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

013888

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

**DATE: December 8, 1999**

**MEMORANDUM**

**SUBJECT:** ***4,5-dichloro-2-n-octyl-3(2H) isothiazolone [C9211; RH-287]*** - Report of the Hazard Identification Assessment Review Committee.

**FROM:** Timothy F. McMahon, Ph.D.
Risk Assessment and Science Support Branch
Antimicrobials Division (7510C)

**THROUGH:** Pauline Wagner, Co-Chairman, Pauline Wagner 12/9/99
and
Jess Rowland, Co-Chairman Pauline Wagner 12/9/99
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

**TO:** Timothy F. McMahon, Ph.D.
Risk Assessment and Science Support Branch
Antimicrobials Division (7510C)

**PC Code:** 128101

On November 16, 1999, the Health Effects Division's Hazard Identification Assessment Review Committee evaluated the toxicology data base of **RH-287,** established a an acute and chronic Reference Dose (RfD) and selected the toxicological endpoints for acute and chronic dietary as well as occupational exposure risk assessments. The HIARC also addressed the potential enhanced sensitivity of infants and children from exposure to RH-287 as required by the Food Quality Protection Act (FQPA) of 1996. The Committee's conclusions are presented in this report.

Committee Members in Attendance

Members present were: David Anderson; Bill Burnam; Virginia Dobozy; Pam Hurley; Tina Levine; Nancy McCarroll; Sue Makris; Nicole Paquette; Kathleen Raffaele; Jess Rowland; P.V. Shah; and Pauline Wagner. Data was presented by Tim McMahon of the Antimicrobials Division.

Data Presentation:
and
Report Presentation

Tim McMahon.
Senior Toxicologist
Risk Assessment and Science Support Branch

## I. INTRODUCTION

4,5-dichloro-2-n-octyl-3(2H) isothiazolone, also known as C9211 or RH-287, is an antimicrobial active ingredient registered for use on a variety of use sites, including wood treatment, food processing water systems, metalworking cutting fluids, and materials preservative uses, including paint preservation. The HIARC was requested to select endpoints for dietary and non -dietary risk assessments for this chemical.

## II. HAZARD IDENTIFICATION

### A1. Acute Reference Dose (RfD) [Females 13-50]

Study Selected: Developmental Toxicity - rat

**MRID No.:** 43471604

**Executive Summary:** In a developmental toxicity study in rats (MRID # 43471604), groups of pregnant female CD rats (25/dose) were administered RH-287 (98.8% purity) by gavage at dose levels of 0, 10, 30, and 100 mg/kg/day on gestation days 6 through 15. At 100 mg/kg/day, clinical signs of toxicity were observed in maternal animals, consisting of scant feces, soft feces, and/or diarrhea. One dam died at the 100 mg/kg/day dose level. Decreased body weight gain was observed at 100 mg/kg/day (73% of control in pregnant dams). There were no significant differences in the number of corpora lutea/dam, implantations/dam, live fetuses/dam, resorptions/dam, or in pre- or post-implantation losses, litter weight, or fetal body weight. There were no fetal external variations or developmental retardations, and there were no fetal soft tissue developmental retardations. Fetuses at the high dose showed an increase in the number of fetuses with wavy ribs, along with an increase in number of litters with this effect as well as the severity of the effect. The Maternal NOAEL is determined to be 10 mg/kg/day, based on decreased food consumption during dosing and clinical signs at 30 mg/kg/day. The Developmental NOAEL is determined to be 30 mg/kg/day, based on increased litters with wavy ribs at 100 mg/kg/day.

Dose and Endpoint for Establishing Acute RfD: NOAEL of 30 mg/kg/day, based on increased numbers of litters with wavy ribs at 100 mg/kg/day (LOAEL).

Comments about Study/Endpoint: The developmental endpoint of wavy ribs presumed to occur after a single exposure and thus is appropriate for this risk assessment. Also, since this is an *in utero* effect, it is relevant for risk assessment for females 13-50.

Uncertainty Factor (UF): 100 (10x intraspecies uncertainty factor, 10x interspecies uncertainty factor).

$$\textbf{Acute RfD} = \frac{\text{30 mg/kg [LOAEL]}}{\text{100 [UF]}} = \textbf{0.3 mg/kg}$$

**This Risk Assessment is required.**



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A2. Acute Reference Dose (RfD) [General Population]

Study Selected: Developmental Toxicity - rat

**MRID No.:** 43471604

**Executive Summary:** In a developmental toxicity study in rats (MRID # 43471604), groups of pregnant female CD rats (25/dose) were administered RH-287 (98.8% purity) by gavage at dose levels of 0, 10, 30, and 100 mg/kg/day on gestation days 6 through 15. At 100 mg/kg/day, clinical signs of toxicity were observed in maternal animals, consisting of scant feces, soft feces, and/or diarrhea. One dam died at the 100 mg/kg/day dose level. Decreased body weight gain was observed at 100 mg/kg/day (73% of control in pregnant dams). There were no significant differences in the number of corpora lutea/dam, implantations/dam, live fetuses/dam, resorptions/dam, or in pre- or post-implantation losses, litter weight, or fetal body weight. There were no fetal external variations or developmental retardations, and there were no fetal soft tissue developmental retardations. Fetuses at the high dose showed an increase in the number of fetuses with wavy ribs, along with an increase in number of litters with this effect as well as the severity of the effect. The Maternal NOAEL is determined to be 10 mg/kg/day, based on decreased food consumption during dosing and clinical signs at 30 mg/kg/day. The Developmental NOAEL is determined to be 30 mg/kg/day, based on increased litters with wavy ribs at 100 mg/kg/day.

Dose and Endpoint for Establishing Acute RfD: A Maternal NOAEL of 30 mg/kg/day was determined *for this risk assessment only*, based upon decreased food consumption observed on days 6-10 of dosing at 100 mg/kg/day.

Comments about Study/Endpoint: The HIARC did not consider the decrease in food consumption at 30 mg/kg/day to be toxicologically significant; however, the effect at 100 mg/kg/day was considered relevant. Thus, for the present risk assessment, the effect on food consumption at 100 mg/kg/day was used.

Uncertainty Factor (UF): 100 (10x intraspecies uncertainty factor, 10x interspecies uncertainty factor).

$$\textbf{Acute RfD} = \frac{\text{30 mg/kg [LOAEL]}}{\text{100 [UF]}} = \textbf{0.3 mg/kg}$$

**B. Chronic RfD**

Study Selected: 28-Day Toxicity Study - Rats

MRID No.: 42214903

**Executive Summary :** In this study, 40 male and female Sprague-Dawley rats were assigned to 4 groups of 10 rats each. RH-287 was administered by gavage in olive oil at doses of 0, 20, 100, or 500 mg/kg/day once a day for 28 days. At 500 mg/kg/day, mortality was observed in 3 females. Males at the 500 mg/kg/day dose displayed clinical signs of toxicity, including anal staining, reduced spontaneous movements, salivation, hypothermia, and abdominal distension. Similar findings were observed in female rats. Significant reductions in body weight were observed in male rats at 500 mg/kg/day. Alterations in hematological parameters (decreased MCV, decreased MCH, decreased MCHC) were observed in male rats at 100 and 500 mg/kg/day. In female rats, these alterations were observed primarily at 500 mg/kg/day. Significant elevation in SGOT was observed in male rats at 100 and 500 mg/kg/day and in female rats at 500 mg/kg/day. Hyperplasia of the mucosa of the non -glandular stomach and granulation of the tunica propria mucosa of the non -glandular stomach was observed at 100 and 500 mg/kg/day in male and female rats at the end of the study. The NOAEL for this study was determined to be 20 mg/kg/day, based on the altered hematological/clinical chemistry changes and microscopic lesions of the stomach observed at 100 mg/kg/day.

Dose and Endpoint for Establishing Chronic RfD: Systemic NOAEL of 20 mg/kg/day, based on altered hematological/clinical chemistry changes and microscopic lesions of the stomach observed at 100 mg/kg/day.

Uncertainty Factor(s): 1000 (10x intraspecies uncertainty factor, 10x interspecies uncertainty factor, 10x for lack of chronic studies).

$$\textbf{Chronic RfD} = \frac{20 \text{ mg/kg/day ( NOAEL )}}{1000 \text{ [UF]}} = \textbf{0.02 mg/kg/day}$$

Comments about Study/Endpoint/Uncertainty Factor: The 28-day study was selected for the chronic RfD as similar lesions of the stomach were observed as in the 90-day study, but at a lower dose. Lacking a true chronic toxicity study, the 28-day NOAEL was felt to be a conservative estimate of risk. In addition, the NOAEL of the dietary 90-day study (32.5/36/7 mg/kg/day) supports the selection of the endpoint used for the chronic RfD. An additional Uncertainty Factor of 10x is required for the use of a short-term exposure study for establishing Chronic RfD (i.e., lack of chronic studies).

**This risk assessment is required.**



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## C. Occupational/Residential Exposure

### 1. Dermal Absorption

Dermal Absorption Factor:

Dermal absorption of RH-287 was examined in male Crl:CD:BR rats (MRID # 43471610). There were six experimental groups of 4 rats each. Two concentrations of RH-287 were employed, 3% and 0.045%. Dermal application was made to a shaved 2 x 2 cm area on the interscapular region of the back, which was fitted with a contoured glass ring secured with cyanoacrylate glue and a porous top secured with rubber bands after application of the test substance in a dose aliquot of 60 $\mu$l. Two groups (A and B) received either 3% of 0.045% RH-287 and urine and feces samples obtained at 10 hours post-dose, at which time the animals were killed and analysis for radioactivity performed in whole blood, plasma, and remaining carcass. Two additionalk groups 9C and D) received either 3% or 0.045% RH-287 and were subjected to the same procedures as groups A and B, except exposure duration was 24 hours. The last two groups (E and F) received either 3% or 0.045 % RH-287, and urine and feces samples taken at 0, 10, 24, 48, and 72 hours post-dose. Animals in this group were sacrificed at 72 hours post-dose and analysis for radioactivity performed as for the other groups. Results of this study showed that at a dose of 0.045% RH-287, 44-50% of the dose was absorbed after a 10 hour exposure, and 70% after a 24 hour exposure. Administration of 3% RH-287 resulted in 31-34% absorption after 10 hours of exposure, and 52% absorption after 24 hours exposure.
Based on the data in this study, the HIARC recommended use of a 50% dermal absorption factor for dermal risk assessments.

### 2. Short-Term Dermal - (1-7 days)

Study Selected: 28-Day Toxicity - Rats

MRID No.: 42214903

Executive Summary: see summary under chronic dietary

Dose and Endpoint for Risk Assessment: see chronic dietary assessment

Comments about Study/Endpoint:. No other appropriate studies were available for assessing short-term dermal risk; therefore, this dose/study was selected. Since an oral NOAEL was selected, the default dermal absorption value of 50% should be used for dermal risk assessments. A Margin of Exposure of 100 is considered adequate for this risk assessment.

**This risk assessment is required.**

**3. Intermediate-Term Dermal (7 Days to Several Months)**

Study Selected: 28-Day Toxicity - Rats

MRID No.: 42214903

Executive Summary: see summary under chronic dietary

Dose and Endpoint for Risk Assessment: see chronic dietary assessment

Comments about Study/Endpoint:. No other appropriate studies were available for assessing intermediate-term dermal risk; therefore, this dose/study was selected. Since an oral NOAEL was selected, the default dermal absorption value of 50% should be used for dermal risk assessments. A Margin of Exposure of 100 is considered adequate for this risk assessment.

**This risk assessment is required.**

**4. Long-Term Dermal (Several Months to Life-Time)**

Study Selected: 28-Day Toxicity - Rats

MRID No.: 42214903

Executive Summary: see summary under chronic dietary

Dose and Endpoint for Risk Assessment: see chronic dietary assessment

Comments about Study/Endpoint: No other appropriate studies were available for assessing long-term dermal risk; therefore, this dose/study was selected. Since an oral NOAEL was selected, the default dermal absorption value of 50% should be used for dermal risk assessments.

**This risk assessment is required.**



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**5. Inhalation Exposure** (Any Time period).

Study Selected: 90-Day Inhalation Toxicity - Rats

A subchronic inhalation toxicity study was available for RH-287 (MRID # 43487501).

In this study, groups of 32 male and 32 female Crl;CD BR rats received nose-only inhalation exposure for 6 hours per day, 5 days per week, for thirteen weeks to air, an aerosol of o-xylene (the vehicle) at 238.5 mg/m$^3$, or RH-287 at concentrations of 0.02, 0.63, and 6.72 mg/m$^3$. At the end of the thirteen week exposure period, half of the animals in each group were necropsied, 5 from each group were necropsied at six months, and the remaining animals were necropsied at the end of a one-year recovery period. Mean mass median aerodynamic diameter of RH-287 was 1.4 $\mu$m, and the mean geometric standard deviation was 4.6, with 72% respirable fraction. Increased mortality was observed in the vehicle control group of female rats during the exposure period, but was attributed to over-restraint in the nose-only tubes. There was no other treatment-related increase in mortality either during the treatment period or during the recovery period. The incidence of rales was increased in high dose males and females beginning at weeks 2-3 of exposure. Significant differences were observed in body weight gain between the air control and vehicle control group during treatment, indicating an effect of vehicle on body weight gain. When compared with the vehicle control, the test material resulted in decreased body weight gain of approximately 20% at the high dose level beginning at week 2 and persisting throughout the thirteen week exposure period for male and female rats. During recovery, there were no significant effects on body weight gain in treated male or female rats. No statistically significant differences were observed in treated rats vs. vehicle or control rats in clinical chemistry or hematology parameters at any dose tested. Treatment-related microscopic lesions in the nose, larynx, and lungs were observed in mid- and high-dose treated rats. Minimal or mild subacute inflamation of the nose was observed in increased incidence, as was transitional respiratory epithelial hyperplasia and goblet cell hyperplasia. In the epiglottis, hyperplasia of the squamous and cuboidal epithelium was observed in mid- and high dose rats, as was chronic-active inflammation of the epiglottis. Goblet cell hyperplasia and acute inflammation was observed in increased incidence in the lungs of high dose rats. Based upon the histopathological alterations observed in the nose, larynx, and lungs, the systemic LOAEL is determined to be 0.63 mg/m$^3$, and the systemic NOAEL is determined to be 0.02 mg/m$^3$.

Dose and Endpoint for Risk Assessment: Systemic NOAEL of 0.02 mg/m$^3$, based on histopathological alterations of the nose, larynx, and lung at 0.63 mg/m$^3$.

Comments about Study/Endpoint:. A Margin of Exposure of 100 is considered adequate for this risk assessment.

**This risk assessment is required.**



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D. Margins of Exposures for Occupational/Residential Exposure Risk Assessments

For short-, intermediate-, and long-term dermal and inhalation occupational risk assessments, a MOE of 100 is adequate.

## III. CLASSIFICATION OF CARCINOGENIC POTENTIAL

RH-287 has not been classified as to carcinogenic potential. There are no cancer studies available for this chemical. These data may be required as a condition of future registrations.

## IV. MUTAGENICITY

MRID # 43471605: In two independent microbial gene mutation assays, Salmonella strains TA1535, TA1537, TA98, and TA100 were exposed to non-activated doses of 0.3, 1, 3, 10, or 30 $\mu$g/plate (initial trial) or 0.1, 0.3, 1, 3, or 7.5$\mu$g/plate (confirmatory trial) or S9-activated doses of 3, 10, 30, 100, or 300 $\mu$g/plate (initial trial) or 1, 3, 7.5, 30, or 75 $\mu$g/plate (confirmatory trial) of RH-287 technical. Cytotoxicity was achieved at levels $\geq$ 3 $\mu$g/plate -S9 and $\geq$ 75 $\mu$g/plate +S9. There was no evidence of a mutagenic response at any dose either in the absence or presence of S9 in either trial. All strains responded in the expected manner to the corresponding nonactivated and S9-activated positive controls. This study is classified as acceptable and satisfies the guideline requirement for a microbial gene mutation assay.

MRID # 43471606: RH-287 : In two independent Chinese hamster ovary (CHO) in vitro gene mutation assays, cell cultures were exposed to non activated concentrations of 0.005, 0.025, 0.05, 0.1, or 0.5 $\mu$g/ml (initial trial) or 0.025, 0.05, 0.1, 0.2, 0.4, 0.5, or 0.75 $\mu$g/ml (confirmatory trial) or S9-activated concentrations of 0.5, 1.0, 2.5, 5.0, 10, or 25 $\mu$g/ml (initial trial) or 2.5, 5.0, 6.0, 8.0, 9.0, 10, or 15 $\mu$g/ml (confirmatory trial). In both trials, cytotoxicity was achieved at concentrations $\geq$ 0.5 $\mu$g/ml -S9 and $\geq$ 10 $\mu$g/ml +S9. There was no evidence of a mutagenic response at any concentration either with or without S9 activation in either trial. This study is classified as acceptable and satisfies the guideline requirement for an in vitro mammalian cell gene mutation assay.

MRID # 43471607: In this study, RH-287 was tested in two independent Chinese hamster ovary in vitro cytogenetic assays. Cell cultures were exposed to non activated concentrations of 0.3, 0.6, or 0.7 $\mu$g/ml (initial trial) or 0.5, 0.6, or 0.7 $\mu$g/ml (confirmatory trial) or S9-activated concentrations of 6.0, 7.0, or 8.0$\mu$g/ml (both trials). Cell harvest times were: 23 hours (initial nonactivated trial), 23 and 47 hours (confirmatory nonactivated trial), 20 hours (initial S9-activated trial), or 20 and 44 hours (confirmatory S9-activated trial). Cytotoxicity as indicated by reduced mitotic indices (~50%) was seen at $\geq$ 0.7 $\mu$g/ml -S9 and 8.0 $\mu$g/ml +S9; interference with cell-cycle kinetics was also observed at nonactivated doses as low as 0.05 $\mu$g/ml and at S9-activated levels $\geq$ 4.0 $\mu$g/ml. Slight increases in the frequency of cells bearing structural aberrations, particularly complex aberrations, were noted in cultures harvested after the prolonged recovery from exposure to the highest nonactivated or S9-activated concentrations. Complex structural aberrations were also scored at the remaining doses +/- S9. However, the



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increases in aberrant cells never exceeded 3% of the examined population and never approached a level of statistical significance. The evidence is, therefore, not sufficient to conclude that RH-287, tested to cytotoxic levels, induced a clastogenic response in the presence or absence of S9 activation. This study is classified acceptable and satisfies the guideline requirement for an in vitro mammalian cell cytogenetic assay.

MRID # 43471608: In an in vivo micronucleus assay, groups of CD-1 mice (5, 5, or 7/dose/sex/sacrifice time) received single oral gavage administrations of 32.5, 162.5, or 325 mg/kg RH-287 technical in corn oil. Bone marrow cells were examined 24 and 48 hours post-treatment for the frequency of polychromatic erythrocytes (MPEs). The observation of mild and transient clinical signs (passive behavior and scant feces in high dose males and females) suggests that the maximum tolerated dose (MTD) was not achieved. There was also no evidence of target cell cyototoxicity at any dose or harvest time. A slight but dose-related increase in MPEs was observed in male mice of the mid- and high-dose groups at the 24 hour sacrifice. The increase was significant at 325 mg/kg ($p < 0.05$). However, the findings do not provide sufficient evidence to classify RH-287 as clastogenic/aneugenic in this test system.

Additional information submitted by the registrant to resolve the issue of the MTD led to the following conclusion by HED: "TBII has reached the decision that testing at a higher dose level would likely cause mortality. In light of this decision, we also agree that the significant increase in micronuclei seen in the high dose males was probably an anomalous finding since increases were not seen at 48 hours and were not observed in females at any dose or harvest time. We conclude that nothing further would be gained by repeating the micronucleus assay. RH-287 technical is, therefore, considered to be negative in this in vivo test system. The study is considered acceptable and satisfies the guideline requirement for a micronucleus assay."

## V. FQPA CONSIDERATIONS

1. Adequacy of the Data Base

The database is incomplete with regard to performance of an FQPA risk assessment. Only a single developmental toxicity study in the rat is considered acceptable. An FQPA analysis is required for certain use patterns of this chemical (food processing water systems, pulp and paper mill systems, in-can paint preservative).

2. Neurotoxicity Data

There are no data specific to the neurotoxicity of RH-287. It is noted that in the 28-day toxicity study in rats, signs of possible neurotoxicity (reduced spontaneous movements, salivation) were observed at a dose of 500 mg/kg/day. No other studies in the available database indicate neurotoxic potential of RH-287.



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3. Developmental Toxicity

(i) Developmental Toxicity

In a developmental toxicity study in rats (MRID # 43471604), groups of pregnant female CD rats (25/dose) were administered RH-287 (98.8% purity) by gavage at dose levels of 0, 10, 30, and 100 mg/kg/day on gestation days 6 through 15. At 100 mg/kg/day, clinical signs of toxicity were observed in maternal animals, consisting of scant feces, soft feces, and/or diarrhea. One dam died at the 100 mg/kg/day dose level. Decreased body weight gain was observed at 100 mg/kg/day (73% of control in pregnant dams). There were no significant differences in the number of corpora lutea/dam, implantations/dam, live fetuses/dam, resorptions/dam, or in pre- or post-implantation losses, litter weight, or fetal body weight. There were no fetal external variations or developmental retardations, and there were no fetal soft tissue developmental retardations. Fetuses at the high dose showed an increase in the number of fetuses with wavy ribs, along with an increase in number of litters with this effect as well as the severity of the effect. The Maternal NOAEL is determined to be 10 mg/kg/day, based on decreased food consumption during dosing and clinical signs at 30 mg/kg/day. The Developmental NOAEL is determined to be 30 mg/kg/day, based on increased litters with wavy ribs at 100 mg/kg/day.

(ii) Reproductive Toxicity:

There are no studies on the reproductive toxicity of RH-287.

4. Determination of Susceptibility

The developmental toxicity study in the rat showed no increased susceptibility to the effects of treatment with RH-287. However, a complete assessment is not currently possible with only a single study in the database.

5. Determination of the Need for Developmental Neurotoxicity Study

(I) Evidence supporting a developmental neurotoxicity study

None

(ii) Evidence that does not support a developmental neurotoxicity study

Toxicity responses from non -acute data for RH-287 show no specific evidence of neurotoxicity to either adult animals or offspring although the database assessing sensitivity of offspring is incomplete. At this time, a developmental neurotoxicity test is not warranted until the developmental / reproductive toxicity database is complete.

4. Hazard-Based Determination of the FQPA Factor:

Based upon the hazard profile for RH-287 (with no consideration of exposure) and the lack of a complete database for developmental and reproductive toxicity, the HIARC recommended that the 10x FQPA safety factor be retained. The final determination of the FQPA safety factor required for RH-287 will be made by the HED FQPA Safety Factor Committee.

## VII. DATA GAPS

There are several data gaps for RH-287. These are; a developmental toxicity study in a second species (rabbit); a 2-generation reproduction toxicity study in the rat; a chronic toxicity study in the dog; a chronic toxicity/carcinogenicity study in the rat; and a carcinogenicity study in the mouse. The requirement for acute and subchronic neurotoxicity studies as well as a developmental neurotoxicity study is reserved at this time.

## VIII. ACUTE TOXICITY

Acute Toxicity of RH-287

| Guideline No. | Study Type* | MRID #(S). | Results | Toxicity Category |
|---|---|---|---|---|
| 81-1 | Acute Oral | 42977701 | $LD_{50}$ = 1636 mg/kg | III |
| 81-2 | Acute Dermal | | waiver for technical material | I |
| 81-3 | Acute Inhalation | 43471602 | $LC_{50}$ not determined (Corrosive) | I |
| 81-4 | Primary Eye Irritation | | waiver for technical material | I |
| 81-5 | Primary Skin Irritation | | waiver for technical material | I |
| 81-6 | Dermal Sensitization | 263188 | waiver for technical material (sensitizer) | |



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## IX. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

| EXPOSURE SCENARIO | DOSE (mg/kg/day) | ENDPOINT | STUDY |
|---|---|---|---|
| Acute Dietary (females 13+) | Developmental NOAEL= 30 mg/kg/day<br><br>UF = 100 | increased number of litters with wavy ribs at 100 mg/kg/day | Developmental Toxicity - Rat |
| | **Acute RfD = 0.3 mg/kg/day** | | |
| Acute Dietary (General Pop.) | Maternal NOAEL = 30 mg/kg/day<br><br>UF = 100 | decreased food consumption at 100 mg/kg/day in maternal animals. | Developmental Toxicity - Rat |
| Chronic Dietary | NOAEL =20 mg/kg/day<br>UF = 100 | histopathologic lesions and hematological /clinical chemistry changes at 100 mg/kg/day. | 28-Day Toxicity - Rat |
| | | ***Chronic RfD = 0.2 mg/kg/day*** | |
| Short-Term[a] (Dermal) | Oral NOEL = 20 mg/kg/day | histopathologic lesions and hematological /clinical chemistry changes at 100 mg/kg/day. | 28-Day Toxicity - Rat |
| Intermediate-Term[a] (Dermal) | Oral NOEL = 3 | histopathologic lesions and hematological /clinical chemistry changes at 100 mg/kg/day. | 28-Day Toxicity - Rat |
| Long-Term (Dermal)[a] | Oral NOEL = 3 | histopathologic lesions and hematological /clinical chemistry changes at 100 mg/kg/day. | 28-Day Toxicity - Rat |
| Inhalation (Any time point) | NOEL= 0.02 $mg/m^3$ [0.0037 mg/kg/day] | histopathological alterations of the nose, larynx, and lungs at 0.63 $mg/m^3$ | 90-Day Inhalation Toxicity - Rat |

[a]Based on the use of an oral endpoint for dermal risk assessments, the dermal absorption value of 50% will be used in dermal risk assessments.