CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
HUMAN HEALTH ASSESSMENT BRANCH

SUMMARY OF TOXICOLOGY DATA

Acrolein

Chemical Code # 3**, Document Processing Number (DPN)** 50032
SB 950 # 4
August 7, 1986
December 12, 1986, February 8, 1988, November 23, 1988, November 7, 1990,
August 18, 1994, August 3, 2015

DATA GAP STATUS

Chronic toxicity, rat:	Data gap, no adverse effect indicated
Chronic toxicity, dog:	No data gap, possible adverse effect
Oncogenicity, rat:	No data gap, possible adverse effect
Oncogenicity, mouse:	Data gap, no adverse effect indicated
Reproduction, rat:	No data gap, possible adverse effect
Developmental toxicity, rat:	No data gap, no adverse effect indicated
Developmental toxicity, rabbit:	No data gap, no adverse effect indicated
Developmental toxicity, mouse:	No data gap, possible adverse effect
Gene mutation:	No data gap, possible adverse effect
Chromosome effects:	No data gap, no adverse effect indicated
DNA damage:	No data gap, no adverse effect indicated
Neurotoxicity:	Data gap

Toxicology one-liners are attached.

All record numbers for the above study types through 283479 (Document No. 50032-0077) were examined. This includes all relevant studies indexed by DPR as of 8/3/15.

In the 1-liners below:
indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.

File name: T150803
Revised by T. Moore, 8/3/15

NOTE: The following symbols may be used in the Table of Contents which follows:
* = data adequately address FIFRA requirement
† = study(ies) flagged as "possible adverse effect"
N/A = study type not currently required

This record contains summaries of studies. Individual worksheets may be useful for detailed assessment.

Table of Contents

METABOLISM AND PHARMACOKINETICS 3
GUIDELINE ACUTE STUDIES ON ACTIVE INGREDIENT 3
Acute oral toxicity, rat 3
Acute dermal toxicity 5
Acute inhalation toxicity, rat 5
Primary eye irritation, rabbit 5
Primary dermal irritation 6
Dermal sensitization 6
SUBCHRONIC STUDIES 6
Rat Subchronic Oral Toxicity Study 6
Mouse 14-Day Oral Toxicity Study 7
Oral toxicity, non-rodent: 7
Rabbit 21-Day Repeated Dosing Dermal Toxicity Study 7
CHRONIC STUDIES 9
Chronic, rat 9
Chronic, dog 10
Oncogenicity, rat 10
Oncogenicity, mouse 10
GENOTOXICITY 11
Gene mutation 11
Chromosome damage 12
DNA damage or miscellaneous effects 13
REPRODUCTIVE TOXICITY, RAT 13
DEVELOPMENTAL TOXICITY 14
Rat 14
Rabbit 14
Mouse 15

NEUROTOXICITY 15
Acute neurotoxicity, rat 15
90-day neurotoxicity, rat 15
Developmental neurotoxicity, rat 15
Delayed neurotoxicity, hen 15
IMMUNOTOXICITY 15
ENDOCRINE DISRUPTOR STUDIES 15
SUPPLEMENTAL STUDIES 15
Publications Regarding Acrolein 16
Published Versions of Some of the Studies Submitted Under SB950 16

METABOLISM AND PHARMACOKINETICS

Study not submitted.

GUIDELINE ACUTE STUDIES ON ACTIVE INGREDIENT

Acute oral toxicity, rat

50032-0072 283474; Acute oral toxicity; 811; Rat: Sprague-Dawley; Microbiological Associates Inc. (MBA), Bethesda, MD; Study # G-7230.220, MRID # 41257001; David, R. M.; 9/19/89; Acrolein, Inhibited (Lot Number 4035) (Acrolein, 96.58%); 50 animals, 5/sex/dose level; administered by oral gavage to assess acute oral toxicity; Dose: 10, 15, 20, 25, 30 mg/kg; Mortality (M/F): 10 (2/5 M, 1/5 F), 15 (4/5 M/F), 20 (5/5 M/F), 25 (5/5 M/F), 30 mg/kg (5/5 M/F); Clinical observations: lethargy, and/or hypothermia, and/or gasping, and/or rapid and shallow respiration, or no clinical signs of toxicity prior to death within 1 hour or 1 day of dosing; no clinical signs of toxicity were noted for any of the surviving animals at a dose level of 10 mg/kg; one male and female animal survived oral exposure to 15 mg/kg, and exhibited hypothermia and lethargy at 3 hours after dosing, with recovery by day 2; the male also showed rales during days 8-14; all the surviving animals gained weight by day 8, but lost weight by day 15; Gross necropsy: no visible lesions in the decedents, following terminal sacrifice, no visible lesions were noted for the surviving animals, with the exception of two male animals at 10 mg/kg level exhibiting mottled kidneys and petechial hemorrhage in the lungs, respectively; Reported LD (F): 11.8 (7.9-17.6) mg/kg, LD50 (M): 10.3 (6.4-16.7) mg/kg. **Toxicity Category: I; Study Acceptable.** (Guo, 4/16/15)

50032-0073 283475; Acute oral toxicity; 811; Rat: Sprague-Dawley; Bioassay Systems Corporation (BSC), Woburn, MA; BSC Project No.: 10258, MRID # 00141027; Muni, I. A.; 5/06/81; Acrolein (Lot No. SFSL-5893) (Acrolein, 95%); 50/sex animals, 10/sex/dose level; administered by oral gavage to assess acute oral toxicity; Dose: 0, 20, 25, 30, 40 mg/kg; Mortality (M/F): 0 (0/10 M/F), 20 (2/10 M, 0/10 F), 25 (0/10 M/F), 30 (8/10 M, 4/10 F) and 40 mg/kg (10/10 M, 7/10 F); Clinical observations: immediately following dose administration, Level III (30 mg/kg) and Level IV (40 mg/kg) animals showed signs of lethargy, respiratory distress and squinted eyes until death within 15 hours of dosing (18/M, 10/F) or by day 4 (1/F); the surviving animals exhibited similar signs for varying lengths of time through the observation period; Levels I (20 mg/kg) and II (25 mg/kg) animals showed similar signs but in most cases,

the conditions were less severe and did not persist as long in the survivors, except for 2 Level I male animals that died within 15 hours of dosing; control animals remained healthy throughout the observation period; the body weight data for the surviving animals were not reported; Gross necropsy: overall reddening of the lungs, hemorrhagic stomach and intestines (blood-filled), and dilation of blood vessels on the brain's surface in the decedents with deaths within 4 hours of dosing; darkening of the medulla of the kidneys was evident in most animals which died greater than 5 hours after dosing; all levels of the surviving animals sacrificed at study termination showed few, non-specific lesions (several pin-point black spots on lungs); Reported LD50 (F): 33.3 (30.0-36.9) mg/kg, LD (M): 25.0 (22.9-27.5) mg/kg, or LD50 (M/F): 29.0 (26.6-31.6) mg/kg. **Toxicity Category: I; Study Acceptable.** (Guo, 4/14/15)

50032-0074 283476; Acute oral toxicity; 811; Mouse: CD-1; Bioassay Systems Corporation (BSC), Woburn, MA; BSC Project No.: 11479, MRID #: NA; Mansur, C. A.; 3/17/83; Acrolein (Acrolein, > 96%); 10 males/dose level; administered by oral gavage to assess acute oral toxicity; Dose: 0.0, 11.0, 13.2, 15.84, 19.0 mg/kg; Mortality (F): 0.0 (0/10), 11.0 (4/10), 13.2 (4/10), 15.84 (8/10), 19.0 mg/kg (6/10); Clinical observations: a total of 22 animals died within two days after dosing; immediately following dose administration, through day 3 post-dosing, the majority of animals in Levels I to IV (11.0-19.0 mg/kg) showed signs of lethargy, squinted eyes, rough coats, hunching, and piloerection; the surviving animals in Levels I-IV showed rough coats for varying lengths of time through most of the observation period; blackening, followed by necrosis and breaking of the tip of the tail, was noted for several of the survivors with the exception of the controls; control animals remained healthy throughout the observation period; all the surviving animals exhibited weekly weight gains during the study, with the exception of one animal in the 13.2 mg/kg group losing weight by day 14; however, the surviving animals at all levels still showed reduced weight gains of -26.8% to -53.7% by day 7 and -11.6% to -28.6% by day 14, when compared to controls; Gross necropsy: reddening of the lungs, and hemorrhagic stomach and intestines in most decedents, one Level II (13.2 mg/kg) animal exhibited reddening of the lungs at terminal sacrifice; all other animals sacrificed at the termination of the study showed minimal, non-specific lesions; Reported LD50 (M): 13.9 (12.8-15.1) mg/kg. **Toxicity Category: I; Study Acceptable.** (Guo, 4/10/15)

50032-0075 283477; Acute oral toxicity; 811; Mouse: CD-1; Bioassay Systems Corporation (BSC), Woburn, MA; Study #10258, MRID # 00141031; Muni, I.A.; 12/30/81; Acrolein (Acrolein, > 96%); 10 females/dose level; administered by oral gavage to assess acute oral toxicity; Dose: 0.0, 11.0, 13.2, 15.8, 19.0 mg/kg; Mortality (F): 0.0 (0/10), 11.0 (0/10), 13.2 (0/10), 15.8 (3/10), 19.0 mg/kg (6/10); Clinical observations: immediately following dose administration, Level III (15.8 mg/kg) and Level IV (19.0 mg/kg) animals exhibited signs of lethargy, respiratory distress and squinted eyes until death occurred on day 1, 2 or 3; the surviving animals exhibited similar signs for varying lengths of time through most of the observation period; blackening, followed by necrosis and breaking of the tip of the tail, was noted for several surviving animals in the 15.8 and 19.0 mg/kg groups; the animals receiving 11.0 or 13.2 mg/kg all survived and showed similar signs except for no evidence of evident respiratory distress, but their conditions were less severe and did not persist as long as that in the other surviving animals; control animals remained healthy throughout the observation period; all the surviving animals gained weight during the study; there were no obvious differences in mean body weight change between the control group and the acrolein-treated groups (surviving animals only); Gross necropsy: reddening of the lungs, hemorrhagic stomach and intestines (blood-filled), dilation of blood vessels on the brain's surface and darkening of the medulla of the kidneys in the decedents, all the surviving animals sacrificed at the termination of the study exhibited minimal, non-specific lesions, with no evident differences from those in control animals; Reported LD50 (F): 17.7 (16.3-19.2) mg/kg. **Toxicity Category: I; Study Acceptable.** (Guo, 4/08/15)

Acute dermal toxicity

50032-0070 283472; Acute dermal toxicity; 812; Rabbit: New Zealand White; Bioassay Systems Corporation (BSC), Woburn, MA; BSC Study # 10258, MRID # 00141028; Muni, I. A.; 9/17/81; Acrolein (Lot No. SFSL-5993) (Acrolein, purity: 95%); 10/sex animals/dose level; topical, dermal application; Dose: 200, 240, 288 mg/kg (Levels I to III) or 0 mg/kg (untreated control and vehicle control); ; Mortality (M/F): 0 (0/10, M/F), 200 (3/10 M, 4/10 F), 240 (7/10 M/F), 288 mg/kg (5/10 M, 8/10 F); Clinical observations: approximately 1 to 2 minutes after dose administration, all acrolein-treated animals exhibited signs of severe pain including screaming and severe hyperactive behavior; these conditions lasted for 10-20 minutes following dose application; thereafter, the animals became lethargic, and had squinted eyes and evidence of respiratory distress; cyanosis became evident in varying intensity on the day of dosing in acrolein-treated rabbits; evidence of lethargy, mild respiratory problems and mild nasal discharge continued for varying lengths of time throughout the study period for both males and females; a total of 11 males and 18 females died within 24 hours after dosing, and all the other deaths occurred by days 3 (1 male each at 200 and 288 mg/kg), 6 (1 male at 240 mg/kg) and 9 (1 male and 1 female at 200 mg/kg); skin lesions of varying severity were noted throughout the observation period for acrolein-treated rabbits; control animals (vehicle-treated and untreated) remained healthy throughout the study period; all the surviving animals gained body weight during the study; Gross necropsy: macroscopic postmortem findings for the decedents were not included in the report; as to microscopic findings in cutaneous structure of the dose site skin, hemorrhage and edema within the hypodermis and dermis, and/or necrosis and mineralization of skeletal muscle, and/or vascular necrosis and thrombosis, and/or the overlying epidermis and dermis, or more advanced tissue injury (ulcerated epidermis, interstitial infiltration of necrotic heterophils and macrophages, a heterophil-laden fibrin-rich zone of edema and extravasated erythrocytes within the hypodermis, and fragmentation, loss of cross striations, mineralization and proliferation of sarcolemmal nuclei of individual myofibers within the panniculus carnosus), or no significant lesions were reported for the decedents or the acrolein-treated surviving animals; other than acrolein-associated dermatopathy (discoloration (yellow-brown) of the dose site skin, an intimately adherent red-brown scab for the ulcerated skin, or the firm, wrinkled, non-pliable and overlying skin when not ulcerated, edematous and hemorrhagic hypodermis, and the glistening and gelatinous appearance of the cubcutis extending to the axillary and inguinal regions (dependent edema)), the only gross lesions occurring consistently at all treatment levels are pulmonary petechiae, atelectasis and discoloration at scheduled sacrifice and necropsy; no gross lesions or only minimal, nonspecific lesions were reported for the untreated and vehicle-treated control animals; LD50 (95% confidence limit): (M) 240.0 (217.3-265.1) mg/kg, (F) 223.1 (200.1-248.7) mg/kg, or (M/F) 231.4 (216.5-247.4) mg/kg. **Toxicity Category: II; Study Acceptable.** (Guo, 4/22/15)

Acute inhalation toxicity, rat

Study not submitted.

Primary eye irritation, rabbit

50032-0068 283470; Primary eye irritation; 814; Rabbit: New Zealand White; Bioassay Systems Corporation (BSC), Woburn, MA; BSC Study # 10258, MRID # 00141025; Dunn, G.R. and Goodband, J.; 7/20/81; DOT Acrolein Inhibited (Acrolein, 95%); 9 males; Dose: 0.1 mL into an eye of each rabbit; Mortality (M): 1/9; Clinical observations: one test animal died at 4 days after instillation; score 4 corneal opacity and score 2 iritis were noted for 9/9 treated eyes at 24 through 72 hours and for 8/9 treated eyes at 4 and 7 days after instillation; score 2 to 3 conjunctival redness (score 2, 8/9; score 3, 1/9) was reported for the treated eyes at 24 through 72 hours; score 2 conjunctival redness was reported for 8/9 treated eyes at 4 and 7 days; score 4 conjunctival chemosis was noted for 9/9 treated eyes at 24 through 72 hours, and for 8/9

treated eyes at 4 and 7 days after instillation; all the surviving animals gained or maintained body weight by 72 hours post-treatment, with the exception of three animals losing weight. **Toxicity Category: I; Study Acceptable.** (Guo, 4/20/15)

Primary dermal irritation

50032-0069 283471; Primary dermal irritation; 815; Rabbit: New Zealand White; Bioassay Systems Corporation (BSC), Woburn, MA; BSC Study # 10258, MRID # 00141026; Dunn, G. R. and Goodband, J.; 3/21/81; DOT Acrolein inhibited (DOT E8249) (Acrolein, 95%); 6 males; topical, dermal application; Dose: 0.5 mL/site, one intact site and one abraded site per animal; 24-hour exposure; Mortality (M): 2/6; Clinical observations: two test animals died with 24 hours of test substance application; score 1 to 2 erythema was noted for the abraded test sites (score 1, 1/4; score 2, 2/4) and unabraded test sites (score 2, 2/4) at 24 hours after application; score 1 to 3 erythema was reported for the abraded test sites (score 1, 2/4; score 3, 1/4) and unabraded test sites (score 2, 2/4) at 72 hours; score 1 to 2 erythema was noted for the abraded test sites (score 2, 2/4) and unabraded test sites (score 1, 1/4; score 2, 1/4) at 4 days after application; score 1 to 4 erythema was reported for the ubabraded test sites at 8 and 9 (score 1, 1/4), 10 through 12 (score 1, 2/4), and 13 and 14 days (score 2, 2/4, score 4, 1/4), with injuries in depth, bleeding and open sore observed at one unabraded test site on days 13 and 14; score 1 to 3 erythema was noted for the abraded test sites at 7 (score 1, 1/4; score 3, 1/4), 8 and 9 (score 1, 1/4, score 2, 1/4; score 3, 1/4), 10 and 11 (score 1, 1/4; score 2, 2/4), 12 (score 1, 2/4; score 2, 1/4), and 13 and 14 days (score 1, 1/4; score 2, 2/4); score 1 to 4 edema was reported for both the abraded and unabraded test sites at 24 (score 1, 1/4; score 3, 1/4; score 4, 2/4) and 72 hours (score 2, 2/4; score 3, 1/4; score 4, 1/4) and at 4 days (score 3, 3/4; score 4, 1/4) after application; score 2 to 3 edema was noted for the unabraded test sites at 7 (score 2, 2/4; score 3, 1/4), 8 and 9 days (score 2, 1/4; score 3, 2/4), and for the abraded test sites at 7 and 8 (score 2, 3/4; score 3, 1/4), and 9 days (score 2, 2/4; score 3, 2/4); score 1 to 4 edema was reported for the unabraded test sites at 10 (score 1, 1/4; score 2, 1/4; score 4, 2/4), 11 (score 1, 1/4; score 3, 1/4; score 4, 2/4), and 12 through 14 days (score 2, 1/4; score 4, 3/4); score 2 to 4 edema was noted for the abraded test sites at 10 (score 2, 2/4; score 4, 2/4), 11 (score 2, 1/4; score 3, 1/4; score 4, 2/4), 12 and 13 (score 2, 1/4; score 4, 3/4), and 14 days (score 3, 1/4; score 4, 3/4); by day 7, the sample test sites exhibited yellow discoloration (4/4), and/or swelling (2/4), and/or minimal flaking of skin (1/4), whereas the control sites showed normal appearance (2/4), and/or no swelling plus moderate flaking of skin (1/4), and/or discoloration (slightly red and yellow) plus swelling (1/4, for abraded control sites only); yellow discoloration, large area of necrotic skin, dark patches and some open sores were noted for the test sites at 14 days after application, with one animal showing a large open sore at the test site and scabs and flaking skin at the control site; all the surviving animals gained body weight during the study. **Toxicity Category: I; Study Acceptable.** (Guo, 4/22/15)

Dermal sensitization

Study not submitted.

SUBCHRONIC STUDIES

Rat Subchronic Oral Toxicity Study

50032-0076 283478; “Subchronic Oral Toxicity of Acrolein (Lot No. SFSL-5893) in Rats”; (Muni, I. A.; Bioassay Systems Corporation (BSC), Woburn, MA; BSC Project No.: 10258, MRID # 001413029; 9/11/81). Thirty Sprague-Dawley rats/sex/dose level were dosed orally by gavage with 0.0 (vehicle: deionized water), 0.05, 0.5 or 5.0 mg/kg/day (5 days per week) of Acrolein (Lot No. SFSL-5893, a.i.: 95%, diluted with deionized water) for 13 consecutive weeks. One male animal in the 0.5 mg/kg group died by week 5 due to gavage accident; all other animals survived to their designated sacrifice dates. No obvious clinical signs were consistently seen in

acrolein-treated rats. Several non-specific clinical signs were noted sporadically over the course of the study. No obvious numerical differences in body weight means or weekly mean food consumption were present between control and treated groups (males and females). Hematology, clinical chemistry and urinalysis evaluations revealed that overall, there were no differences of significance between dose levels or between treatment and control groups. No treatment-related effect was noted in the mean absolute or relative organ weights. No treatment-related gross abnormalities were noted. The gross lesions observed were characterized by their apparent random nature, low frequency, and lack of consistency in type, and most likely they are incidental findings unrelated to test substance administration. The histopathological examination did not reveal any treatment-related lesions. **Rat Subchronic Dietary NOEL: 5.0 mg/kg;** based on the data collected over the course of the 90-day study, no significant toxicological effects were found in rats dosed with 0.05, 0.5 and 5.0 mg/mL of acrolein. **Study acceptable.** (Guo, 5/25/15)

Mouse 14-Day Oral Toxicity Study

50032-0077 283479; "14-Day Oral Toxicity Test in Mice"; (Mansur, C. A.; Bioassay Systems Corporation (BSC), Woburn, MA; BSC Project No.: 11496; 6/20/83); Acrolein (Acrolein, > 96%); 10 animals/sex/dose level; administered by oral gavage to assess acute oral toxicity of acrolein in mice over a 14-day period; Dose: 0.0, 4.6, 5.8, 7.2, 9.0 mg/kg; Mortality (M/F): 0.0 (0/10 M/F), 4.6 (0/10 M/F), 5.8 (0/10 M, 1/10 F), 7.2 (2/10 M, 0/10 F), 9.0 mg/kg (1/10 M, 0/10 F); Clinical observations: two males dosed at 7.2 mg/kg and one male at 9.0 mg/kg died by day 3 or 4, and one female dosed at 5.8 mg/kg died on day 6; lethargy, and/or rough coat, and/or hunched posture, and/or squinted eyes, and/or exudate around eyes, and/or extreme, very shallow breathing were noted for the above animals prior to their death; all ten males receiving 9.0 mg/kg showed rough coat during days 2-12, and other signs in some of these males were piloerection (1/10, on day 8), reddening of the tip of the tail (2/10, during days 10-14), bite wounds on back (3/10, during days 11-14), closed eyes (1/10, during days 4-8 and 10-14), and orange stain around left eye (1/10, during days 4-8); reddening of the tip of the tail was noted for 2 females dosed at 9.0 mg/kg during days 10-14, and for one female at 7.2 mg/kg during days 10-12; one male receiving 7.2 mg/kg exhibited lethargy, rough coat, and squinted eyes by day 3; another male in the 7.2 mg/kg group showed blood around the mouth after dosing on day 14, and the injury might be an artifact of gavage; all other animals appeared healthy during the study; all the surviving animals and the control animals gained weight during the study period; Gross necropsy: the most common findings at necropsy were in the squamous portion of the gastric mucosa; one male dosed at 5.8 mg/kg, 2 males at 7.2 mg/kg, 9 males and 6 females receiving 9.0 mg/kg showed white and thickened gastric mucosa in the squamous portion of the stomach; five males dosed at 7.2 mg/kg and 2 females at 9.0 mg/kg had pinpoint raised foci or nodules in the squamous portion of the stomach; other observations include hemorrhagic lungs and tail darkened near the tip. **Mouse Subchronic Dietary NOEL:** Not established at this time, due to the limited time frame of dosing. Based on the mortality and necropsy observations seen in the 14-day toxicity study, the levels recommended for the chronic study are 5.8, 4.6 and 2.3 mg/kg in male mice and 7.2, 5.8 and 4.6 mg/kg in female mice. **Study acceptable.** (Guo, 4/27/15)

Oral toxicity, non-rodent:

Study not submitted.

Rabbit 21-Day Repeated Dosing Dermal Toxicity Study

** 50032-0071; 283473; "21-Day Dermal Test of Acrolein in Rabbits"; (Muni, I. A.; Bioassay Systems Corporation (BSC), Woburn, MA; BSC Project No.: 10258, MRID # 00141030;

7/28/82). The skin of 10 New Zealand White rabbits/sex/group was treated with 0.0, 7.0, 21.0 or 63.0 mg/kg/day of Acrolein (Lot Number SFSL-5993) (Acrolein, > 96%) 6 hours per day for 21 days (5 days per week). Prior to application, the test substance was diluted with a 50:50 (v/v) solution of deionized water and absolute ethanol. Two females dosed at 21.0 or 63.0 mg/kg died by day 5 or 4, and two females receiving 7.0 or 63.0 mg/kg were sacrificed moribund (likely due to broken backs attributable to hyperactivity behavior following dosing) at 5 days after the first application. Slight to moderate conditions of nasal mucus (discharge) and lethargy were seen more frequently in the acrolein-treated animals than in the controls. Several acrolein-treated animals also showed slight to moderate diarrhea, and/or apparent weight loss. After the first dose application, slight to moderate erythema and edema at the dose site were noted for almost all rabbits treated with acrolein at a level of 7.0 or 21.0 mg/kg; the animals receiving 63.0 mg/kg had similar severity of erythema, along with a more prominent edema formation. In general, for both male and female rabbits as the study progressed, the erythema and edema conditions became more pronounced in all acrolein-treated groups. Overall, the animals dosed at 63.0 mg/kg showed more pronounced skin damage (higher erythema/edema scores) than those in the 7.0 and 21.0 mg/kg groups. Skin damage was similar between animals with abraded skin and those with unabraded skin. By contrast, no notable redness or swelling was seen on the skin of the untreated or vehicle control animals. No significant differences were observed between the control and acrolein-treated groups for body weights, although acrolein-treated males exhibited lower (not significantly lower) final body weights than the controls. However, there were significantly smaller body weight changes (final minus initial body weights) ($p < 0.01$) in both sexes among acrolein-treated groups when compared with controls. A significant effect ($p < 0.01$) of the test substance on food consumption was found among male animals, but not among females. No treatment-related effects were noted in the hematological and blood chemistry evaluations, organ weights, organ-to-body weight ratios and organ-to-brain weight ratios. No visible lesions were observed in the untreated or vehicle control animals, other than some liver and lung abnormalities. Epidermal application of acrolein caused firm, thickened, reddened epidermis and dermis, skin discoloration, hemorrhage, edema, necrosis, and ulceration, or firm, thickened, corrugated and folded epidermis or epidermal crusts overlying the epidermis, with the severity of skin damage in a dose-related pattern. As to the animals that died or were sacrificed moribund during the first week of dosing, the gross abnormalities include vertebral column-subluxated at the T12-L1 region, swollen, edematous, discolored epidermis (brown or reddened) at dose site, the presence of blood in urine, liver with multiple white depressed spots and congested lungs, and gastrointestinal tract with liquid-like contents. The histological examination revealed that at higher dose levels, chronic topical administration of acrolein produces severe necrotizing and ulcerative dermatitis, resulting in healing with marked dermal fibrosis, hyperkeratosis and occasionally pseudoepitheliomatous hyperplasia. These are expected reactions of the integument to severe but reversible injury. There were significant skin lesions in the animals dosed at 7.0 mg/kg: epidermal necrosis, loss of adnexa, marked infiltrate of heterophilic cells and dermal edema. Mild pulmonary lesions (lymphoid hyperplasia and multifocal nonsuppurative interstitial pneumonia) were observed at this dose level, with mild bilateral nonsuppurative interstitial nephritis seen in 5/20 animals. At 21.0 mg/kg, necrotizing dermatitis was accentuated, and also observed were early reparative changes: hyperkeratosis, acanthosis, dermal fibrosis at the periphery of the ulcerated epidermis, and marked fibrosis in the area of the ulcer. Pulmonary lesions were intensified and a more diffuse nonsuppurative interstitial pneumonia was observed in 13/20 animals. Nonsuppurative interstitial nephritis was seen in 7/10 animals, with mesangioproliferative glomerulopathy noted for 3/20 animals. At 63.0 mg/kg, severe necrotizing dermatitis was observed, along with extensive hyperkeratosis, acanthosis and parakeratosis, which was accompanied by dermal fibrosis. Severe diffuse nonsuppurative interstitial pneumonia was observed in 16/20 animals. Renal lesions in this group were the same as those observed in the 21.0 mg/kg dose group. No significant

histopathological lesions of the skin were noted for the untreated or vehicle control animals. Overall, fewer histopathological lesions in the kidneys, eyes, liver and trachea were found among the control animals, with interstitial pneumonia in the lungs noted for 7/20 control animals. Of note, cholangiohepatitis secondary to Eimeria steidiae infestation was prominent in all dosage groups. Therefore, it was impossible to evaluate the toxicity of acrolein on the liver in this study. **21-Day Repeated Dose Dermal Toxicity NOEL:** Not established because of the compelling evidence of toxicity at all doses tested; **Dermal Irritation NOEL:** Not established due to the compelling evidence of toxicity at all doses tested; **Study acceptable.** (Guo, 5/18/15)

CHRONIC STUDIES

Chronic, rat

****50032-028 085062** "24-Month Chronic Toxicity and Oncogenicity Study in the Rat with Acrolein," (Long, J.E. & Johnson, J.A., Tegeris Laboratories, Inc., Laboratory Project No. TL 85047; 9/6/89). Acrolein, purity N96%, was administered by gavage at the nominal concentrations of 0 (water), 0.05, 0.5 and 2.5 mg/kg to 70-75 Sprague-Dawley rats/sex/group, for 102 weeks. Analytical testing of dosing solutions was done only 0-4 times/month for the first 18 months of the study. Dose levels were based on a short (6-week) pilot study, which was also included in the report. At 13 weeks and at 1 y, 5 high-dose rats (both sexes) and 10 rats/sex/group were sacrificed, respectively. Also, gavaging-induced deaths and loss of tissues due to autolysis effectively reduced the number of rats/sex/treatment level, depending on the tissue in question. There were no obviously treatment-related effects on the following: survival, bodyweights, organ weights, clinical signs, serum chemistry, hematology, urinalysis, and gross findings. The ophthalmology portion of this study was inadequate for interpretation. Two possible histological findings were increased incidences of hepatocellular adenomas and acinar-cell adenomas of the pancreas in the males; both tumor types exhibited dose responses and maximum percentages affected that were clearly greater than the values observed in the supplied historical control data. No histological findings were noted in the obvious target organ, the forestomach. This study was considered unacceptable when first reviewed (Rinkus, 8/13/90); and upgrading would require the submission of supplemental information that addressed the many concerns that DPR MT had about the study. The Registrant responded by submitting re-cords 097781, 124586 and 126430. These records are discussed in worksheet W085062.S01. Based on these submissions, record 085062 is considered margin-ally **ACCEPTABLE** only as an oncogenicity study. Hepatocellular adenomas in males have been dropped as an adverse-effect finding but pancreatic acinar cell tumors (adenoma and carcinoma) remain as adverse effects, with a **LOAEL of 0.05 mg/kg**. Record 085062 is **NOT ACCEPTABLE** and **NOT UPGRADABLE** as a chronic-toxicity study (inadequate hematology). (Rinkus, 3/18/94)

011 059502. Status at 30 weeks in terms of survivors. Doses of 0, 0.05, 0.5, and 2.5 mg/kg are being given by oral gavage. Doses were selected based on a 6-week range-finding study. Document is dated December 23, 1986. No review sheet. (Gee 2/5/88)

50032-044 097781 This record uses a question-and-answer format to address is-sues raised in worksheet W085062.835. **Supplemental information**. (Rinkus, 5/18/94).

50032-047 124586 This record is the pilot study on which the selection of the high dose for the rat reproduction study (record 092721) was based. **Supplemental information.** (Rinkus, 5/18/94).

50032-048 126430 This record contains three mailings of explanatory information regarding the statistical analyses contained in record 097881 for hepatic and pancreatic tumors in males. **Supplemental information.** (Rinkus, 5/18/94).

Chronic, dog

****50032-026 073320** "Acrolein--Chronic (12 Month) Oral Toxicity Study in the Dog," (Long, J.E., Tegeris Laboratories Inc., Project I.D. no. TL #85016; 10/23/87). Acrolein, purity of ≥ 94%, was administered by gelatin capsule at concentrations of 0, 0.1, 0.5 or 2.0 mg/kg/day to 6 beagle dogs/sex/group for 12 months. Dose levels were based on a range-finding study, which was included in the report. The only effects identified in the first review (9/11/90) as related to treatments were: vomiting in the mid and high-dose groups (both sexes), with the frequency being greater in the high-dose groups; and de-creases in the serum levels for calcium and albumin (consequently total protein, too) for the high-dose male and female groups, with both reductions being seen at each of the 3-month testing intervals. When first reviewed, this study was considered unacceptable, but upgradable upon submission of the ophthalmology raw data, a complete list of protocol deviations and resolution of matters concerning the route of exposure, preparation of dosing solutions, controlling of mites, frequency of dosing per week, and assaying for serum gamma-glutamyl transpeptidase. The Registrant responded by submitting records 097215 and 128724. These records are discussed in worksheet W073320.S01. A decrease in the activated partial thromboplastin time (hypercoagulation) is now being identified as a possible adverse effect (**NOAEL = 0.1 mg/kg**), for reasons discussed in worksheet W073320.S01. This study is now considered **ACCEPTABLE**. (Rinkus, 5/13/94).

Oncogenicity, rat

See Rat Chronic Toxicity above.

Oncogenicity, mouse

50032-029 090136, "18-Month Oncogenicity Study in the Mouse with Acrolein," (Long, J.E. & Johnson, J.A., Tegeris Laboratories, Inc., Laboratory Project No. TL 86057; 10/16/89). Acrolein, purity 96%, was administered by gavage at concentrations of 0 (water), 0.5, 2.0, and 4.5 mg/kg to CD-1 Swiss Albino mice for 18 months. Dose levels were based on a short (6 week) pilot study, which was also included in the report. Although the original study design called for 70-75 mice/sex/group, gavaging-induced deaths during the first few weeks of the study reduced the "effective number" of mice/sex/group to 37-67; and autolysis prevented the histological examination of some tissues, thereby reducing further the "effective number" for some organs. Excluding the gavaging-induced deaths occurring before week 3, there was no evidence that survival was affected in this study. Also, there was no evidence of a treatment-related effect on the following: bodyweights; clinical signs; wet organ weights (terminal sacrifice) for the brain, liver, kidneys, and testes; WBC differentials; and ophthalmology. Neither gross nor microscopic examinations identified any treatment-related effects, including no effects on the obvious target organ for this direct-acting agent, the forestomach. **NOEL > 4.5 mg/kg.** This study was considered **UNACCEPTABLE** when first reviewed (Kishiyama and Rinkus, 7/5/90) and upgrading would require the submission of supplemental information that would address the following: whether the highest dose tested was sufficiently close to the maximum tolerated dose; mice brought late into the study; the choice of the oral route of exposure over inhalation; amendments and deviations to the protocol; and discontinued QA inspections. The Registrant responded by submitting record 097780 and its contents are discussed in worksheet W090136.S01. This study is considered **UNACCEPTABLE** and **NOT UPGRADABLE (MTD not tested, poor study conduct, data for a parallel study not sub-mitted)**. (Rinkus, 9/7/93).

006 042959. Protocol reviewed. Study due Jan., 1989.

011 059216. Status report at week 5 for mouse study with survivors. Doses of 0, 0.5, 2.0, and 4.5 mg/kg are being given by oral gavage. A cover letter, dated July 10, 1987, discusses the problems Tegeris Laboratories is having with the dosing, resulting in numerous deaths. Additional mice will be added to the original 70/sex/group at the same doses so that an adequate number should be available at termination of the study. Status report is dated December 23, 1986. No review sheet. (Gee 2/5/88). Inspection of the data for the full study (record 090136) indicates that the water-gavaged mice also were dying as much as the acrolein-gavaged mice were. Therefore, the dying in this study appears to have been due to the gavaging technique and not the fact that three of the four dosing solutions contained acrolein. (Rinkus, 9/28/90).

50032-043 097880 This record uses a question-and-answer format to address is-sues raised in worksheet W090136.832. **Supplemental information.** (Rinkus, 5/18/94).

GENOTOXICITY

Gene mutation

Summary. The data requirement for gene mutation studies (842) is considered filled, with an adverse effect indicated. The results from bacterial testing included positive results (records 061604 & 061607), borderline results (re-cords 061603, 061605, 061606 &061609), and negative results (records 061602 & 061603). The two studies indicating a reproducible mutagenic effect also have provided a rationale for why other studies may have failed to demonstrate mutagenicity and this has persuaded CDFA to treat acrolein as a potential mutagen. The fact that acrolein is very reactive with sulfhydryl groups makes it very cytotoxic; as a result, "nonstandard" test procedures are needed to demonstrate mutagenicity. In record 061607, the new Salmonella tester strain TA104 was used with a liquid preincubation method of exposure; also, it was found that the presence of the plasmid pKM101 and deletion of the uvrB gene facilitated the detection of acrolein and that adding glutathione after the liquid preincubation period reduced the cytotoxicity but not the mutagenicity of acrolein. In record 061604, TA100 was used with a liquid preincubation method; afterwards, the cells were isolated by centrifugation and resuspended into fresh phosphate buffer for plating. Elsewhere one of the authors of record 061604 has reported that the liquid preincubation method using an increased cell density is necessary for demonstrating the mutagenicity of acrolein (Naunyn-Schmied. Arch. Pharmacol. 316 (Supplement), Abstract 54, 1981); these same conditions also are critical for detecting 3-methylacrolein (Environ. Molec. Mutagen. 14: 146-148, 1989). (Rinkus, 9/28/90).

**50032-027 075135 "CHO/HGPRT Mutation Assay with Confirmation," (J.W. Har-bell, Microbiological Associates Inc., Laboratory Study No. T8403.332001; 5/25/89). Acrolein, 96% purity, was tested as dimethylsulfoxide solutions for mutagenicity at the HGPRT locus (6-thioguanine resistance) using Chinese hamster ovary $K_{\leftarrow}$-$BH_{\leftarrow}$ cells. Test concentrations ranged from 0.0002 to 0.008 ml/ml and testing was done in the absence and presence of a Aroclor-induced rat liver S-9 activation system; in both cases, cells were exposed to acrolein for 5 h. Testing also involved the routine use of two negative controls (no treatment & DMSO at 1% v/v) and two positive controls (ethyl methanesulfonate and benzo(a)pyrene), which in all cases gave satisfactory results. Three trials, each involving testing up to concentrations that produced significant cytotoxicity, were conducted. In the first two trials, testing in the absence and presence of a S-9 mix was done, while in the third trial, no metabolic activation system was used. Slightly increased mutant frequencies were observed with concentrations of 0.0060 ml/ml in the presence of S-9 in the first trial and 0.0008 ml/ml in the absence of S-9 in the second trial.

However, in both cases, these increased mutant frequencies were not observed again in re-testing that either included the suspect concentration or testing up to high cytotoxicity. Therefore, **no reproducible mutagenicity was demonstrated. ACCEPTABLE.** (Kishiyama & Rinkus, 9/21/90).

006 042949, "In vitro Gene Mutation Assay (HGPRT Locus) in Cultured Chinese Hamster Ovary (CHO) Cells on Acrolein," (Bioassay System Corp., 4-28-82). Acrolein (>95%) at 0, 0.04, 0.06, 0.08, 0.1, 0.2, and 0.3 ug/ml with S9 rat liver activation, and 0, 0.1, 0.2, 0.3, 0.4, and 0.5 ug/ml - S9 on Chinese Hamster cells (CHO); HGPRT system; single trial, duplicate cultures; No evidence of increased mutation frequency; UNACCEPTABLE (No repeat trial). (Gee 8-4-86).

** 013 061602, "Salmonella Liquid Suspension Mutant Fraction Assay on Acrolein", (Bioassay Systems, Project no. 10258, 12-30-80). Acrolein, > 99%, was assayed with Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538 at concentrations of 1, 3, 10, 20, or 40 ug/ml in DMSO with and without S9 activation, duplicate samples, repeat trials with three strains. Suspensions were plated for viability and revertants. At 40 ug/ml, survival was less than 5%. No increase in revertants was noted. ACCEPTABLE. (Shimer 1-13-88 and Gee 2-1-88).

Note: Although this report conforms with guidelines with minor variations, the negative results are in contrast to the positive findings of other investigators also using Salmonella strains. The overall conclusion for gene mutation is that acrolein is a mutagen. See Summary above. (Gee 2/5/88; Rinkus 9/28/90).

Chromosome damage

Note: CDFA is aware of the following reports in the open literature that indicate positive and equivocal effects under this category: the induction of sister-chromatid exchanges in CHO cells (Au et al., Cytogenetics and Cell Genetics 26:108-116, 1980; Galloway et al., Environ. Molec. Mutagen. 10 (Suppl. 10): 1-175, 1987).

** 006 042952, "Effects of Acrolein on the In Vitro Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells", (Bioassay Systems Corp., 5/1/82). Acrolein (>95%) tested 0, 0.01, 0.3, 0.5, and 0.75 mg/ml on CHO cells, +S9, 4 hours; at 0, 0.3, 0.5, and 0.75 mg/ml -S9, for 30 hours. NO evidence for SCE formation; ACCEPTABLE. (Gee 8-4-86)

** 006 042951, "Effects of Acrolein on the In Vitro Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells", (Bioassay Systems Corp., 7/23/82). Acrolein (>95%) tested at 0, 0.4, 0.6, 0.8, 1.0, 1.5, and 2.0 mg/ml +S9 on CHO cells, 2 hours, and 0, 0.2, 0.4, 0.6, 0.8, 1.0, and 2.0 -S9 for 6 hours; single time of harvest, duplicate cultures; No adverse effects reported; ACCEPTABLE with variances (single time of harvest and varying number of cells analyzed.) (Gee 8-4-86).

006 042950, "Effects of Acrolein on the In Vivo Induction of Chromosomal Aberrations in Rat Bone Marrow Cells", (Bioassay Systems Corp., 11/17/82).Acrolein (>95%) given at 0, 1, 2.1, and 4.1 mg/kg in a single i.p. injection to Sprague-Dawley rats, 3 to 5 males/group; sampling times of 6, 12, and 24 hours; No evidence of increased chromosomal aberrations; UNACCEPTABLE (males only). (Gee 8-7-86).

DNA damage or miscellaneous effects

Note: CDFA is aware of the following reports in the open literature that indicate a positive effect under this category: the induction of DNA single-strand breaks, as measured by the alkaline elution assay (Erickson et al., Cancer Research 40: 4216-4220, 1980); and the formation of DNA adducts (Chung et al., Cancer Research 44: 990-995, 1984; Wilson et al., Proceedings of the American Association for Cancer Research 31:95 (Abstract No. 563), 1990).

** 006 042953, "Effect of Acrolein on the Incidence of C3H/10T1/2 transformed cells In Vitro", (Bioassay System Corp., 4/28/82). Acrolein (>95%) tested at 0, 0.04, 0.06, 0.08, and 0.1 ug/ml on mouse fibroblasts (C3H/10T1/2), exposed for 3 days; 20 dishes/concentration; scored at 6-7 weeks; No increased incidence of type II - III foci reported; ACCEPTABLE. (Gee 8-4-86).

REPRODUCTIVE TOXICITY, RAT

007-8 50058-9, "Two Generation Reproductive Study of Acrolein in Albino Rats", (Bioassay Systems Corporation, 12-7-84). Acrolein by gavage at 0, 4.0, 5.4 and 7.2 **mg**/kg/day. Reproductive NOEL > 7.2 mg/kg. Chronic toxicity NOEL < 4.0 mg/kg (decreased body weight F1 males, stomach lesions F0 and F1). **UNACCEPTABL**E; cannot be upgraded (limited histopathology and necropsy, poor study performance, gestation period ranged from 11 to 27 days). No adverse effect. (Parker 12/16/86). Rebuttal by Baker Performance Chemicals and supplemental data (Record 067445) led to no change in evaluation. (Davis 10/5/88).

021 067445, "Report Amendment: Two Generation Reproductive Study of Acrolein in Albino Rats." Supplemental material (revisions and corrections for the report; dosing solution analyses; dosing records; breeding observations) in support of the rebuttal in volume 021, part 1. (Davis, 10/5/88).

025 072525. Audit of the study prepared at Argus Research Laboratories. No worksheet. (Gee, 2/16/89).

****50032-035 092721** "Reproductive Effects of Acrolein Administered Orally via Gavage to Crl:CD*(SD)BR Rats for Two Generations, with One Litter per Generation," (Alan M. Hoberman, Argus Research Laboratories, Inc., Horsham, PA; Re-port # 603-003, 4/12/91). Acrolein, >96% purity, was administered by gavage once daily at 0 (water), 1, 3, and 6 mg/kg, to 30 Crl:CD*(SD)BR rats/sex/dose in the F0 generation and to 40 rats/sex/dose in the F1 generation. F0 rats and F1 rats, derived from F1a litters, were exposed for N10 weeks before their single mating trials and were exposed for a total of 93-149 daily dosings be-fore they were sacrificed. No effects on the mating, fertility, or gestation indices were observed in either mating trial. Forestomach hyperplasia and (or) hyperkeratosis was seen at ≥ 80% incidence in the 6 mg/kg groups (both sexes, both generations); also, an incipient effect was present at the 3 mg/kg level (females only, both generations). The incidences of mortalities and respiratory complications (e.g., rales, gasping) were increased significantly in the 6 mg/kg groups (both sexes, both generations). The composite picture that emerges from considering these mortalities and their respective clinical, necropsy and histology data is that aspiration of the dosing solution was common-place, it resulted in lung damage, and in many instances this resulted in deaths. That is, these aspiration-associated lung effects and deaths may not represent a systemic or gastrointestinal effect by acrolein; rather, they are directly dependent on the use of gavage to accomplish oral dosing with a known pulmonary toxicant. **Parental NOAEL = 1 mg/kg (hyperplasia/hyperkeratosis).** The only progeny effect was a significant reduction in pup bodyweights, starting on lactation day 7 for the 6 mg/kg group (F1a offspring only). For the F1

males (but not the F1 females) derived from the F1a 6 mg/kg pups, this reduction in bodyweight (relative to the controls) persisted till their sacrifice at the end of the study. **Progeny NOAEL = 3 mg/kg (reduced F1a pup bodyweights during lactation).** This study is considered **ACCEPTABLE**. (Rinkus, 4/12/94).

50032-047 124586 This record is the pilot study on which the selection of the high dose for the rat reproduction study (record 092721) was based. **Supple-mental information.** (Rinkus, 5/18/94).

50032-046 124351 This record is the protocol for the rat reproduction study (record 092721). **Supplemental information.** (Rinkus, 5/18/94).

50032-046 124343 This record is the protocol for the pilot rat reproduction study (record 124586). **Supplemental information.** (Rinkus, 5/18/94).

DEVELOPMENTAL TOXICITY

Rat

**004 021617 "Teratology study of Acrolein in Rats", (Bioassay Systems Corp., 11-12-82, Project No. 10258). Acrolein, Batch 6151, 96.48%; analysis in 063285; given by oral gavage to Sprague-Dawley CD rats, days 7-19 (day of mating = day 1) at 0, 3.6, 6.0, or 10 mg/kg/day; maternal NOEL = 3.6 mg/kg/day (decreased weight gain, increased mortality and clinical signs), developmental NOEL = 6.0 mg/kg/day (decreased fetal weight and increased skeletal variants). Initially reviewed by J. Christopher, 3/27/85. Rereviewed by J. Parker, 8/6/86, as not showing an adverse developmental effect. Submission of supple-mental data in 063285 provides sufficient additional information to upgrade the study to ACCEPTABLE status with minor deficiencies. No adverse effect. (Gee, 2/5/88, with Parker).

EPA 1-liner: Minimum. Maternal NOEL = 3.6 mg/kg (decreased body weight gain and increased mortality), fetotoxic NOEL = 6.0 mg/kg (decreased fetal weights, delayed ossifications), teratogenic NOEL = 6.0 mg/kg (fetal runts).

014 063285 "Report Amendment--Teratology Study of Acrolein in Rats," (MacRill, G.E.; Baker Performance Chemicals, Inc.; "revised" 8/14/87). This is also entitled "Appendix F" (to record 021617). It contains supplementary data to ad-dress the concerns raised by the then CDFA toxicologists that reviewed record 021617. These concerns are summarized in a question-and-answer format in a four-page letter dated October 23, 1987 from the Registrant to then CDFA that accompanied this submission; this letter (no record number) appears in the front of 50032-014. **Supplementary information.** (Rinkus, 5/18/94).

50032-003 920144 This record is a two-page summary of the results for the rat teratogenicity study (record 021617) and the mouse teratogenicity study (record 021618). A letter dated November 2, 1982 from the Registrant to then CDFA accompanied this submission; this letter (no record number) appears in 50032-003 just before record 920144. **Supplemental information.** (Rinkus, 5/18/94).

Rabbit

** 015 063594, "Developmental Toxicity (Embryo/Fetal Toxicity and Teratogenic Potential) Study of Acrolein Administered Orally (Stomach Tube) to New Zealand White Rabbits", (Argus Research Laboratories, Inc., Report no. 603-001, 5-20-87). Acrolein, 96.15% was administered to inseminated New Zealand White rabbits on days 7-19 of gestation at 0, 0.1, 0.75, and 2

mg/kg/day, 20/group. Maternal NOEL = 0.75 mg/kg/day (initial reduction of body weight gain; Developmental NOEL = 0.75 mg/kg/day (increase in number of resorptions not statistically significant). No adverse effect. ACCEPTABLE. (Shimer 1/12/88 and Gee 2/3/88).

Mouse

003 021618, "Teratology Study of Acrolein in Mice", (Bioassay Systems Corp., 9-1-82). Acrolein, Batch 6104, 96%, by oral gavage on days 7 - 17 of gestation, at 0, 4.0, 6.3, and 10 mg/kg/day. Developmental NOEL less than 4.0 (Resorptions at 10, increase in structural changes at all dose levels). Maternal NOEL = 6.3 mg/kg (decreased weight gain). UNACCEPTABLE, not upgradeable and **possible adverse effect indicated**. (Christopher 3-28-85, Parker 8-6-86).

EPA 1-liner: Supplementary. Maternal NOEL <= 4 mg/kg (LDT) (decreased body weight gain); fetotoxic NOEL <= 4 mg/kg (generalized delayed ossification); teratogenic NOEL, not established: possible cleft plate at 6.3 and 10 mg/kg. Conclusion could not be reached due to lack of critical data in report.

NEUROTOXICITY

Acute neurotoxicity, rat

Study not submitted.

90-day neurotoxicity, rat

Study not submitted.

Developmental neurotoxicity, rat

Study not submitted.

Delayed neurotoxicity, hen

Study not submitted nor required at this time.

IMMUNOTOXICITY

Study not submitted.

ENDOCRINE DISRUPTOR STUDIES

Study not submitted nor required at this time.

SUPPLEMENTAL STUDIES

013 061605, "Comparison of the Mutagenicity and Teratogenicity of Cyclophosphamide and Its Active Metabolites, 4-Hydroxycyclophosphamide, Phosporamide Mustard, and Acrolein", (McGill University, Montreal, Cancer Research (1982) 42, 3016-3021). Acrolein (a metabolite of cyclophosphamide) was one of the 4 chemicals given to rats by an intra-amniotic injection to fetuses in one uterine horn on day 13 of gestation. At 100 ug/fetus, 98% of fetuses were dead or resorbed, at 10 ug/fetus, 100% of fetuses were dead or resorbed. At 1 ug/fetus, 85.7% of the fetuses had malformations very similar to those caused by cyclophosphamide (edema, hydrocephaly, open eyes, cleft palate, omphalocele and forelimb, hindlimb and tail defects.) At 0.1 ug, 0.002 umol/fetus, acrolein had no effect on resorption or malformation rate compared with saline control. Fetal weight was decreased at both 0.1 and 1 ug/fetus. The chemicals were also tested in an Ames assay with strain TA1535 of S. typhimurium at 0.001 to 50 ug/plate. Acrolein was very bacteriotoxic, not mutagenic without S9 and very weakly mutagenic with S9

activation. Supplementary. Not a guideline type study. Possible adverse developmental effect in fetuses and weakly mutagenic in bacteria. (Shimer 11/13/87 and Gee 2/2/88).

Publications Regarding Acrolein

Anon. (1985) Acrolein. In: IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Volume 36, pp. 133-161. World Health Organization, Lyon, France.

Beauchamp, Jr., et al. (1985) A Critical Review of the Literature on Acrolein Toxicity. CRC Critical Reviews in Toxicology 14: 309-380.

Witz, G. (1989) Biological Interactions of a,b-Unsaturated Aldehydes. Free Radical Biology & Medicine 7: 333-349.

Selley et al. (1990) Effects of Acrolein on Human Platelet Aggregation. Chem.-Biol. Interactions 76:101-109.

Lijinsky, W. and Reuber, M.D. (1987) Chronic Carcinogenesis Studies of Acro-lein and Related Compounds. Toxicology and Industrial Health 3:337-345.

Published Versions of Some of the Studies Submitted Under SB950

Parent et al. (1992) Two-Year Toxicity and Carcinogenicity Study of Acrolein in Rats. J. Appl. Toxicol. 12:131-139.

Parent et al. (1992) One Year Toxicity of Orally Administered Acrolein to the Beagle Dog. J. Appl. Toxicol. 12:311-316.

Parent et al. (1992) Oncogenicity Study of Acrolein in Mice. J. Am. Coll. Toxicol. 10:647-659.

Parent et al. (1992) Reproductive Study of Acrolein on Two Generations of Rats. Fundam. Appl. Toxicol. 19:228-237.