents a reasonable maximum application rate. Based on this information, HED conducted a conservative, high-end subsistence fisherman exposure assessment using the exposure assumptions provided below.

Dietary Exposure Assumptions

- 68 ppb acrolein concentration in water (mean LC50 for salmon)
- 0.33 ppm glycidol concentration in fish (based on 0.1 ppm glycidol in fish at 20 ppb water concentration adjusted for assumed 68 ppb concentration)
- 70 g/day mean dietary fish intake (mean subsistence fish harvest EFH Volume II, 1997).
- 26 application days/fishing days/fish consumption days per year
- 70 kg adult body weight
- 70 year lifetime
- $Q_1^* = 0.16$ mg/kg/day^{-1}

Estimated Dietary Intake

0.00033 mg glycidol/g fish x 70 g/day x 26/365 days ÷ 70 kg bw = 0.0000234 mg/kg/day

Estimated Lifetime Cancer Risk

0.0000234 mg/kg/day x 0.16 = 3.7 X 10^{-6}

Based on this conservative analysis, estimated cancer risk to subsistence fishermen is 3.7 X 10^{-6} which is slightly above OPP's cancer risk level of concern of 1 X 10^{-6}. A slightly more refined, but still conservative assessment which assumes an acrolein water concentration of 34 ppb (the mean LC50 for a variety of fish) results in estimated cancer risks of 1.9 X 10^{-6}.

8.0 OCCUPATIONAL AND RESIDENTIAL EXPOSURE AND RISK

Acrolein products, MAGNACIDE H and MAGNACIDE B are restricted use pesticides. The sale and use of these products is limited to certified applicators or persons under there direct supervision. The products may be applied for uses covered by the certified applicators certification. Occupational and residential exposures to acrolein may occur from the use of

MAGNACIDE H for control of vegetation in irrigation canals. Exposures to acrolein from use of MAGNACIDE B are not expected based on the use pattern. Therefore, only potential exposures resulting from use of the herbicide MAGNACIDE H are assessed for this RED. (B. Daiss, D320995, 7/26/07)

8.1 MAGNACIDE H Air Monitoring Studies

Air monitoring data from three different submissions, one from the registrant and two from the California Air Resources Board (CARB) were evaluated and used to assess inhalation exposures to workers and residential bystanders (T. Dole, D321006, 7/3/07). The Baker Petrolite submission consists of a study entitled, "MAGNACIDE H HERBICIDE Air Monitoring Studies" (MRID 469769-12) which provides data from an industrial hygiene monitoring study and a field air monitoring study. The CARB submissions provides data on 1) samples collected by CARB during the application of acrolein into an irrigation canal as part of pilot study to determine the applicability of the proposed field test methods before proceeding to the full scale study (MRID 470734-01) and 2) samples collected by CARB during the subsequent full scale study (http://www.cdpr.ca.gov/docs/empm/pubs/tac/studies/acrolein.htm). While the available air monitoring data is generally of high quality based on the sampling methodologies employed, it is important to note that the data does not represents the potential broad set of conditions and locations relative to the range of possible application parameters, conditions, and potential sampling sites.

8.1.1 Industrial Hygiene Monitoring Data

The Baker Petrolite Corporation submitted summary results from a MAGNACIDE H HERBICIDE Industrial Hygiene Monitoring Study. The Industrial Hygiene Monitoring Results reported by Baker Petrolite indicated that applicator acrolein exposures were all below the limit of detection (LOD) which ranged from 2.2 to 70 ppb. The results of the study are summarized in Table 7.

Table 7. Results of Acrolein Industrial Hygiene Monitoring Samples (MRID 469769-12)

Date	Operation	Sample Duration	Air Concentration (ppb)
1991	Applying MAGNACIDE H into irrigation canal	N/A	<16
1991	Hook up of MAGNACIDE H application	N/A	<70
1991	Disconnect of MAGNACIDE H application	N/A	<70
6/27/96	Area monitoring during MAGNACIDE H applications	N/A	<50
6/27/96	Running acrolein residuals near application site	8 hours	<18
6/27/96	Working in area of application point in canal	8 hours	<11
6/27/96	Sampling treated water from canal	8 hours	<50
7/27/99	Shadowing applicator* during MAGNACIDE application in reservoir	127 minutes	<2.2
7/28/99	Shadowing applicator* during MAGNACIDE application in canal	272 minutes	<2.2

* The air sampling technician followed the worker around and kept the sampler near the worker's

Table 7. Results of Acrolein Industrial Hygiene Monitoring Samples (MRID 469769-12)			
Date	**Operation**	**Sample Duration**	**Air Concentration (ppb)**
breathing zone. This is often done when the sampling device is too large to be worn by the worker or when legal complications prevent the collection of samples directly from the worker.			

8.1.2 Field Monitoring Data

California Air Resources Board (CARB) collected acrolein air monitoring during the application of acrolein into an irrigation canal as part of full scale study conducted in 2006. Air monitoring was conducted during a 4 hour application period and for 4 hours post-application. The results are included in Tables 8 and 9. Acrolein levels ranged from 8.4 to 24 ppb during application and from 1.2 to 5.3 ppb in the post-application period. CARB also collected acrolein air monitoring during the application of acrolein into an irrigation canal as part of pilot study conducted in 2005 to determine the applicability of the proposed field test methods before proceeding to the full scale study. The results of the pilot study are provided in Table 10. Acrolein levels ranged from 15.9 to 59.8 ppb. The highest levels were recorded on the west bank. There were no equipment malfunctions or leaks reported during the sampling period and the weather conditions were normal.

Table 8. Results of CARB Monitoring of Acrolein During Application (http://www.cdpr.ca.gov/docs/empm/pubs/tac/studies/acrolein.htm)		
Test Location Application Rate Canal Flow	**Sampling Site (AP = Application Point) 4 Hour Application Period**	**Air Concentration (ppb)**
Kern County California 4.0 ppm 357 cfs	1. West bank AP	11
	2. West bank AP collocated sample	10
	3. East bank AP	11
	4. East bank AP collocated sample	15
	5. West bank 25 m south, 9.6 m west of AP	10
	6. East bank 19.5 m south, 10 m east of AP	9.5
	7. West bank 50 m south of AP at Canal's Edge	8.4
	8. East bank 42 m south of AP at Canal's Edge	14
	9. West bank 100 m south of AP at Canal's Edge	17
	10.East bank 88 m south of AP at Canal's Edge	20
	11. West bank 150 m south of AP at Canal's Edge	16
	12. East bank 137 m south of AP at Canal's Edge	13
	13. West bank 200 m south of AP at Canal's Edge	13
	14. East bank 187 m south of AP at Canal's Edge	18
	15. West bank 250 m south of AP at Canal's Edge	24
	16. East bank 237 m south of AP at Canal's Edge	11

Table 9. Results of CARB Monitoring of Acrolein Post-Application (http://www.cdpr.ca.gov/docs/empm/pubs/tac/studies/acrolein.htm)		
Test Location Application Rate	**Sampling Site (AP = Application Point)**	**Air Concentration (ppb)**

Canal Flow	4 hour Post-Application Period	
2.7Kern County California 4.0 ppm 357 cfs	1. West bank AP	5.3
	2. East bank AP	3.2
	3. West bank 25 m south, 9.6 m west of AP	1.4
	4. East bank 19.5 m south, 10 m east of AP	2.2
	5. West bank 50 m south of AP at Canal's Edge	2.7
	6. East bank 42 m south of AP at Canal's Edge	2.7
	7. West bank 100 m south of AP at Canal's Edge	1.9
	8.East bank 88 m south of AP at Canal's Edge	2.2
	9. West bank 150 m south of AP at Canal's Edge	2.6
	10. East bank 137 m south of AP at Canal's Edge	3.2
	11. West bank 200 m south of AP at Canal's Edge	1.2
	12. East bank 187 m south of AP at Canal's Edge	1.4
	13. West bank 250 m south of AP at Canal's Edge	2.4
	14. East bank 237 m south of AP at Canal's Edge	1.7

Table 10. Results of CARB Monitoring of Acrolein (MRID 470734-01)

Test Location Application Rate Canal Flow	Sampling Site (AP = Application Point) During Application	Air Concentration (ppb)
Oildale, California 3.9 ppm 400 cfs	1. East Bank – 70 ft south and 30 ft east of AP	18.3
	2. East Bank - 115 ft south and 30 ft east of AP	15.9
	3. East Bank - 119 ft south and 30 ft east of AP	18.1
	4. East Bank - 190 ft south and 30 ft east of AP	18.4
	5. West Bank – 45 ft south and 30 ft west of AP	59.8
	6. West Bank – 110 ft south and 30 ft west of AP	43.2

The MAGNACIDE H Field Air Monitoring samples were collected in 2002 in conjunction with two environmental consulting firms (Intertox, Inc. and Parametrix) to complete a risk assessment in support of an acrolein application permit for the Washington Department of Ecology. A summary of these results is given in Table 10. The highest result of 63 ppb occurred at the California #1 Test Location where a leak reportedly occurred. The results at the other two test locations ranged from Non-Detect to 30 ppb. The limit of detection was not specified but was estimated to be approximately 1 ppb based on the fact that the lowest reported result was 1.5 ppb.

Table 11. Results of MAGNACIDE H Field Air Monitoring (MRID 469769-12)		
Test Location, Application Rate, Canal Flow	**Sampling Site**	**Air Concentration (ppb)**
Washington, 1.98 ppm, 840 cubic feet per second (cfs)	Application point	25
	Downstream, right-of-way	4
	Downstream, right-of-way	None Detected
	Downstream, 150 feet into field	2
	Downstream, 150 feet into field	None Detected
Central California #1 8 ppm for 2 hours 200 cfs	Application point	63*
	Downstream, right-of-way	38
	Downstream, right-of-way	13
	Downstream, 150 feet into field	None Detected
	Downstream, 150 feet into field	7.8
Central California #2 7.2 ppm for 2 hours 48 cfs start 38 cfs finish	Application point	13
	Downstream, right-of-way	20
	Downstream, right-of-way	30
	Downstream, 150 feet into field	1.5
	Downstream, 150 feet into field	7.9
* Equipment leak experienced and operating vehicle entered the test site		

8.2 Occupational Exposure and Risk

8.2.1 Regulatory Standards

The Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) for acrolein is 0.1 ppm as an 8-hour time-weighted average (TWA) concentration. OSHA has also established a 15-minute TWA short-term exposure limit (STEL) of 0.3 ppm. The National Institute for Occupational Safety and Health (NIOSH) has established an Immediately Dangerous to Life or Health (IDLH) level of 2 ppm. The American Industrial Hygiene Association has established an Emergency Response Planning Guideline (ERPG-2) of 0.5 ppm. The ERPG-2 is defined as the maximum airborne concentration below which it is believed that nearly all persons could be exposed for up to 1 hour without experiencing or developing irreversible or other serious health effects or symptoms that could impair their abilities to take protective action. While OPP does consider regulatory levels set by other authorities in assessing risk from pesticides, these Agencies have different legislative requirements, do not have the authority under FIFRA to regulate pesticide exposures, and do not set exposure levels for chemicals used solely for pesticides. The human study used for selection of an inhalation endpoint for this assessment is appropriate for the route of exposure and duration. The study provides the most comprehensive description available of acute/short-term effects in humans and provides the best information available for establishing an endpoint for short-term intermittent inhalation worker and residential bystander exposure scenarios presented by use of acrolein as an herbicide in canals and/or reservoirs.

8.2.2 Application, Training/Certification, and PPE Requirements

For herbicidal use in irrigation canals, the maximum single application concentration of acrolein is 15 ppm. This application rate is used when there is high weed density in the treated canal. Applications can occur multiple times during a year; neither the maximum number of applications, nor the minimum interval between applications is specified on the label. The maximum single application rate used during the year at each irrigation system is most often 8 ppm but applications at 15 ppm commonly occur (reported in at least one irrigation district in 9 of 15 of these states). Acrolein is applied up to 26 times per year in some irrigation systems with an interval as short as 7 days, but 6 applications per year is the most common, with a two or three week interval between applications. Reported treatment durations ranged from 15 minutes to 8 hours.

MAGNACIDE H and MAGNACIDE B are applied through closed system transfer from steel cylinders designed to prevent applicator exposure. Both products are supplied in pressurized containers. Nitrogen is used to pressure the liquid chemical out of the container through a metering device then directly into the canal (MAGNACIDE H) or the injection well pipeline (MAGNACIDE B) through sealed hoses. The applicator must use only specified application equipment built specifically for use of these products.

MAGNACIDE H is injected directly below the surface of moving water where it is carried along by the flow. MAGNACIDE B is injected into closed injection well piping. Applicators of both MAGNACIDE H and MAGNACIDE B must wear a full face air purifying respirator with organic vapor (OV) cartridges approved by NIOSH and butyl rubber gloves when setting up and breaking down application equipment. For visual inspection of equipment during treatment, chemical splash goggles must be worn. The MAGNACIDE H HERBICIDE Application and Safety Manual and the MAGNACIDE B Description and Use Manual contain comprehensive instructions for use of the product. The acrolein labels require that the respective manuals must be in the possession of the applicator during all acrolein application, handling and storage activities and applicators must comply with the procedures specified in the manuals.

The sole registrant, Baker Petrolite, has a comprehensive training program in place to ensure that applicators are competent in the application, handling and storage procedures required for use of both MAGNACIDE H and MAGNACIDE B. All persons handling these products must be properly trained and certified in the correct application techniques. Refresher training is provided at least every three years and more frequently as needed for application of both products. In addition, refresher training in the form of review and safety awareness training videos, which provide step-by-step application and safety procedures is always available to applicators.

The label required training and certification is thorough, comprehensive and effective in ensuring safe application of acrolein compounds. However, there is the possibility of a spill or leak during the use of acrolein. Standard requirements for spill response for highly toxic compounds are included in the MAGNACIDE H Application and Safety Manual and the MAGNACIDE B Description and Use Manual. Under standard spill/leak response requirements, a

supplied-air respirator or self-contained breathing apparatus (SCBA) of specified type is required if the acceptable air concentration level (i.e., IDLH of 2 ppm for acrolein) is exceeded at any time. The specified respirator must be available and required for entry into an affected area in the event of a leak or spill.

8.2.3 Occupational Exposure and Risk Estimates

Occupational exposures to acrolein from use of MAGNACIDE B are not expected because it is applied via a completely closed system. MAGNACIDE B Microbiocide is applied in injection systems associated with petroleum production. The MAGNACIDE B product is applied by pumping acrolein from pressurized containers into closed injection well piping systems. The closed application system combined with stringent training and PPE requirements is expected to effectively prevent exposures of concern MAGNACIDE B biocide product.

Exposure to acrolein from application of MAGNACIDE H is not expected during set up and break down of equipment because applicators must comply with stringent label requirements for PPE (i.e., full face air purifying respirator, butyl rubber gloves, etc.) during these activities. Use of a closed application system combined with stringent training, certification and PPE requirements is expected to effectively prevent dermal exposures of concern to workers during handling and application activities. However, since application of MAGNACIDE H may take from 15 minutes to 8 hours and respiratory protection is not required after initial set up and prior to break down of equipment, inhalation exposures to workers during application may occur. Post application exposures to workers may also occur depending on the length of time the worker remains in the area after application has been completed and the equipment broken down. The exposure level at which inhalation risks are not of concern is 3 ppb (90 ppb LOAEL ÷ UF 30). The target LOC or MOE for short-term inhalation exposure to acrolein is 30. Air monitoring levels in the vicinity of treated canals ranged from 1.5 to 63 ppb. The highest result was reportedly due to equipment leakage and presence of an operating vehicle. These results are similar, however, to the results reported by CARB where no unusual events occurred.

Short-term MOEs for occupational exposure calculated using concentrations from the air monitoring data ranged from 5 to 200. MOEs may exceed HED's level of concern for worker exposure during the application period between set up and break down and after break down. Therefore, MOEs for occupational exposure may exceed HED's level of concern for worker exposure during the application period between set up and break down. Also, depending on the extent to which workers remain in the vicinity of the treated canal after acrolein has been applied and requirement for use of a respirator are no longer applicable, MOEs for worker post-application exposure may exceed HED's level of concern.

Table 12: Estimated Exposure and Risk to Workers

Range of Measured Concentrations (ppb)	LOAEL (ppb)	Target MOE	Calculated MOE
1.5 - 63 (0.0015-0.063 ppm)	90 (0.09 ppm)	30	1.5 – 60

Calculated MOE = Short Term Inhalation NOAEL (90 ppb) ÷ estimated inhalation concentration (1.5 – 63 ppb).

8.3 Residential Exposure and Risk Estimates

There are no residential handler (applicator) uses for acrolein. However, residential exposure via the inhalation pathway can occur as a result of application of MAGNACIDE H to irrigation canals that may be located near residential areas. In addition, since swimming in treated reservoirs or canals is not strictly prohibited, there is potential exposure to acrolein via inhalation, dermal, and oral routes resulting from a swim scenario. Significantly, there are no requirements in the label for establishment of area restrictions in the proximity of the application site or the treated canal. The label contains no provisions for identification of treatment areas or establishment of boundaries to indicate a restricted area and/or prohibit entry. Typically, for applications of this type (e.g., fumigants) there are clear requirements to establish restricted areas in the vicinity of treatment with postings to mark the boundary and prohibit entry by persons other than fumigation personnel during treatment and until air concentrations are below levels of concern.

The acrolein exposure level at which inhalation risks are not of concern is 3 ppb (90 ppb LOAEL ÷ UF 30). The range of measured air concentrations based on monitoring data is 1.5 to 63 ppb. The target LOC or MOE for short-term inhalation exposure to acrolein is 30. Short-term MOEs for residential exposure calculated using concentrations from the air monitoring data ranged from 5 to 200. Therefore, depending on the extent to which residential areas are located within the vicinity of treated canals and/or non-workers are conducting activities near treated canals at or near the time of treatment, inhalation MOEs for residential bystander exposure indicate risks of concern. As the data indicates and as expected, air concentrations of acrolein decrease with distance from the source (e.g., the treated canal). Therefore, the highest potential risks are to persons standing adjacent to the canal. Persons living in residences further from the canal will have lower risk. It should be noted that available monitoring data provide insufficient information to determine the appropriate dimensions of a restricted area relative to the application point or area source (i.e., the canal).

While a separate swimmer assessment was not conducted due to lack of appropriate endpoints for dermal and oral exposure, risks to swimmers from inhalation would be at least as high as or higher than risks to the individuals standing/playing adjacent to the treated water body.

Table 13: Estimated Inhalation Exposure and Risk to Residential Bystanders

Range of Measured Concentrations (ppb)	LOAEL (ppb)	Target MOE	Calculated MOE
1.5 - 63 (0.0015-0.063 ppm)	90 (0.09 ppm)	30	1.5 – 60

Calculated MOE = Short Term Inhalation NOAEL (90 ppb) ÷ estimated inhalation concentration (1.5 – 63 ppb).

9.0 AGGREGATE EXPOSURE AND RISK

Aggregate exposure is assessed when there are potential residential exposures to the pesticide, aggregate risk assessment must consider exposures from three major sources: oral, dermal and inhalation exposures. Since there are no residential uses and exposures occur via the inhalation route only, an aggregate exposure assessment is not required.

10.0 CUMULATIVE RISK

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

EPA does not have, at this time, available data to determine whether acrolein has a common mechanism of toxicity with other substances. Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to acrolein and any other substances and, acrolein does not appear to produce a toxic metabolite produced by other substances which have tolerances in the U. S. For the purposes of this tolerance reassessment action, therefore, EPA has not assumed that acrolein has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's OPP concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/fedrgstr/EPA_PEST/2002/January/Day_16/.

11.0 DATA NEEDS

11.1 Residue Chemistry Data Requirements

- Provided that the registrants submit the data required in the attached data summary tables for the acrolein TGAIs/MPs, and either certify that the suppliers of beginning materials and the manufacturing processes for these TGAIs/MPs have not changed since the last comprehensive product chemistry review or submit complete updated product chemistry data packages, the Agency has no objections to the reregistration of acrolein with respect to product chemistry data requirements.

- If the registrant continues to support the SLN use in reservoirs and labels for these uses are not revised to provide effective fishing prohibitions (e.g., posting, restricted entry, etc.), an enforcement analytical method must be developed and validated, including validation by an independent laboratory, for the determination of glycidol in fish and shellfish.

- If the registrant continues to support the SLN use in reservoirs and labels for these uses are not revised to provide effective fishing prohibitions (e.g., posting, restricted entry, etc.), magnitude of the residue of acrolein and glycidol in fish and shellfish are required. The registrant is urged to submit a protocol before beginning any study.

- A confirmatory nature of the residue study in root and tuber (preferably radish) is required.

11.2 Toxicology Data Requirements

None.

11.3 Occupational and Residential Exposure Requirements

As previously noted, while the available air monitoring data is generally of high quality based on the sampling methodologies employed, the data represents only a minimal set of conditions and locations relative to the range of possible application parameters, conditions, and potential sampling sites. Also, available monitoring data provide insufficient information to determine the appropriate dimensions of a restricted area relative to the application point or area source (i.e., the canal). Additional air monitoring data are required to fully assess and characterize potential exposure and risk to residential bystanders. Additional monitoring data from a full scale air monitoring study conducted by CARB may be available to HED for review and use in refining the risk assessment in the near future. HED will incorporate the new CARB data into the risk assessment once it becomes available. Depending on receipt of additional CARB data and a determination of its adequacy for assessing risk to residential bystanders, additional air monitoring data may be required.

Based on the risk assessment, HED recommends that the MAGNACIDE H label be revised to clearly require the establishment of restricted areas in the vicinity of treatment. The restricted areas should be identified by marking the boundary to clearly prohibit entry. Only fumigation personnel should be allowed within this area during treatment and until air concentrations are below levels of concern.

APPENDICES

1.0 GUIDELINE TOXICOLOGY DATA SUMMARY

1.1 Guideline Data Requirements

Data requirements (40CFR 158.340) for acrolein are provided in table 1. Use of new GL numbers does not imply that new (1998) guideline protocols were used.

Table 1. Guideline Data Requirements

Test		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	no
870.3100	Oral Subchronic (rodent)	yes	yes*
870.3150	Oral Subchronic (nonrodent)	yes	yes
870.3200	21-Day Dermal	yes	yes
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	yes
870.4200a	Oncogenicity (rat)	yes	yes
870.4200b	Oncogenicity (mouse)	yes	yes
870.4300	Chronic/Oncogenicity	yes	yes
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes*
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5375	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5900	Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a	Acute Delayed Neurotox. (hen)	no	-
870.6100b	90-Day Neurotoxicity (hen)	no	-
870.6200a	Acute Neurotox. Screening Battery (rat)	no	-
870.6200b	90-Day Neuro. Screening Battery (rat)	no	-
870.6300	Develop. Neuro	no	-
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	-	-

Table 1. Guideline Data Requirements		
Test	**Technical**	
	Required	**Satisfied**
Special Studies for Ocular Effects		
Acute Oral (rat).....	no	-
Subchronic Oral (rat)	no	-
Six-month Oral (dog).....	no	-

* Non-guideline study

1.2 Toxicity Profiles

Table 2. Acute Toxicity Profile – Acrolein				
Guideline No.	**Study Type**	**MRID No.**	**Results**	**Toxicity Category**
870.1100	Acute oral - rat	41257001	LD_{50} = 11 mg/kg	I
870.1200	Acute dermal - rabbit	00141028	LD_{50} = 231 mg/kg	I
870.1300	Acute inhalation - rat	40945404	LC_{50} = 0.019 mg/L	I
870.2400	Eye irritation - rabbit	00141025	Severely irritating	I
870.2500	Dermal irritation - rabbit	00141026	Severely irritating	I
Non-GL study	Skin sensitization	Sustin and Breienstein, 1990	Suggestive/limited data	

Table 3. Subchronic, Chronic and Other Toxicity Profile: Acrolein		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
Non-guideline, oral gavage – rats	NTP 1995; 0.75, 1.25, 2.5, 5.0 or 10 mg/kg/d in 0.5% methyl cellulose for 13 wks	**LOAEL** = 2.5 mg/kg/day in males; 1.25 mg/kg/day in females, based on forestomach squamous epithelial hyperplasia **NOAEL** = 1.25 mg/kg/day in males; = 0.75 mg/kg/day in females Abnormal breathing and nasal discharge, hemorrhage,and necrosis and chronic-active inflammation of the forestomach and glandular stomach and mortality at 10 mg/kg/day. Hemorrhage of glandular stomach at 5 mg/kg/day.
Non-guideline, oral gavage – mice	NTP 1995; 0, 1.25, 2.5, 5.0, 10.0, 20.0 mg/kg/d in 0.5% methyl cellulose for 13 wks	**LOAEL** = 2.5 mg/kg/day in females; 1.25 mg/kg/day in males, based on forestomach squamous epithelial hyperplasia **NOAEL =** 1.25 ma/kg/day in females, No NOAEL for males. No clinical signs of toxicity. Glandular stomach lesions in the 10 and 20 mg/kg/day males and 20 mg/kg/day females.
Non-guideline, oral gavage – rats	Arumugam *et al* (1999b) 0, 2.5 mg/kg/day for 45 days via intubation in distilled water to 5 male rats/group.	Acrolein resulted in severe depletion of liver cystolic GSH. Electron microscopy revealed loss of mitochondrial lamellae of the cristae accompanied with a 41% decrease in mitochondrial GSH. Citric acid cycle enzymes were also reduced 30 to 56%. The activities of GSH peroxidase and superoxide dismutase were increased significantly ($p<0.001$). Because GSSG was unchanged, GSH depletion was presumed to result from conjugation with acrolein.

Table 3. Subchronic, Chronic and Other Toxicity Profile: Acrolein		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3200 21 - Day dermal toxicity - rabbits	00141030 (1982) **Acceptable/guideline**, 0, 7, 21 or 63 mg/kg/day. 6 hrs/day, 5 days/week for 3 weeks.	**Systemic LOAEL** = 7 mg/kg/day based on decreased body weight gain, and food consumption in both sexes, and minimal to moderate multifocal interstitial pneumonia and moderate bilateral interstitial nephritis in the females. **Systemic NOAEL** was not established **Dermal LOAEL** = 7 mg/kg/day based on dermal irritation: slight to moderate reddening with swelling and firmness of the test site, and scab formation with peeling and microscopic findings in the treated skin (minimal to marked necrosis, hyperkeratosis, parakeratosis, and acanthosis). **Dermal NOAEL** was not established.
870.4100b 12-Month Chronic Oral Toxicity (capsule) - Dogs	41071701 (1987) **Acceptable/guideline**, 0, 0.1, 0.5, 1.5 - 2 mg/kg/day in gelatin capsules for 53 weeks	**LOAEL** = 2.0 mg/kg/day based on vomiting in both sexes. In the range finding study, 2 mg/kg/day for 2-6 days resulted in dose dependent weight loss, decreased food consumption and vomiting (occasionally red-tinged). At a dose of 10 mg/kg/day and above in the range finding study, vomiting preceded death of animals. **NOAEL** = 0.5 mg/kg/day
Non-guideline, oral chronic study -rats	Lijinsky and Reuber, 1987. Male Fischer 344 rats (20/group acrolein in the drinking water 0, 6, 14, or 36 mg/kg/day, 5 days/week for 104-124 weeks. One group of 20 female rats administered the high dose only. (Note: The two highest doses exceed the oral LD_{50} in rats)	Adrenocortical tumors (5/20) and hyperplastic nodules of the adrenal cortex (2/20) were found only in females in the high concentration group. The increased incidence of adrenocortical tumors was considered by the authors to be marginally significant as judged by the Fisher's exact test (p=0.091) and significant for adrenocortical tumors plus hyperplastic nodules (p=0.022). According to the authors, this type of tumor is rare in untreated female Fischer 344 rats; there was one reported in concurrent controls. The historical incidence is approximately 4.8% based on the findings of Solleveld et al. (1984) for untreated female F-344 rats allowed to die naturally. Significant increases in tumor incidence were not found in male rats. There was no treatment-related mortality.
Non-guideline – initiation promotion study - rats	Cohen *et al* (1992) 2 mg acrolein/kg by i.p. injection twice weekly for 6 or 21 weeks. Another group received acrolein for 6 weeks followed by uracil 3% by weight.	No increases in tumor incidence were reported in groups exposed to acrolein alone for either 6 or 21 weeks (severe toxicity occurred during the 21week study). Exposure to acrolein for 6 weeks followed uracil (3% by weight) for 20 weeks resulted in the induction of 18 papillomas and one carcinoma, a significantly greater incidence ($p<0.05$) than following exposure to uracil alone (8/30). While it appears that acrolein may have some tumor initiating capability, it should be noted that the incidence of papillomas and nodular hyperplasias combined, was significantly greater in the uracil only group compared with the group initiated with acrolein ($p<0.05$).

Table 3. Subchronic, Chronic and Other Toxicity Profile: Acrolein		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
Inhalation study - humans	(Weber-Tschopp et al. 1977; MRID 47060601 volunteers were exposed to acrolein in a 30 cubic meter chamber at an 0.1 hourly air exchange rate in 3 trials: (1) A continuous exposure at constantly increasing acrolein concentrations, (2) Discontinuous short exposures to successively increasing concentrations, and (3) Constant concentration for one hour.	Threshold for measured effects: Eye irritation 0.09 ppm Nasal irritation 0.15 ppm Eye blink frequency 0.26 ppm Breathing frequency 0.30 ppm Throat irritation 0.30 ppm
Non-guideline Inhalation –F344 rats	Kutzman (1981); Kutzman *et al* (1985); Costa *et al*(1986) 0, 0.4, 1.4, or 4.0 ppm (0, 0.9, 3.2, 9.2 mg/m^3)/6 hr/day, 5 days/week for 13 weeks	1. High mortality at 4 ppm. 2. Increase in lung collagen at 1.4 and 4 ppm ($p<0.05$). 3. Elastin content in 4 ppm group twice controls. 4. Bronchial necrosis and pulmonary edema at 4 ppm. 5. Parenchymal restriction at 0.4 ppm and obstructive lesions at 4.0 ppm. 6. No cytogenic or sperm abnormalities
Non-guideline Inhalation - Rats Dahl, female (selected for susceptibility or resistance to salt induced hypertension)	Kutzman *et al* 1984, 1986 0, 0.4, 1.4, or 4.0 ppm (0, 0.9, 3.2, 9.2 mg/m^3)/6 hr/day, 5 days/week for 13 weeks	1. All susceptible 4 ppm rats died after 11 days and 60% of resistant rats survived to end of study. 2. Lungs of susceptible rats had severe airway necrosis with edema and hemorrhage but only proliferative changes with resistant rats. 3. No differences in histopath between rat groups at lower doses. 4. No effect of exposure on blood pressure changes.
Non-guideline Inhalation – rats, monkeys, guinea pigs, dogs	Lyon *et al*. 1970 0, 0.22, 1.0 and 1.8 ppm (0, 0.5, 2.3, and 4.1 mg/ m^3) acrolein for 24 hr/day for 90 days	1. Ocular and nasal discharges in dogs and monkeys at 1 ppm; severe at 1.8 ppm. 2. Squamous metaplasia of trachea in all monkeys at 1.8 ppm. 3. Two dogs at 1.8 ppm had confluent bronchopneumonia. 4. Evidence of pulmonary inflammation (guinea pigs at 1 ppm) and focal liver necrosis (rats and guinea pigs at 1 ppm). 5. Nonspecific inflammatory changes in a variety of tissues in both rats and guinea pigs at 1.8 ppm. **LOAEL =** 1 ppm (2.3 mg/m^3) based on inflammation in several organs of one or more species. **NOAEL** = 0.22 ppm (0.5 mg/m^3)

Table 3. Subchronic, Chronic and Other Toxicity Profile: Acrolein		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
Non-guideline Inhalation - rats	Bouley et al. (1975, 1976, cited in IRIS 2003), male SPF OFA rats (110/group) at 0 or 0.55 ppm (0 and 1.3 mg/m^3) acrolein. Exposure length and duration not stated, measurements were reported for exposures up to 77 days. Study limitation: one exposure and histopathology.	Decreased body weight (<80% of controls) by Day 60. Nasal irritation (sneezing) in exposed rats between Days 7 and 21. Sneezing subsequently disappeared. A significant decrease in the number of alveolar macrophages in exposed rats. Liver weights not affected after 22 days of exposure but liver/body weight ratios were decreased in exposed animals after Day 15. Lung/body weight ratios were unchanged after Day 15 or 32, but were significantly elevated ($p<0.002$) after 77 days. No effect on hepatic alcohol dehydrogenase after 15 days of exposure. Serum alkaline phosphatase was unchanged at days 15, 32 and 77. On the other hand, serum acid phosphatase was increased on day 15 ($p<0.001$), but not on days 32 and 77. An LD_{50} inhaled dose of *Salmonella enteritidis* resulted in a higher death rate in treated animals than controls at 18 days, but not at 63 days.
Non-guideline Inhalation - rats	Catilina *et al*, 1966: 10 minutes/day for 8 wks at 262 ppm acrolein	Caused peribronchial hemorrhage and bronchial lumen obstruction
Non-guideline Inhalation - rats	Feron *et al*, 1978. Groups of 12 rats, 20 hamsters, and 4 rabbits were exposed to 0, 0.4, 1.4 or 4.9 ppm acrolein, 6 hours/day, 5 days/week for 13 weeks (0, 0.9, 3.2, 9.2 mg/C)	At 4.9 ppm mortality in rats, ocular and nasal irritation, growth depression and histologic changes in the respiratory tract in all species. At mid dose, squamous metaplasia and neutrophilic infilitration of the nasal mucosa in the rat; minimal inflammatory changes in the hamster. No effects in the mid and low dose rabbits. Intermediate-duration **MRL** of 0.00004 ppm based on **LOAEL** of 0.4 ppm of nasal epithelial metaplasia. The rat was the most sensitive at the lowest exposure. The duration adjusted LOAEL in humans + 0.4 ppm x 24 hr x 5/7 days = 0.071 ppm. Adjusting for the rat and human respiratory surface area for rat (15 cm2) and human (200 cm2), the $LOAEL_{HEC}$ = 0.012 ppm. Adjusting for 300 UF (10 X for LOAEL, 3X for extrapolation from animals to Humans using domestric adjustments, 10 X for human variability), the MRL is 0.012/300 = 0.00004 ppm. **NOAEL** is less than 0.4 ppm
Non-guideline Inhalation - rats	Kutzman (1981) Fischer 344 rats (8/sex/group) via inhalation to acrolein at 0, 0.4, 1.4, or 4.0 ppm 0, 0.9, 3.2 or 9.2 mg/ m^3) 6 hr/day, 5 days/week (62 exposure days) and the animals were evaluated 13.3 weeks after initiation of exposure.	Exposed and control male rats were mated with unexposed females for 6 days and also exposed females were mated with unexposed and exposed males. Parameters evaluated were corpora lutea, viable embryos, early and late deaths, and preimplantation losses. There were no treatment-related effects on reproductive performance. Decreased pulmonary function was observed at 4 ppm.

Table 3. Subchronic, Chronic and Other Toxicity Profile: Acrolein		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
Non-guideline Inhalation Reproduction - rats	Bouley *et al* (1975 cited in IRIS 2003) 3 male and 21 female SPF OFA rats exposed continuously 1.3 mg/ m^3 (0.6 ppm), mated on the 4^{th} day of exposure. Exposures continued for 22 more days when females sacrificed.	No significant differences in the number of and mean weight of fetuses (no data given) were reported. While the results were negative, the minimal results reporting limits conclusions that can be drawn from this study.
870.3800 two gen. Repro. Study - rats	41869101, 1992 0, 1, 3, or 6 mg/kg/d by gavage in a dosing volume of 5 ml/kg	**Maternal LOAEL** = 3 mg/kg/day based on mortality at 6 mg/kg in both F0 and F1males and females and F1 mid-dose animals, most of the latter showing signs of respiratory distress and histopathological lesions in the lungs and stomach (erosions of glandular mucosa and hyperplasia/hyperkeratosis of the forestomach). Respiratory effects may be attributed to possible aspiration of gavage solution. . Significant depressions in body weight gains were noted in the high-dose groups and achieved statistical significance in the mid-dose animals on several occasions. **Maternal NOAEL** = 1 mg/kg/day Reproductive **LOAEL** = 6 mg/kg/day. Reproductive parameters (i.e., mating performance and fertility indices) were unaffected. No treatment-related gross or microscopic effects were observed in the reproductive tissues of any of the F0 or F1 animals. **Offspring LOAEL** = 6 mg/kg/day. There were no statistically significant differences among the groups in the number of F1 litters with gross abnormalities for the pups (F2) during lactation or gross lesions identified in the pups at necropsy.
870.3700 Developmental study - rabbits	40392401 (1987) **Acceptable/guideline**, Pregnant New Zealand white rabbits (20/group) dosed via gavage with 0, 0.1, 0.75, or 2.0 mg/kg-day for days 7 through 19 of presumed gestation and subjected to caesarean sectioning on day 29. Range finding study at 0, 0.5, 1.0, 2.0 4.0 or 6.0 mg/kg/day.	**Maternal LOAEL** = 2 mg/kg/day based on decreased body weights, body weight gains and food consumption. In the range finding study, maternal death, abortion, clinical signs, gastric ulceration, sloughing of the gastric mucosa, and complete litter resorption at ≥4 mg/kg/day. **Maternal NOAEL** = 0.75 mg/kg/day **Developmental LOAEL** = >2 mg/kg/day. Fetal malformations were distributed evenly among the groups and were consistent with historical control data. **Developmental NOAEL** = 2 mg/kg/day, highest dose tested.

Table 3. Subchronic, Chronic and Other Toxicity Profile: Acrolein		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3700a Developmental Toxicity- Rat	00156438 (1982) **Acceptable/guideline**, 40 time-mated females per group dosed via gavage at 0, 3.6, 6 or 10 mg/kg/day from GD 7 through 19	**Maternal LOAEL** = 3.6 mg/kg/day based on mortality with no clinical signs but in a 2-gen repro study,(MRID 41869101) mortality at 3 mg/kg/day with histopathology in the forestomach was observed. **Maternal NOAEL** is less than 3.6 mg/kg/day **Developmental LOAEL** = 10 mg/kg/day based on decreased fetal weights and litter weights and on incomplete ossification of the skeleton and general retarded development of fetuses. **Developmental NOAEL** = 6 mg/kg/day.
870.4200 24-Month Carcinogenicity in Mice	41334901 (1989) **Acceptable/guideline**, 0, 0.5, 2.0 or 2.5 mg/kg/day by gavage for 78 weeks	**LOAEL** = 4.5 mg/kg/day based on increased mortality. No adverse treatment-related effects were observed on clinical signs, body weights, body weight gains, food consumption, hematology, and organ weights, gross or microscopic pathology. **NOAEL** = 2.5 mg/kg/day Not carcinogenic in mice in this test.
870.4100 24-Month Chronic/Carcinogenicity Feeding-Rats	41306401 (1989) 46568001 (2002) 46568002 (2005), **Acceptable/guideline** 0, 0.05, 0.50, or 2.5 mg/kg/day via gavage for 2 years	**LOAEL** = 0.5 mg/kg/day based on increased mortality in both sexes. **NOAEL** = 0.05 mg/kg/day Equivocal evidence of carcinogenicity. After 24 months in the 2.5 mg/kg/day males, there was increased incidence of mammary gland adenoma (8% vs. 3% in concurrent 0-1.5% in. Combined adenoma and carcinoma (<=10%) approximated the historical control range (<=7.1%). Hepatocellular adenoma (8%) exceeded the concurrent (1%) and historical (0-3.5%) controls. Combined adenoma and carcinoma in the liver (<=8%) was within the historical control range (<=14.5%). Initial analysis of the pancreatic neoplasm suggested an increase in the incidence of pancreas acinar cell adenoma but a revised diagnosis according the criteria of Eustis *et al.* (1990) showed it was not related to treatment. Dosing was considered adequate based on increased mortality in both sexes.
870.7485 Metabolism and pharmacokinetics - rats	42031001 (1991) 43177101 (1994) 73275901 (1994) Parent et al (1996) Parent et al 1998) Single dose 2.5 mg/kg (iv or oral), or 2.5 mg/kg after 14 days of unlabeled acrolein (oral), or single 15 mg/kg (oral). Radiolabel monitored in expired air, urine, and feces.	>96% of radioactivity was recovered in excreta within the first 24 hours. Tissue concentrations (including blood) of radioactivity were minimal. Time course of excretion for all groups was similar except for delayed excretion in the high-dose group. No acrolein detected in excreta or tissues. The radiolabel in feces associated with a homopolymer of acrolein, apparently formed in the gastrointestinal tract. The main pathway of acrolein metabolism is the addition of GSH to the activated double bond followed by conversion to mercapturic acid. A second pathway is epoxidation of the double bond followed by attack on the epoxide by glutathione. A third pathway is addition of water to acrolein to form 3-hydroxypropionaldehyde, which can be further metabolized and ultimately incorporated into normal metabolic pathways.

Table 3. Subchronic, Chronic and Other Toxicity Profile: Acrolein		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.5900 In vitro *sister chromatid exchange*	00141032 (1982) **Acceptable/guideline** CHO cell cultures exposed at 0, 0.3, 0.5, or 0.75 µg /mL (-S9) for 29-31 hrs or 0, 0.1, 0.3, or 0.5 µg /mL (+S9) for 4 hours.	Acrolein was tested up to cytotoxic concentrations (0.75 g /mL -S9 and 0.5 g /mL +S9). No significant increases ($p<0.01$) in the number of SCEs/cell were observed at any concentration in either condition. The positive controls induced the appropriate response. **There was no evidence of SCE induced over background.**
In vitro *sister chromatid exchange*	Wilmer *et al*, 1986, IRIS. Cultured human lymphocytes	Acrolein at concentrations of 5, 15, and 20 µM, but not lower doses, induced significant increases in sister chromatid exchanges.
870-5375 *in vitro* mammalian chromosomal aberration assay - CHO	00141033 (1982) **Acceptable/guideline** CHO cell cultures exposed at 0, 0.0, 0.2, 0.4, 0.6, 0.8, 1.0 or 2.0 µg /mL (-S9) for 6 hrs or 0, 0.6, 0.8, 1.0, 1.5 or 2.0 µg /mL (+S9) for 2 hours.	Acrolein was tested up to cytotoxic concentrations (2.0 µg /mL without S9 and $\geq$1.5 µg /mL with S9). No marked increases in break frequency were observed at any concentration in the presence or absence of S9. The positive controls induced the appropriate response. **There was no evidence that Acrolein induced a clastogenic effect in the presence or absence of S9-activation.**
870-5300 (*in vitro* mammalian cell gene mutation assay - CHO – HGPRT locus: hypoxanthineguanine phosphoribosyl transferase	41579501 (1989) **Acceptable/guideline** CHO cell cultures exposed at 0 to .002 uL/mL (-S9) at 0 to 0.006 2.0 uL/mL (+S9).	Acrolein was tested up to cytotoxic concentrations ($\geq$0.003 µL/mL +S9 and $\geq$0.0008 µL/mL -S9). No reproducible significant increases in the mutant frequency were observed in the presence or absence of S9. The positive controls induced the appropriate response in all trials. **There was no evidence that Acrolein induced mutant colonies over background in the presence or absence of S9-activation.**
Non-guideline Bacterial reverse mutation	Foiles *et al* (1989) IRIS	Acrolein induced formation of deoxyguanosine adducts at concentrations of 10 µM, but not 4 or 7 µM, in *Salmonella* tester strain TA104. Lack of response at the lower doses suggests the presence of a saturable repair mechanism. Increasing adduct formation with dose was seen in tester strain TA100 at concentrations of 4 mM and greater.
Non-guideline Chinese hamster ovary cells	Foiles *et al* (1990) IRIS	deoxyguanosine adduct formation increased progressively at concentrations ranging from 0.1 to 1 mM in Chinese hamster ovary cells (CHO).
Non-guideline Human fibroblast cells	Curren *et al* (1988) IRIS	Acrolein was highly mutagenic to human fibroblast cells that were deficient in DNA repair (cells from xeroderma pigmentosum patients). It induced a positive dose-response between 0.2 and 0.8 µM but it did not induce an increase in the mutant frequency of normal fibroblasts
Non-guideline V79 cells	Smith *et al* (1990a) IRIS	Acrolein was mutagenic in V79 cells deficient in DNA repair. Normal V79 cells were not tested.
Non-guideline CHO cells	Au *et al* (1980) IRIS	*In vitro* chromosomal studies of acrolein have produced weakly positive findings in Chinese hamster ovary (CHO) cells
Non-guideline human lymphocytes	Wilmer *et al*. (1986) IRIS	acrolein have produced weakly positive findings in cultured human lymphocytes.

Table 3. Subchronic, Chronic and Other Toxicity Profile: Acrolein		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
Non-guideline Human fibroblast cells	Kawanishi *et al* (1998) IRIS	The majority of the mutations in human fibroblasts were base substitutions (76%) followed by deletions and insertions (24%). Single base substitutions were most frequently found (46%), multiple base substitutions accounted for 18%, and tandem (two adjacent) base substitutions were 12%. Of the base substitutions, G:C to T:A transversions accounted for 44% of the total and G:C to A:T transitions for 24%.
Non-guideline **S. typhimurium**	Vander Veen *et al* (2001) IRIS	when acrolein reacts with guanine residues in *S. typhimurium* to form 8-hydroxypropanodeoxyguanosine, the latter was not mutagenic in *S.typhimurium*.
Non-guideline	Yang *et al*. (2001). IRIS	Acrolein was nonmutagenic in *E. coli*
Non-guideline *S. typhimurium*	IRIS 2003 (literature summary)	In tests for frameshift mutation TA98 gave some positive responses while TA1538 was negative with S-9 and all negative with S+9 except one positive for TA98. Tests for base repair and point mutations (TA100, TA104 and TA1535) were positive in some tests with TA100, in most tests with TA104, but not with TA1535. TA104 has been reported to be more sensitive to carbonyl compounds (Marnett et al., 1985).

2.0 ADDITIONAL TOXICOLOGY STUDIES

Neurotoxicity

The central nervous system does not appear to be a target of acrolein toxicity. The ATSDR (2005) review states: "No information was located regarding neurological effects of acrolein in humans. Symptoms of central nervous system depression were observed in rodents after oral exposure to acrolein, but only after lethal concentrations (Sprince et al. 1979). No such effects were observed in animals after inhalation exposure; the animals died from asphyxia caused by epithelial desquamation and, consequently, respiratory obstruction (Ballantyne et al. 1989; Catilina et al. 1966; Crane et al. 1986; Skog 1950). No behavioral changes were observed in animals exposed to acrolein by any route. Nonspecific histopathological effects on the brains of animals were found in subchronic inhalation studies (Feron et al. 1978; Kutzman et al. 1984, 1985; Lyon et al. 1970). No histopathological changes in neurological tissues were observed after oral exposure (Parent et al. 1991, 1992a, 1992b). No studies regarding neurotoxicity of acrolein after dermal exposure were located. However, the available data do not indicate that the central nervous system is the major target of acrolein toxicity. No data needs have been identified at this time".

Developmental Toxicity

870.3700 Developmental Toxicity Study – Rat

In a developmental toxicity study (MRID 00156438), Acrolein technical (>96% a.i.; Lot/Batch # 6151) in deionized water was administered daily via oral gavage to 40 time-mated Sprague-Dawley CD rats/group at a dose volume of 5 mL/kg at dose levels of 0, 3.6, 6, or 10 mg/kg/day from gestation day (GD) 7 through 19. All surviving dams were killed on GD 20; their fetuses were removed by cesarean section and examined. It was stated that 40 females were assigned to each treatment group in order to achieve an expected minimum of 20 pregnant dams per group. Thus, data (except for mortality) were reported only for 20 dams/group.

Mortality was observed at 3.6 mg/kg/day (1/40 dams), 6 mg/kg/day (3/40 dams) and 10 mg/kg/day (14/40 dams) compared to 0 controls. Wheezing was observed in 6/20 rats for an average of 1.8 days at 6.0 mg/kg/day, and in 18/20 rats for an average of 4.2 days at 10 mg/kg/day. Rough coat was noted in 6/20 rats for an average of 1.5 days at 6.0 mg/kg/day, and in 13/20 rats for an average of 2.2 days at 10 mg/kg/day. Excessive salivation was noted in 2/20 rats for an average of 1.0 day at 6.0 mg/kg/day, and in 6/20 rats for an average of 1.7 days at 10 mg/kg/day. Additionally at 10 mg/kg/day, the following clinical signs of toxicity were observed: piloerection; dyspnea; blood on coat; thin; hunched; lethargy; squinted eyes; decreased body temperature; polypnea; lacrimation; chromodacryorrea; rales; orange stain around mouth; and orange fluid from nose.

At $\geq$ 6 mg/kg/day, maternal body weights were decreased by 3-20% at study termination, and body weights, corrected for gravid uterine weight, were decreased by 7-18% ($p<=0.01$) compared to controls. Corrected (for gravid uterine weight) body weight gains were decreased by

36-78% ($p \leq 0.01$) at these doses. Additionally at 10 mg/kg/day, gravid uterine weights were decreased by 20%.

The only finding at 3.6 mg/kg/day was the single mortality (2.5%). However in a 6-week, dose range-finding gavage study in rats, where doses of 1.0, 2.5, 5.0 or 10.0 mg/kg/day of acrolein were administered the NOAEL was 2.5 mg/kg/day based on mortality and an increased incidence of rough mucosal lesions on the greater curvature of the cardiac portion of the stomach were observed in males at 5 mg/kg/day (MRID 41306401). In a 2-generation rat reproduction study (MRID 41869101), several deaths were observed at 3 mg/kg/day, in addition to dose-related histopathology in the forestomach of females. In an NTP subchronic toxicity study in rats, mortality was observed at 1.25 (1/20), 2.5 (4/20), 5.0 (1/20), and 10.0 (17/20) mg/kg/day. Additionally, stomach hyperplasia was observed in females at 1.25 mg/kg/day and in both sexes at 2.5 mg/kg/day groups. These findings in several studies demonstrate the steep dose-response of acrolein. Therefore, the maternal LOAEL in this study is 3.6 mg/kg/day based on mortality. Clinical signs of toxicity, and decreased body weights and body weight gains in addition to mortality were noted at 6 mg/kg/day. The maternal NOAEL is <3.6 mg/kg/day.

There were no abortions or premature deliveries, and no effects of treatment on the numbers of resorptions, litters, live fetuses, dead fetuses, or on sex ratio or post-implantation loss. There were no treatment-related external, visceral, or skeletal variations or malformations.

At 10 mg/kg/day, fetal and litter weights were decreased by 21-24% ($p<0.01$) compared to controls. Additionally at this dose, retarded development of the skeleton was observed, as noted by incomplete ossification of the: skull plates (10.8% fetuses in 11.1% litters); sternum (34.9% fetuses in 66.7% litters); metacarpus (26.5% fetuses in 50.0% litters); metatarsus (41.0% fetuses in 50.0% litters); and sacro-caudal vertebrae (25.3% fetuses in 66.7% litters). Retarded development of the entire fetus was observed externally in 8/8 fetuses from the same litter (#130). Overall incidence of this finding is 8.4% (8/95 fetuses). Additionally, out of the 8 fetuses in one litter (100%) that were noted with retarded development of the entire fetus, general underdevelopment of the skeleton was confirmed in the 4 fetuses in which the skeleton was examined.

The developmental LOAEL is 10 mg/kg/day based on decreased fetal weights and litter weights and on incomplete ossification of the skeleton and general retarded development of the fetuses. The developmental NOAEL is 6 mg/kg/day.

870.3700 Developmental Toxicity Study - Rabbit

In a developmental toxicity study (MRID 40392401, study published by Parent *et al*, 1993), Acrolein technical (96.15% a.i.; Lot/Batch # B-603-001A through B-603-001D) in deionized water was administered daily via oral gavage to 20 artificially-inseminated New Zealand White [Hra:(NZW)SPF] rabbits/group at a dose volume of 5 mL/kg at dose levels of 0, 0.1, 0.75, or 2 mg/kg/day from gestation day (GD) 7 through 19. All surviving does were killed on GD 29; their fetuses were removed by cesarean section and examined.

Three non-pregnant rabbits were found dead, and findings at necropsy indicated that these deaths were likely due to gavage error/aspiration of the test substance. At 2 mg/kg/day, one rabbit was found dead during the viability check on the morning after the second day of treatment (GD 9). Hemorrhage in the left apical lobe of the lungs was revealed at necropsy, implicating gavage error. Another rabbit at this dose was found dead on GD 8, approximately four hours after the second dose was administered. Findings at necropsy in this animal included white foam around the nose and hemorrhage in the lungs. At 0.1 mg/kg/day, a rabbit exhibited dyspnea on GD 13 and 14 and was found dead on GD 14. This animal had red fluid in the thoracic cavity and hemorrhage in the lungs. All other animals survived to scheduled termination. Aside from the findings associated with aspiration of the test material in these three decedents, there were no other macroscopic findings. Additionally at 2 mg/kg/day, maternal body weight gains were decreased ($p \leq 0.01$) during GD 7-8 and 7-10 (-0.04 to -0.08 kg treated vs. 0.00 to 0.01 kg controls), corresponding to an initial decrease in food consumption of 20% compared to controls for GD 7-10. Although this effect was transient in the definitive study, substantial decreases in body weight gains and food consumption were observed for the treatment interval (GD 7-19) at this dose in the range-finding study, with decreases even more severe at 4 mg/kg/day. Thus, the weight of evidence when considering the definitive study and range-finding study together demonstrate a treatment-related effect at 2 mg/kg/day. The maternal LOAEL is 2 mg/kg/day based on decreased body weights, body weight gains, and food consumption. The maternal NOAEL is 0.75 mg/kg/day.

There were no abortions, premature deliveries, complete litter resorptions, or dead fetuses. There were no effects of treatment on the sex ratio or on the numbers of litters, live fetuses, or resorptions (early, late, or complete litter). At 2 mg/kg/day, fetal body weights were increased by 17-19% ($p<=0.01$) in both sexes. However, these increases were not considered adverse and likely reflect the increased food consumption and body weight gains in the maternal animals at the end of the treatment period and throughout post-treatment. Furthermore, it is doubtful that the increased fetal body weights were due to treatment, because a comparable increase in body weight was noted in the male fetuses at 0.1 mg/kg/day (incr. 17%; $p<=0.01$). There were no treatment-related external, visceral, or skeletal malformations, variations, or retardations. The developmental LOAEL was > 2 mg/kg/day. The developmental NOAEL is 2 mg/kg/day (the highest dose tested).

Maternal rabbits were not dosed until the day before expected parturition (i.e., GD 28), but were only dosed until GD 19. However, because the dosing period encompasses organogenesis in the rabbit, any potential teratogencicity of the test material would be demonstrated. Furthermore, this dosing period was considered adequate under the EPA Subdivision F Guidelines (revised November 1984).

Reproductive Toxicity

870.3800 2-Generation Reproduction Study in Rats.

In a two-generation reproduction toxicity study (MRID 41869101, study published by Parent *et al*, 1992b), Acrolein technical (96.05-96.72% a.i; Lot #s 060889-89446 and UTLX

89445 010290D) was administered once daily via oral gavage to Crl:CD®(SD)BR rats (30 rats/sex/dose) at dose levels of 0, 1, 3, or 6 mg/kg bw/day. The P generation parents were dosed for 70 days before they were mated to produce the F1 litters. The F1 pups were weaned on postnatal day (PND) 21, and 40 rats/sex/group were randomly selected to continue on study and were dosed (beginning on PND 22) for a pre-mating period of at least 72 days. Out of these 40 rats/sex/dose, 30 F1 adult rats/sex/group were randomly selected prior to mating to produce the F2 litters. Males of each generation were terminated after completion of the mating period, and dams were euthanized after weaning of their litters (or on GD 25 for females that did not deliver a litter).

At 6 mg/kg/day, incidences of mortality were significantly ($p<=0.05$) increased over controls in both sexes of both generations. Dying rats exhibited clinical signs of toxicity (rales in both sexes and both generations; labored breathing in the P males and females and F1 males; gasping in the F1 males and females; ungroomed coat, yellow to reddish brown oral substance, excess salivation, and chromorrhinorrhea in the P males; and abdominal distension and emaciated appearance in the F1 males), body weight loss, and decreased food consumption prior to death. At necropsy, treatment-related gross lesions in both sexes in both generations were generally limited to the stomach and lungs in the animals that were found dead. The lung lesions were likely due to aspiration of the test material. These deaths were considered to be due to the direct effects on the stomach and/or the indirect effects on the lungs. The following microscopic lesions were observed in the stomach of the 6 mg/kg/day rats (including decedents and rats surviving to scheduled termination): (i) edema/ inflammation of the submucosa, erosion(s) and/or focal hyperplasia of the glandular mucosa, and hyperplasia/ hyperkeratosis of the forestomach in both sexes and both generations; (ii) congestion and focal adenomatous hyperplasia of the glandular mucosa in the P males; (iii) cyst(s) in the forestomach of the P females and F1 males and females; (iv) diverticulum of the glandular mucosa in both sexes of the P generation; (v) hemorrhage of the forestomach and hyperplasia of the glandular mucosa in the F1 males; (vi) focal hemorrhage of the glandular mucosa of the forestomach in both sexes of the F1 generation; (vii) mononuclear infiltration of the submucosa in the P males and females and F1 males; (viii) ulcers in the forestomach in the P males and F1 males and females; (ix) ulcers in the glandular mucosa in the P and F1 males; and (x) focal necrosis in the forestomach in the P females.

Body weights, body weight gains, absolute food consumption, and relative food consumption were comparable to controls in the treated P and F1 females throughout gestation and lactation. Treatment-related effects at the 6 mg/kg/day dose on body weights and body weight gains were observed in both sexes and both generations during pre-mating; and food consumption was decreased in both sexes in the F1 generation.

The only findings at 3 mg/kg/day were minor, transient decreases in body weights, and body weight gain, and food consumption. Incidences of gastric lesions at this dose were limited to hyperkeratosis/hyperplasia in 4/30 P females and 2/40 F1 females and focal hyperplasia of the glandular mucosa in 1/40 F1 females. In the absence of other lesions, these minimal incidences of hyperplasia/hyperkeratosis are not considered adverse. There were no mortalities at this dose which could be attributed to treatment.

The LOAEL for parental toxicity is 6 mg/kg/day, based on decreased body weights, body weight gains, and food consumption in both sexes and both generations during pre-mating and on gross and microscopic findings in the stomach. The NOAEL is 3 mg/kg/day.

There were no effects of treatment on gestation duration, the number of implantations, sex ratio, or on live birth, viability, or lactation indices in either generation. There were no treatment-related clinical signs in the F1 or F2 pups. At 6 mg/kg/day, body weights of the F1 pups were decreased by 7-8% ($p<=0.01$) on PND 7, 14, and 21. Pup body weights of the treated F2 litters were comparable to controls throughout the post-natal period. The LOAEL for offspring toxicity is 6 mg/kg/day based on decreased pup body weights in the F1 generation. The NOAEL is 3 mg/kg/day.

There were no treatment-related effects on any reproductive parameter in either generation. Pre-coital interval and fertility, pregnancy, and gestation indices of the treated groups were comparable to controls. Weights of the testes and epididymides in the treated males were comparable to controls. The LOAEL for reproductive toxicity was not observed. The NOAEL is 6 mg/kg/day.

Subchronic Toxicity

870.3100 90-Day Oral Toxicity

RATS and MICE: In a 13-week daily gavage study of acrolein (in 0.5% methyl cellulose) conducted for the National Toxicology Program (NTP), 10 F344 rats/sex/dose were administered 0.75, 1.25, 2.5, 5.0, and 10 mg acrolein/kg; 10 B6C3F1 mice/sex/dose were administered 0, 1.25, 2.5, 5.0, 10 and 20 mg/kg. Dose volume was 5 ml/kg for rats and 10 ml/kg for mice. Treatment resulted in similar dose-related effects in both sexes of rats: hemorrhage and necrosis and chronic-active inflammation of the forestomach and glandular stomach and secondary changes associated with acrolein-induced mortality in high-dose animals (NTP, 1995; Pathology Working Group, 1997). Hemorrhage of the glandular stomach was also confirmed in 5 and 10 mg/kg males and 10 mg/kg females. Abnormal breathing and nasal/eye discharge were among the clinical findings in high-dose rats. Nearly all high-dose animals died or were removed from study because of gastrointestinal toxicity. Forestomach squamous epithelial hyperplasia was observed in male rats at 2.5 mg/kg and higher (no-observed-adverse-effect level, NOAEL, of 1.25 mg/kg-day) and in females at 1.25 mg/kg and higher (NOAEL of 0.75 mg/kgday).

There were no clinical signs of toxicity in mice. The forestomach lesions in mice were similar to those in the rat. Glandular stomach lesions were only seen in the 10 and 20 mg/kg males and in the 20 mg/kg females. Statistically significant increases in absolute and relative liver weights were seen in male mice at 10 mg/kg without attendant hepatic histopathology. Forestomach squamous epithelial hyperplasia was observed in one male mouse at the lowest dose of 1.25 mg/kg (i.e., no NOAEL for the male mice), and in female mice at 2.5 mg/kg-day and higher (NOAEL of 1.25 mg/kg-day).

870.3200. 21-day Dermal Toxicity – Rabbits

In a 21-day dermal toxicity study (MRID 00141030), Acrolein (>96% a.i) in ethanol:deionized water (50:50 v/v) was applied (2 mL/kg) to the shaved skin of 10 New Zealand White rabbits/sex/dose at dose levels of 0, 7, 21, or 63 mg/kg/day, 6 hours/day, 5 days/week for 3 weeks (total of 15 applications). The skin of the treatment site was abraded in 5 animals/sex/dose and unabraded in the other 5 animals/sex/dose. Dermal irritation was evaluated daily using the Draize method.

No compound-related effects on body weight, organ weights, hematology, or clinical chemistry parameters were observed.

At >=7 mg/kg/day, body weights were slightly decreased in the males (10-15%, NS) compared to controls on Day 20, and overall body weight gain was decreased ($p<0.05$) by 28-91% in both sexes. Food consumption was decreased ($p<0.05$) throughout the majority of the study by 5-38% in both sexes. Dermal irritation characterized by slight to severe reddening with swelling and firmness of the test site, and scab formation with cracking and peeling was observed in all animals. The severity of both the erythema and edema increased with time and dose. Increased incidence (# affected/10 vs 0 controls; unless otherwise stated) of the following histopathological effects were noted at all doses (unless otherwise indicated): (i) treated skin, minimal to severe necrosis (5-10 males and 7-10 females) and minimal to marked hyperkeratosis, parakeratosis, and acanthosis (7-10 males and 9-10 females); (ii) lungs, minimal to severe multifocal interstitial pneumonia (6-8 males at >=21 mg/kg/day vs 6 controls and 6-8 treated females vs 1 control); and (iii) kidneys, minimal to severe bilateral interstitial nephritis (3-5 males at >=21 mg/kg/day vs 1 control and 2-4 treated females vs 1 control). The effects mentioned above occurred with similar frequency in the abraded and unabraded animals.

Additionally, one female each from the 21 and 63 mg/kg/day groups was found dead on Days 4 and 5, respectively. In addition, one female each from the 7 and 63 mg/kg/day groups was sacrificed *in extremis* on Day 5. It was determined that the animals sacrificed *in extremis* had broken backs attributable to hyperactive behavior following dosing. The cause of death in the animals found dead was not determined.

Treatment-related clinical signs of toxicity were limited to increased incidence of slight to moderate lethargy noted in the 63 mg/kg/day males (4/10 treated vs 0/10 controls).

The systemic LOAEL was 7 mg/kg/day based on decreased body weight gain, and food consumption in both sexes, and minimal to moderate multifocal interstitial pneumonia and moderate bilateral interstitial nephritis in the females. The systemic NOAEL was not established.

The dermal LOAEL was 7 mg/kg/day based on dermal irritation characterized by slight to moderate reddening with swelling and firmness of the test site, and scab formation with peeling and microscopic findings in the treated skin (minimal to marked necrosis,

hyperkeratosis, parakeratosis, and acanthosis). The dermal NOAEL was not established.

870.4100. Chronic Study – dogs.

In a chronic toxicity study in dogs (MRID 41071701), acrolein (98.6% a.i.) in deionized water was administered daily in gelatin capsules to 6 beagle dogs/sex/dose for 1 year at doses of 0, 0.1, 0.5, or 2.0 mg/kg/day in males/females. The high dose group received 1.5 mg/kg/day for the first 3 weeks. The doses were based on a range-finding study in (MRID 41068801), where acrolein was administered in capsules at dose levels of 10 or 40 mg/kg as a single dose or at 2.0, 2.5, or 5.0 mg/kg/day for 2-6 days, or at 1.0 or 1.5 mg/kg/day for 28 days. Each dose group consisted of 1-2 dogs/sex. Vomiting occurred within 5-10 minutes at 40 mg/kg and within 2 hours at 10 mg/kg; these dogs were sacrificed moribund at Day 3 (40 mg/kg) and Day 4 (10 mg/kg). Esophageal and gastric ulceration and hemorrhage were noted upon pathological examination. Administration of 2.0, 2.5, or 5.0 mg/kg/day, resulted in dose-dependent body weight loss, decreased food consumption, and vomiting (occasionally red-tinged), but no hemorrhage in the gastro-intestinal tract was noted. Administration of 1.0 or 1.5 mg/kg/day resulted in variable body weights and sporadic vomiting. In the main study, no treatment-related adverse effects were observed on mortality, body weights, body weight gains, food consumption, ophthalmoscopic examination, hematology, clinical chemistry, urinalysis, organ weights, or gross and histological pathology.

Vomiting was increased dose-dependently in the ≥0.5 mg/kg/day males and ≥0.1 mg/kg/day females. However, the frequency of vomiting was substantially increased at 2 mg/kg/day (13-23% of the total observations) vs controls (1% of the total observations). The incidence of vomiting at 0.1 and 0.5 mg/kg/day was considered minimal (≤5% of possible observations) and not adverse. Vomiting was noted at the first observation (Week 2) in the 2.0 mg/kg/day group. In the range finding study at ≥10mg/kg, vomiting preceded death, and severe hemorrhagic and fibrinopurulent gastritis and moderate to severe fibrinopurulent esophagitis were observed pathologically in these animals. Consequently, vomiting is considered a very important indicator of acrolein toxicity. From the range-finding study, it was also apparent that the dose-response curve was steep.

The LOAEL is 2.0 mg/kg/day, based on vomiting in both sexes. The NOAEL is 0.5 mg/kg/day.

870.4200. Carcinogenicity Study - Mice.

In a carcinogenicity study (MRID 41334901; published form of this study is Parent *et al*, 1991b), 70-75 CD-l Swiss albino mice/sex/dose were exposed to Acrolein (96.0% a.i) in deionized water by oral gavage (10mL/kg) at nominal concentrations of 0, 0.5, 2.0, or 4.5 mg/kg/day for up to 78 weeks.

No adverse treatment-related effects were observed on clinical signs, body weights, body weight gains, food consumption, and hematology, and organ weights, gross or microscopic pathology.

Mortality (including only deaths **not due** to dosing error) in both sexes at 4.5 mg/kg/day was

increased [7-36% vs. 0-23% in controls (not significant, NS)] throughout the study.

The LOAEL is 4.5 mg/kg/day, based on increased mortality. The NOAEL is 2.0 mg/kg/day.

No indication of carcinogenic potential was observed. At the doses tested, there was not a treatment-related increase in tumor incidence when compared to controls. Dosing was considered adequate based on increased mortality. Also, dosing was considered adequate based on the chemical/toxic properties noted for the test compound.

870.4300. Combined chronic/Carcinogenicity – Rats.

In this combined chronic toxicity/carcinogenicity study (MRIDs 41306401, 46568001, and 46568002; a published form of this study is Parent *et al*, 1992c), acrolein (95-98% a.i.; Lot Nos.: 426-2-1 and 487-32) in deionized water was administered by daily gavage to 70 (or 75 in high dose) Sprague-Dawley rats/sex/dose at nominal concentrations of 0, 0.05, 0.50, or 2.50 mg/kg/day for up to 2 years. Five rats/sex from the high dose were sacrificed at Week 13 to check for stomach lesions. Ten rats/sex/dose were sacrificed at 12 months, and the remaining survivors were sacrificed at 24 months.

No adverse, treatment-related effects were observed on clinical signs, body weights, body weight gains, food consumption, ophthalmoscopic findings, hematology, clinical chemistry, urinalysis, organ weights, or gross or histological pathology.

At Month 12 in both sexes, decreases in survival compared to controls were noted at 0.50 (decr 7-10%) and 2.50 mg/kg/day (decr 22-26%). At Month 18 in the 0.50 and 2.50 mg/kg/day rats, dose-dependent decreases in survival were observed in males (decr 6-11%) and females (decr 12-29%). There was no dose-related effect in either sex at Month 24. For unspecified reasons, mortality was generally high at 2 years (only 21% of the male controls survived and only 24% of the 0.50 mg/kg/day females), which may have masked a treatment-related effect at that time. Other studies cited by the Sponsor corroborate increased mortality at low doses. In a 2-generation rat reproduction study (MRID 41869101), several deaths were observed at 3 mg/kg/day. In the NTP subchronic toxicity study in rats, 4/20 rats died at 2.5 mg/kg/day.

The LOAEL is 0.50 mg/kg/day, based on increased mortality in both sexes. The NOAEL is 0.05 mg/kg/day.

After 24 months in the 2.5 mg/kg/day males, the incidence of mammary gland adenoma (8%) exceeded the concurrent (3%) and historical (0-1.5%) controls. The incidence of combined adenoma and carcinoma in the mammary gland of treated animals (<=10%) approximated the historical control range (<=7.1%). Also, the incidence of hepatocellular adenoma (8%) exceeded the concurrent (1%) and historical (0-3.5%) controls. The incidence of combined adenoma and carcinoma in the liver of treated animals (<=8%) was within the historical control range (<=14.5%), suggesting the apparent increases in these adenomas may be incidental. Initial

analysis of the pancreatic neoplasm suggested an increase in the incidence of pancreas acinar cell adenoma but a revised diagnosis according the criteria of Eustis *et al.* (1990) showed it was not related to treatment. Dosing was considered adequate based on increased mortality in both sexes.

The IRIS report on Acrolein (2003) cites a study by Male Fischer 344 rats (20/group) were administered acrolein in the drinking water at concentrations providing average daily doses of 0, 1.9, 5.0, or 12.5 mg/day, 5 days/week for 104- 124 weeks (Lijinsky and Reuber, 1987). On the remaining 2 days, tap water was provided. High-dose animals stopped drinking the solution before the other groups. Drinking water solutions were prepared weekly and stored at unspecified refrigerator temperatures until dispensed. Each cage of four rats was given a measured amount (80 ml) of drinking water over the span of the study. The daily dose per kg BW could not be calculated from the data given. The maximum tolerated dose was not determined. Major organs and tissues were reported as being examined histopathologically (if there were any non-proliferative lesions they were not reported). One group of 20 females also received the highest dose on the same schedule as the males. Adrenocortical tumors (5/20) and hyperplastic nodules of the adrenal cortex (2/20) were found only in females in the high concentration group. The increased incidence of adrenocortical tumors was considered by the authors to be marginally significant as judged by the Fisher's exact test (p=0.091) and significant for adrenocortical tumors plus hyperplastic nodules (p=0.022). According to the authors, this type of tumor is rare in untreated female Fischer 344 rats; there was one reported in concurrent controls. The historical incidence is approximately 4.8% based on the findings of Solleveld et al. (1984) for untreated female F-344 rats allowed to die naturally. Significant increases in tumor incidence were not found in male rats. There was no treatment-related mortality. Lijinsky and Reuber (1987) also exposed rats to acrolein diethylacetal, acrolein oxime, and allyl alcohol, agents that can be expected to be hydrolyzed to acrolein in the stomach acids, with negative results. A reevaluation of the tumors in this study is described in the IRIS report. According to Parent *et al*. (1992c) an independent pathology working group (PWG) was convened to reevaluate the cortical tumors reported by Lijinsky and Reuber (1987). According to the PWG (cited in Parent et al., 1992c), the "slightly elevated incidence of pheochromocytomas (3/20; 15%) in the treated females were well within limits for historical controls (3/34; 9%) and were of no biological significance," and "it is the opinion of the PWG that there is no evidence of any carcinogenic effect of acrolein on the adrenal glands of female rats in this study." The PWG noted that the slides evaluated were taken from archived tissue blocks because the original slides for the high-dose females were not available for reexamination and only one of the original control slides was available. Parent et al. (1992c) identify additional weaknesses in the Lijinsky and Reuber (1987) studies that brings into question the dose levels and the overall conclusions. They reexamined the Lijinsky and Reuber (1987) reported intake levels, and calculated an estimated daily dose of 50 mg/kg BW for the high-dose group under the assumption that each of the four rats/cage in the group drank an equal share of the 80 ml delivered in the drinking water container. This dose, however, exceeds the LD50 for rats, and would have been ingested for five days a week for 132 weeks. Parent et al. (1992c) suggest that the acrolein in the drinking water solution might not have been as stable as Lijinsky and Reuber (1987) assumed, or that intake levels were lower than reported. An additional question was raised as to why Lijinsky and Reuber (1987) observed no increases in adrenal tumors from comparable studies with the acrolein parent compounds – diethylacetal, acrolein oxime, and allyl alcohol – compounds that are expected to be hydrolyzed to

acrolein in the stomach acids.

Lijinsky and Reuber (1987) also exposed hamsters to acrolein, but the dose proved to be too toxic to complete the cancer bioassay. A single, 1 mg dose via gavage in corn oil killed all of the animals within a few hours; hamsters reportedly drank too little water to make the study feasible.

3.0 TOXICOKINETICS

3.1. Absorption and Distribution

Respiratory uptake studies with acrolein in dogs indicate that acrolein is retained at rates of 75-80% in the upper respiratory tract (URT) with a lesser rate of retention (65-70%) for the lower respiratory tract. At inhaled concentrations of 176-264 ppm (400-600 mg/m3), 80-85% was retained in the total respiratory track at varying ventilation rates, suggesting little distribution elsewhere (Egle, 1972). Acrolein's strong reactivity with tissues is proposed to result in little systemic distribution (Beauchamp et al., 1985). This hypothesis is supported by the results from McNulty et al. (1984) who observed no reduction in liver glutathione (GSH) following inhalation of acrolein by rats, indicating that inhaled acrolein does not reach the liver to any great extent.

Deposition efficiency of inhaled acrolein (nominal concentrations of 0, 0.9, 4.5 and 9.1 ppm or 0, 2.1, 10.4, and 20.9 mg/m3) in the upper respiratory tract of the anesthetized male F344 rat was examined by Morris (1996). During nose-only exposures of the surgically-isolated URT for 40 minutes, steady-state concentrations were not attained or maintained during the exposure, and uptake slowly decreased, suggesting limited uptake at these concentrations and durations.

Evidence for systemic absorption of acrolein from the gastrointestinal tract was reported by Draminski et al. (1983), who identified low levels of acrolein-derived conjugates in the urine of rats after ingestion of a single dose of 10 mg/kg body weight. This dose, however, resulted in 50% mortality and would be expected to cause severe gastrointestinal damage under these conditions. Damage to the stomach lining, especially endothelial cells (Patel and Block, 1993), may allow some absorption to occur. The likelihood of significant absorption from the gastrointestinal tract at lower concentrations is uncertain.

The distribution of [2,3-14C]acrolein administered to Sprague-Dawley rats (5/sex/group) after intravenous (iv) or oral gavage was evaluated by Parent et al. (1996a, 1998). Doses were 2.5 mg/kg (iv and oral), 2.5 mg/kg after 14 consecutive days of unlabeled acrolein (oral), and 15 g/kg (oral). Radiolabel in expired air, urine, and feces was measured at 4, 12, and 16 and 24 hours post-dosing, then every 24 hours for the next 6 days. Data in the report demonstrate that the large majority of label (>96%) was recovered in excreta within the first 24 hours. Tissue concentrations (including blood) of radioactivity were minimal (<1.2% from the iv dosing and <0.7% from the oral dosing) and time course of excretion for all groups was similar except for delayed excretion in the high-dose group. Radiolabel measured in excreta and in tissues was associated with various acrolein metabolites and not attributed to parent compound. The radiolabel in feces was later determined to be associated with a homopolymer of acrolein, which was apparently formed in the gastrointestinal tract (Parent et al., 1998). These studies indicate little systemic distribution of acrolein.

The high reactivity of acrolein is due to the polarization of the double bond by the aldehyde group, and the resulting increased potential for nucleophilic addition. Because acrolein readily reacts with sulfhydryl and amino groups on proteins, it is unlikely to distribute

systemically, and thus its adverse effects are characterized in terms of cytotoxicity at the site of entry. Additional evidence of the reactivity of acrolein can be seen in conflicting data reported in the literature for the *in vitro* mutagenic potential of acrolein. In a series of Ames assays, Parent et al. (1996b) resolve many of the different outcomes by considering the presence or absence of non-DNA nucleophiles from the S9 activation mixture, in the test chemical solution, or in the plating solutions. If non-DNA nucleophiles were present, acrolein would rapidly and indiscriminately react with any available species and not reach the DNA target. While the possibility of some transport of acrolein or a metabolite of acrolein to systemic sites remains, the critical target sites, as noted in the toxicology section, are those at the point of contact, the respiratory system, the gastrointestinal tract, mucous membranes, and skin.

3.2. Metabolism And Excretion

Absorbed acrolein reacts directly with protein and non-protein sulfhydryl groups, and with primary and secondary amines found in proteins and nucleic acids (Ghilarducci and Tjeerdema, 1995). In proteins, it preferentially attacks free SH groups of cysteine residues, $\in$- amino groups of lysine residues and histidine residues (Esterbauer et al., 1991). Uchida et al. (1998a,b) has shown that, *in vitro*, acrolein binds to serum albumin and low-density lipoproteins. Acrolein's role as a lipid peroxidation byproduct and possible mediator in various human diseases has been recently reviewed by Uchida (1999). It is well-documented that the conjugation of the α-carbon of acrolein with sulfhydryl groups is rapid and essentially irreversible (Esterbauer et al., 1976), and leads to thiazolidine derivatives and a decrease in glutathione (GSH) stores without an increase in oxidized GSH (GSSG). This pathway results in an acrolein-GSH adduct which is then further metabolized by both high- and low-affinity forms of mitochondrial and cytosolic aldehyde and alcohol dehydrogenase (Mitchell and Peterson, 1989); one resultant product has been identified as 3-hydroxypropylmercapturic acid (Clapp et al., 1969; Kaye and Young, 1970). This product has been isolated from urine of rats after subcutaneous injection of acrolein (Kaye, 1973) and after inhalation and intraperitoneal (ip) injection of Wistar rats (Linhart et al., 1996). The reduction of the acrolein-GSH adduct by alcohol dehydrogenase to 3-hydroxypropylmercapturic acid was postulated as a potentially important pathway (Mitchell and Peterson, 1989). There is increasing evidence that aldehydes such as acrolein are generated endogenously during the process of lipid peroxidation (Esterbauer et al., 1991); the rate constant for reaction of acrolein with cysteine at pH 7.4 was 220 M-1 sec-1 compared to 121 with GSH. Among all α,β-unsaturated aldehydes, acrolein is the strongest electrophile, which accounts for its high reactivity with nucleophiles (Witz, 1989). Thiol adducts of acrolein are considerably more stable than adducts formed by all other α,β - unsaturated aldehydes (Esterbauer et al., 1991).

When radiolabeled acrolein was administered by gavage (0.82 mg/kg) to one lactating goat, incorporation of radioactivity appeared to follow incorporation of metabolites into normal biosynthetic pathways (Sharp et al., 2001).

Elucidation of the major pathways of metabolism has been greatly enhanced by the studies of Parent and colleagues. Parent et al. (1998) synthesized and characterized the potential metabolites of acrolein in the feces and urine of rats administered acrolein either orally or intravenously. The

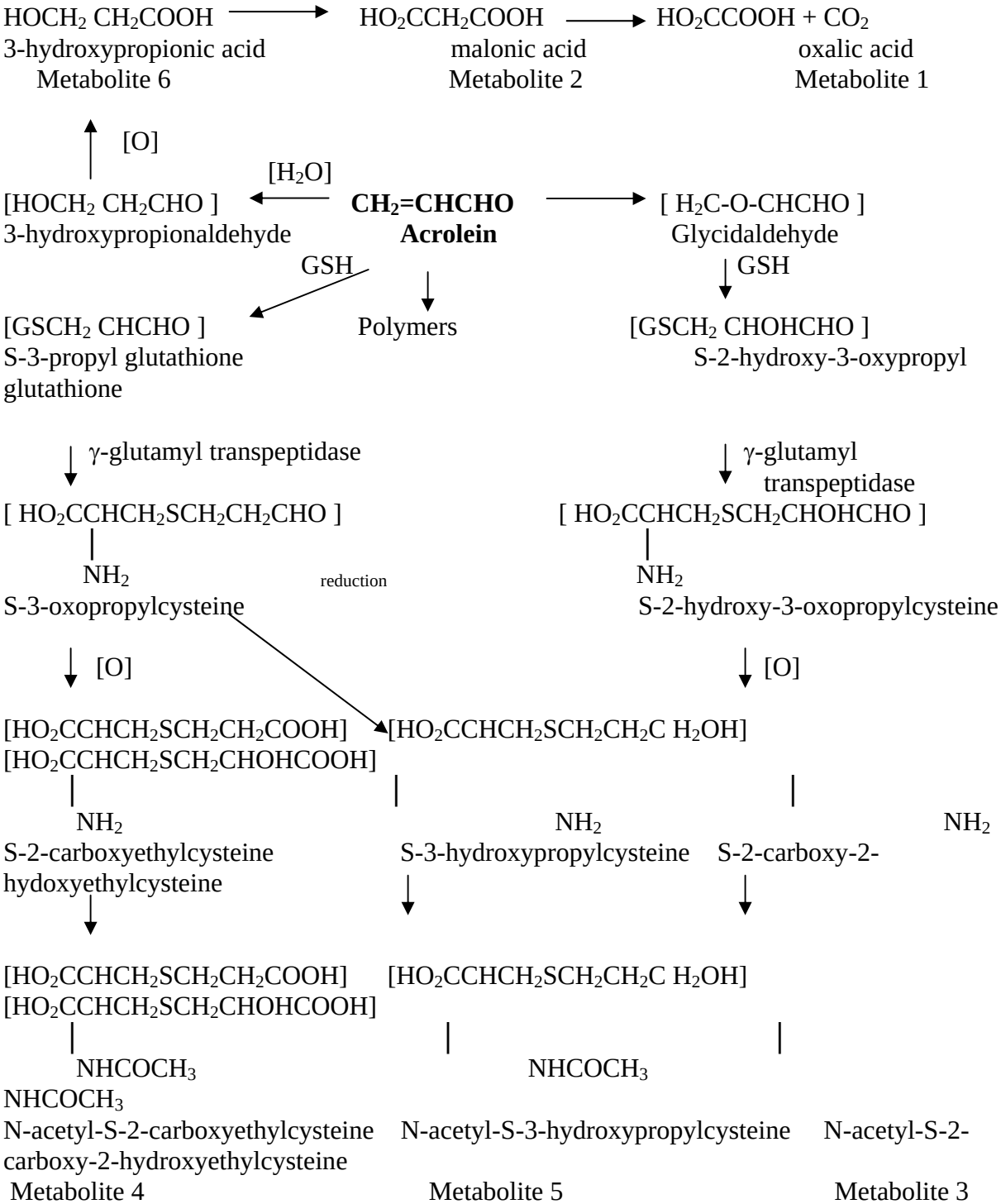
pathways of metabolism proposed by Parent et al. (1998) are illustrated in Figure 1. The main pathway appears to be an addition of GSH to the activated double bond, followed by processing to mercapturic acid derivatives, the three compounds at the bottom of the figure, which are then excreted in the urine after either oxidation or reduction of the aldehyde, with reduction predominating. Another pathway of metabolism is that of epoxidation of the double bond followed by attack of GSH on the epoxide. A third pathway involves addition of water to acrolein to form 3-hydroxypropionaldehyde, which is further oxidized to malonic acid and ultimately oxalic acid. Some of these compounds can be incorporated into normal metabolic pathways. For example, glycidaldehyde can be hydrated to glyceraldehyde (Patel et al., 1980).

None of the unconjugated metabolites resulting from the epoxidation of acrolein, such as those reported by Patel et al. (1980), were found in the excreta by Parent et al. (1998). A polar and a nonpolar fraction were extracted with a molecular weight range of 2,000-20,000 Da (Parent et al., 1998). They concluded that these compounds were either homopolymers of acrolein, or that the polyacrolein in this fraction was originally a copolymer with a natural polymer, either a protein or polysaccharide.

Marinello et al. (1984) incubated [14C]acrolein with purified cytochrome P450 in the absence of NADPH and observed the binding of label. GSH inhibited the binding of label to hepatic microsomes by 90%. Binding to microsomes was substantially enhanced in the presence of NADPH. Addition of the P450 inhibitor, SKF-525A, in the presence of NADPH prevented binding of label.

Incubation of Wistar liver microsomes with 5 mM acrolein for 30 seconds resulted in a two-fold stimulation of GSH transferase and 0.1 mM for 30 minutes reduced GSH protection against lipid peroxidation (Haenen et al., 1988).

3.3 Metabolic Pathway



Proposed metabolism of acrolein in rats. Structures in brackets represent postulated intermediates. Reproduced from MRID 43275901 and IRIS 2005 after Parent et al, 1998.

4.0 SLOPE FACTOR FOR GLYCIDOL

The National Toxicology Program (NTP) conducted two-year gavage cancer studies in rodents in 1990 (NTP Testing Report 374). Glycidol caused many tumors in rats and mice and the NTP concluded that there was clear evidence for the carcinogenicity of glycidol in rats and mice of both sexes.

The tumor type with the highest incidence was observed in male rats – peritoneal mesotheliomas of the tunica vaginalis, and it is this tumor response that has been modeled to generate a slope factor for use in risk assessment.

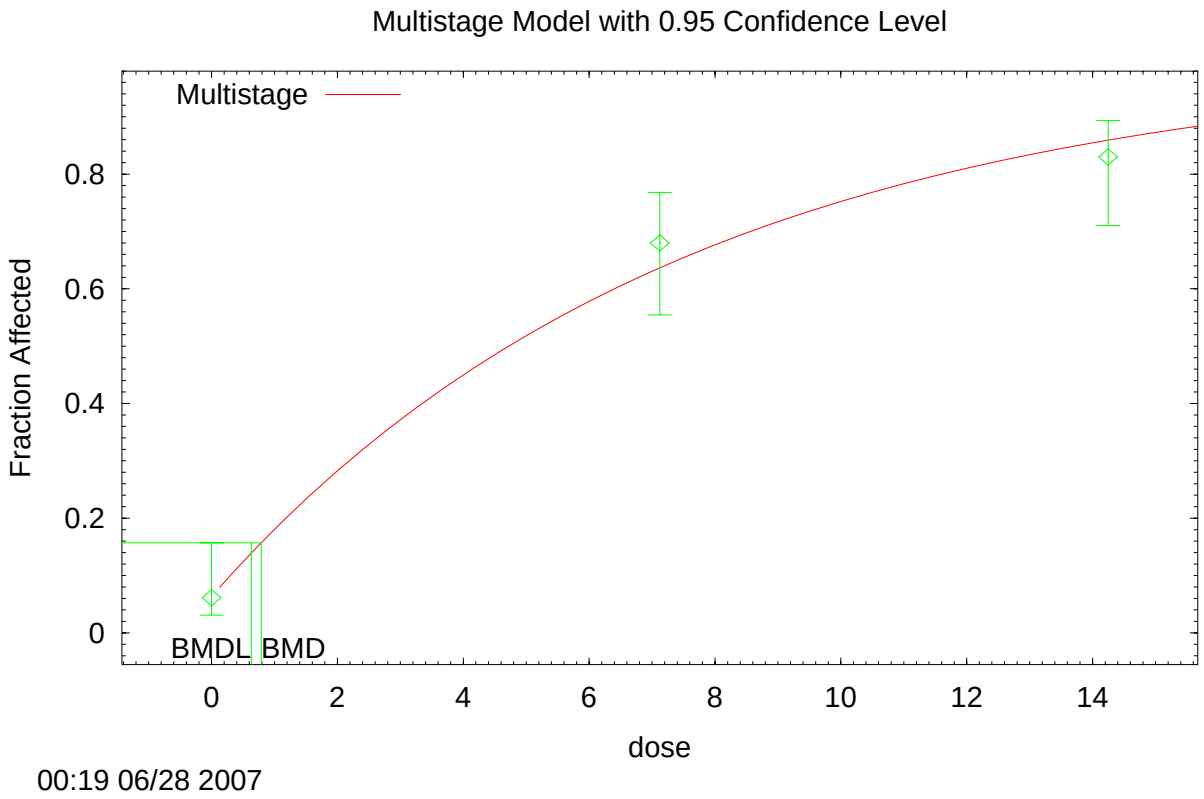
Human equivalent dose. Rats were administered doses of 0, 37.5 or 75 mg/kg/day glycidol by gavage for 5 days per week for two years and the corresponding tumor incidences were (3/49, 34/50 and 39/47). The lifetime average daily dose is equal to the administered dose multiplied by a factor of 0.714 (5 divided by 7) to account for dosing five days per week. The lifetime average daily dose in rats was therefore 0, 26.8 or 53.6 mg/kg/day. Based on the concept of dose equivalency across species when doses are expressed in $mg/kg^{0.75}$, the human equivalent LADD is obtained by multiplying the rat LADDs by 0.266, the ratio of rat body weight to human body weight raised to the ¼ power $(0.35 \text{ kg} \div 70 \text{ kg})^{0.25}$. The human equivalent LADDs are 0, 7.1 and 14.2 mg/kg/day.

Modeling. The Agency's Benchmark Dose software (version 1.3.2) was used to fit a multistage model to the human LADDs. The benchmark response was arbitrarily selected to be 10% (when calculating slope factors, the selection of benchmark response does not greatly affect the calculated slope factor). The BMD_{10} was calculated to be 0.79 mg/kg/day and the lower 95% confidence limit on the BMD_{10}, the $BMDL_{10}$ was calculated to be 0.63 mg/kg/day. The slope factor is obtained by dividing the benchmark response level (0.1 or 10%) by the $BMDL_{10}$ of 0.63 mg/kg/day which equals **$0.16 \text{ (mg/kg/day)}^{-1}$.**

Comment. The method to derive a slope factor differs slightly from the method normally used in HED. Both use benchmark dose methodology, but the benchmark response normally used in HED is 10^{-6} and the BMR used here is 10% which is consistent with current Agency guidance to pick BMRs in the visible region of the dose-response curve. The usual HED method would result in a slope factor slightly higher than the method used here. Also, there was a substantial negative effect of glycidol treatment on survival in male rats. In HED the Weibull time-to-tumor model is used whenever such differential survival is observed rather than the multistage model. The Weibull model typically results in slightly higher slope factors than does the multistage model when the models are compared with a given data set. For the limited use of assessing risks from use of acrolein, the glycidol slope factor is adequate even though it might be somewhat higher if calculated according to HED's usual methods.

```
==========================================================================
        Multistage Model. $Revision: 2.1 $ $Date: 2000/08/21 03:38:21 $
        Input Data File: H:\BMDS STUFF\CASE
STUDIES\GLYCIDOL\GLYCIDOL.(d)
        Gnuplot Plotting File:  H:\BMDS STUFF\CASE
STUDIES\GLYCIDOL\GLYCIDOL.plt
                                        Thu Jun 28 00:19:40 2007
 ========================================================================
 Glycidol - peritoneal mesotheliomas in male rats
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   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 =     0.128329
                        Beta(1) =     0.119865
                        Beta(2) =            0

           Asymptotic Correlation Matrix of Parameter Estimates
           ( *** The model parameter(s)  -Beta(2)
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

             Background      Beta(1)
Background            1        -0.57
   Beta(1)        -0.57            1



                         Parameter Estimates

       Variable           Estimate            Std. Err.
     Background          0.0633592            0.137342
        Beta(1)            0.13342           0.0256554
```

```
        Beta(2)                   0               NA

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         -64.0718
   Fitted model         -64.4378     0.731912      1          0.3923
  Reduced model         -101.076      74.0087      2         <.0001

           AIC:          132.876

                      Goodness  of  Fit

     Dose     Est._Prob.    Expected    Observed     Size     Chi^2 Res.
  ----------------------------------------------------------------------
-
i: 1
    0.0000     0.0634         3.105         3          49      -0.036
i: 2
    7.1227     0.6379        31.894        34          50       0.182
i: 3
   14.2454     0.8600        40.420        39          47      -0.251

 Chi-square =       0.74     DF = 1        P-value = 0.3884

   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =       0.789688

            BMDL =       0.632826
```


Multistage Model with 0.95 Confidence Level
Multistage
Fraction Affected
0
0.2
0.4
0.6
0.8
BMDL
BMD
0
2
4
6
8
10
12
14
dose
00:19 06/28 2007

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