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

014292

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: August 14, 2000

MEMORANDUM

SUBJECT: ***5,5 - Dimethylhydantoin*** - Report of the Hazard Identification Assessment Review Committee.

FROM: Timothy F. McMahon, Ph.D. 8/14/00
Senior Toxicologist, Risk Assessment and Science Support Branch
Antimicrobials Division (7510C)

THROUGH: Jess Rowland, Co-Chair 8/18/00
and
Elizabeth Doyle, Co-Chair SD 8/18/00
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Timothy F. McMahon, Ph.D. 8/17/00
Risk Assessment and Science Support Branch
Antimicrobials Division (7509C)

PC Code: 028501, 006315, 006317, 028502, 115501, 115502, 128826

On July 25, 2000, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for 5,5-Dimethylhydantoin with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to 5,5-Dimethylhydantoin was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996. The conclusions drawn at this meeting are presented in this report.

Committee Members in Attendance

Members present were: William Burnam, Pamela Hurley, Tina Levine, Elizabeth Mendez, David Nixon, Yung Yang, Jess Rowland, Jonathan Chen, Ayaad Assaad, and Brenda Tarplee.

Member(s) in absentia: Elizabeth Doyle

Data evaluation prepared by: Timothy F. McMahon, Antimicrobials Division

Data Evaluation / Report Presentation

Timothy F. McMahon
Senior Toxicologist

1. INTRODUCTION

On July 25, 2000 , the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for 5,5-dimethylhydantoin with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. . The potential for increased susceptibility of infants and children from exposure to 5,5-dimethylhydantoin was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996.

Bromochlorodimethylhydantoin, dichlorodimethylhydantoin, and dichloroethylmethylhydantoin are active ingredients used in Dantobrom and Dantochlor formulations for use in the control of bacteria, fungi, and algal slimes in recirculating cooling water systems and sewage systems, industrial air washer systems, once-through industrial cooling water systems, swimming pool water systems, ornamental ponds, fountains, and aquaria, toilet bowls and urinals, and air filters/air ducts. The Office of Pesticide Programs through discussion with the registrant (memorandum from Joycelyn Stewart to Jeffrey Kempter dated August 14, 1989) stated that the moiety of toxicological concern was for 5,5-dimethylhydantoin and 5 ethyl-5 methyl hydantoin. Based on the preponderance of dimethylhydantoin in Dantobrom, toxicology data on dimethylhydantoin would be accepted as representative of the active ingredient to support all of the included chemicals listed above.
Dietary and drinking water exposure are expected from use of the dimethylhydantoins as indirect food additives. Non-dietary exposure is expected from the use of dimethylhydantoins in swimming pools and as preservatives in paint.

2. HAZARD IDENTIFICATION

2.1a Acute Reference Dose (RfD) (Females 13-50)

Study Selected: Developmental toxicity - rabbits § 870.3700

MRID No.: 42413101

Executive Summary: In a developmental toxicity study (MRID # 42413101), groups of artificially inseminated New Zealand White Rabbits (20 /dose) were administered 5,5-dimethylhydantoin by gavage on gestation days 6 through 18 at doses of 0, 100, 500, and 1000 mg/kg/day in a dose volume of 5 ml/kg. Maternal toxicity was observed at the 1000 mg/kg/day dose level as decreased body weight gain during the dosing period and decreased food consumption during the dosing period. Developmental toxicity was observed at the 500 mg/kg/day dose level as an increased incidence of skeletal variations of the 27th presacral vertebrae (fetal incidence of 39/134, 42/140, 82/145, and 91/123; litter incidence of 11/16, 11/18, 17/19, and 17/17 respectively). The increased incidence at 500 mg/kg/day exceeded both

concurrent and historical control incidence. The Maternal NOAEL was determined as 500 mg/kg/day, and the Developmental toxicity NOAEL was determined as 100 mg/kg/day.

Dose and Endpoint for Establishing RfD: Developmental NOAEL of 100 mg/kg/day, based on increased incidence of skeletal variations observed at 500 mg/kg/day.

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

Comments about Study/Endpoint/Uncertainty Factor: The developmental endpoint is presumed to occur after a single exposure. Based on the endpoint selected, the proposed acute RfD is applicable to females 13-50.

Acute RfD =	$\frac{100 \text{ mg/kg}}{100}$	=	**1 mg/kg**

2.1b Acute Reference Dose (general population)

Since the developmental endpoint is applicable only for the female 13-50 subpopulation, an endpoint for the general population should be considered. However, the maternal effects observed (decreased body weight gain and food consumption) are not considered effects that occur after a single dose. Therefore, there are no relevant endpoints for assessing acute dietary risk to the general population from the available data and thus an acute dietary risk assessment for the general population is not necessary.

2.2a Chronic Reference Dose (RfD) (females 13-50)

Study Selected: Developmental toxicity - rabbits § 870.3700

MRID No.: 42413101

Executive Summary: In a developmental toxicity study (MRID # 42413101), groups of artificially inseminated New Zealand White Rabbits (20 /dose) were administered 5,5-dimethylhydantoin by gavage on gestation days 6 through 18 at doses of 0, 100, 500, and 1000 mg/kg/day in a dose volume of 5 ml/kg. Maternal toxicity was observed at the 1000 mg/kg/day dose level as decreased body weight gain during the dosing period and decreased food consumption during the dosing period. Developmental toxicity was observed at the 500 mg/kg/day dose level as an increased incidence of skeletal variations of the 27th presacral vertebrae (fetal incidence of 39/134, 42/140, 82/145, and 91/123; litter incidence of 11/16, 11/18, 17/19, and 17/17 respectively). The increased incidence at 500 mg/kg/day exceeded both concurrent and historical control incidence. The Maternal NOAEL was determined as 500 mg/kg/day, and the Developmental toxicity NOAEL was determined as 100 mg/kg/day.

Dose and Endpoint for Establishing RfD: Developmental NOAEL of 100 mg/kg/day, based on increased incidence of skeletal variations observed at 500 mg/kg/day.

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

Comments about Study/Endpoint/Uncertainty Factor: The HIARC selected a separate chronic RfD for the subpopulation females 13-50 because this was an unusual case where the developmental NOAEL was lower than the lowest NOAEL available for chronic toxicity. The rabbit developmental toxicity study was therefore selected in order to provide adequate protection for the female 13-50 subpopulation.

Chronic RfD = $\frac{\text{100 mg/kg/day (NOAEL}}{\text{100 (UF)}}$ = **1 mg/kg/day**

2.2b **Chronic Reference Dose** (general population)

Study Selected: Chronic toxicity / carcinogenicity - rats Guideline #: 870.4300

MRID No.: 43397701

Executive Summary: In a chronic toxicity / carcinogenicity study, 5,5-dimethylhydantoin (DMH) was administered in the diet to groups of 60 male and female rats at dose levels of 0, 0, 100, 300, or 1000 mg/kg/day for 104 weeks. At the 1000 mg/kg/day dose, there was no evidence of compound related clinical signs, mortality, food consumption and organ weights, or on clinical chemistry. At the high dose, a significant ($p < 0.01$ for the first control, $p < 0.05$ for the second control) effect on body weight was observed in females at weeks 90-96, where body weight was decreased 14-15% from the first control and 9% lower than the second control. Weight gain was decreased 23-24% from the first control and 16% from the second control. A significant increase in the incidence of hyperplasia of the submandibular lymph nodes in high dose male rats (5/19 [26%] vs. 0/31 and 1/33 in controlswas observed in this study. This increase was considered to be related to administration of DMH. There was no evidence of carcinogenicity of DMH in this study. The NOAEL for systemic toxicity was determined to be 300 mg/kg/day and the LOAEL was determined to be 1000 mg/kg/day based on decreases in body weight and body weight gain in females, and hyperplasia of submandibular lymph nodes in males.

Dose and Endpoint for Establishing RfD: NOAEL of 300 mg/kg/day, based on effects in male and female rats at the 1000 mg/kg/day dose level.

Uncertainty Factor(s): 10x intraspecies; 10x interspecies

Chronic RfD = 300 mg/kg/day (NOAEL) / 100 (UF) = **3 mg/kg/day**

Comments about study/endpoint/uncertainty factor: A separate endpoint for the general population was selected because this was an unusual case where the developmental toxicity NOAEL was lower than the NOAEL from the chronic toxicity studies. The chronic RfD for the general population provides a more appropriate endpoint for individuals other than females. Also, dietary risk from exposure to formaldehyde through use of the dimethylhydantoins in food contact applications can be assessed using the RfD value of 0.2 mg/kg/day established in the U.S. EPA's IRIS assessment of formaldehyde. As there is no acute RfD value established for formaldehyde, acute dietary risk will be assessed using the published chronic RfD value.

2.3 Occupational/Residential Exposure

2.3.1 Short-Term (1-7 days) Incidental Oral Exposure

Study Selected: Developmental toxicity - Rabbits § 870.3700

MRID No.: 42413101

Executive Summary: see acute dietary

Dose and Endpoint for Risk Assessment: Maternal NOAEL of 500 mg/kg/day, based on decreased body weight gain at 1000 mg/kg/day during the dosing period.

Comments about study/endpoint/uncertainty factor: This endpoint (maternal toxicity) is appropriate for the population of concern (toddlers) and duration of exposure (short-term).

2.3.2 Intermediate-Term (7 Days to Several Months) Incidental Oral Exposure

Study Selected: Subchronic oral toxicity - Rats § 870.3100

MRID No.: 42009201

Executive Summary: 5,5-dimethylhydantoin was administered by gavage 5 days a week for 13 weeks to groups of 15 male and female Crl:CDBR rats at dose levels of 0, 100, 300, and 1000 mg/kg/day. At 1000 mg/kg./day, group mean absolute and relative liver weight was decreased significantly from control. Decreased body weight was observed in

male rats at 1000 mg/kg/day but was not considered biologically significant.

Dose and Endpoint for risk assessment: NOAEL of 300 mg/kgday, based on body weight and liver effects observed at 1000 mg/kg/day.

Comments about study/endpoint/uncertainty factor: This endpoint is appropriate for the population of concern (toddlers) and duration of exposure (short-term).

2.3.3 Dermal Absorption

There are no dermal absorption data available for 5,5-dimethylhydantoin. A route-specific study (90-day dermal toxicity in rats) was available for assessing dermal risk.

2.3.4 Short-Term Dermal (1-7 days) Exposure

Study Selected: Subchronic Dermal Toxicity - Rats § 870.3250

MRID No.: 43173901

Executive Summary: In a subchronic dermal toxicity study in rats, male and female CD rats were treated with DMH by dermal occlusion at doses of 0, 39, 130, or 390 mg/kg/day for 6 hours per day, 5 days per week, for 13 weeks. No statistically significant differences in group mean body weights or cumulative weight gain was observed at any dose level. There were no treatment-related effects on mortality, skin irritation, or clinical signs of toxicity in males or females at any dose level. DMH caused no significant changes in hematology, clinical chemistry, or gross and microscopic pathology in males or females. Absolute weight of the adrenal gland was significantly decreased in male rats at the 39 and 390 mg/kg/day dose levels (12.5% and 14.3% reduction respectively) as well as adrenal / brain weight ratios (15.2% and 13.6% respectively). Adrenal to body weight ratio was also decreased by 11.1% in female rats at 130 ppm. The differences in adrenal weight were considered unrelated to treatment as there was no definitive dose-response and there was no evidence of microscopic lesions. In this study, the NOAEL was determined to be 390 mg/kg/day, and the LOAEL > 390 mg/kg/day. Higher doses of DMH were not possible in this study; thus, although a limit dose was not tested, the study is considered acceptable.

Dose and Endpoint for Risk Assessment: NOAEL of 390 mg/kg/day.

Comments about Study/Endpoint: The endpoint selected is from a study examining toxicity by a relevant route of exposure. Although there was no LOAEL established, the results of this study are appropriate for determination of dermal risk.

2.3.5 Intermediate-term Dermal (1-Week to Several Months) Exposure

Study Selected: Ninety Day dermal toxicity - Rats Guideline #: 870.3250

MRID No.: 43173901

Executive Summary: see summary for short-term dermal

Proposed Dose and Endpoint: see short-term dermal

Comments about Study/Endpoint: see short-term dermal

2.3.6 Long-term Dermal (Several Months to Lifetime)

Study Selected: Ninety Day dermal toxicity - Rats Guideline #: 870.3250

MRID No.: 43173901

Executive Summary: see summary for short-term dermal

Dose and Endpoint for Risk Assessment: see short-term dermal

Comments about Study/Endpoint: see short-term dermal

Inhalation Exposure (All Durations)

Study Selected: Developmental toxicity - rabbit §870.3700

MRID No.: 42413101

Executive Summary: In a developmental toxicity study (MRID # 42413101), groups of artificially inseminated New Zealand White Rabbits (20 /dose) were administered 5,5-dimethylhydantoin by gavage on gestation days 6 through 18 at doses of 0, 100, 500, and

8

1000 mg/kg/day in a dose volume of 5 ml/kg. Maternal toxicity was observed at the 1000 mg/kg/day dose level as decreased body weight gain during the dosing period and decreased food consumption during the dosing period. Developmental toxicity was observed at the 500 mg/kg/day dose level as an increased incidence of skeletal variations of the 27th presacral vertebrae (fetal incidence of 39/134, 42/140, 82/145, and 91/123; litter incidence of 11/16, 11/18, 17/19, and 17/17 respectively). The increased incidence at 500 mg/kg/day exceeded both concurrent and historical control incidence. The Maternal NOAEL was determined as 500 mg/kg/day, and the Developmental toxicity NOAEL was determined as 100 mg/kg/day.

Dose and Endpoint for Risk Assessment: Developmental NOAEL of 100 mg/kg/day, based on increased incidence of skeletal variations observed at 500 mg/kg/day.

Comments about Study/Endpoint: There are no appropriate inhalation studies. Therefore, an oral study should be used with the default absorption factor of 100%. The inhalation exposure component (i.e. μg a.i /day) using 100% absorption rate (default value) and application rate should be converted to an **equivalent oral dose** (mg/kg/day). Comparison of the converted dose to the oral NOAEL should then be made for calculation of the Margin of Exposure.

The inhalation component of exposure cannot be combined with the dermal component as there are differing endpoints selected for dermal and inhalation risk assessments.

2.0.1 Margins of Exposure for Occupational/Residential Risk Assessments

A Margin of Exposure of 100 is considered acceptable for occupational/residential risk assessments by the dermal and inhalation route.

2.1 Recommendation for Aggregate Exposure Risk Assessments

For aggregate **dietary** exposure risk assessments, **acute** aggregate dietary exposure is assessed by combining the high end exposure values from food + water and comparing it to the acute RfD. For **chronic** aggregate dietary exposure risk assessment, average exposure values for food + water are added and compared to the chronic RfD for the general population. For females 13-50, chronic aggregate risk is calculated from the average exposure through food + water as well as the average inhalation exposure value and this is compared to the chronic RfD for females 13-50. The inhalation exposure value

is added for females 13-50 as the endpoint selected is a developmental effect from an oral study and appropriate route-specific data are lacking.

Exposures and MOEs for **Short- and intermediate-term** aggregate exposure risk assessment for **oral, dermal,** and **inhalation** exposures **cannot be combined** due to the lack of a common endpoint of toxicity from the different routes of exposure, as noted in the endpoint selection portion of this HIARC document.

3.0 CLASSIFICATION OF CARCINOGENIC POTENTIAL

3.1 Combined Chronic Toxicity/Carcinogenicity Studies in Rats

MRID #: 43397702

Discussion of Tumor Data: There was no evidence of carcinogenicity of DMH in this study when tested up to dose levels of 1000 mg/kg/day in rats. Hyperplasia of the submandibular lymph nodes was increased in male rats at the 1000 mg/kg/day dose level (incidence of 5/19 rats [26%] vs. 0/31 rats and 1/33 rats in control [0-3%].

Adequacy of the Dose Levels Tested: The 1000 mg/kg/day dose is considered a limit dose for non -acute toxicity testing. In this study, the 1000 mg/kg/day dose level produced signs of toxicity but these signs were not excessive. The lack of excessive toxicity at the limit dose supports the conclusion that the dose levels were adequate for carcinogenicity testing of DMH.

MRID # 44095901

Discussion of tumor data: In this study, DMH was also tested up to a limit dose of 1000 mg/kg/day in the same strain of rat (CD). Among the high dose male and female rats which died early in ths study, pituitary pars distalis adenomas were stated to have contributed to the early death of these animals. At week 52 of the study, the incidence of these tumors was increased at the high dose in males and females, but the increase was significant only for females. At week 105, incidence of these tumors was not significantly different among control or treated rats. Thus, while there is a possibility that development of pituitary pars distalis tumors was enhanced at the high dose of DMH at week 52, the available evidence does not support a conclusion of carcinogenicity for DMH.

Adequacy of dose levels: As with previous studies, this study employed a limit dose which did not demonstrate excessive toxicity. Thus, DMH was tested adequately.

3.2 Carcinogenicity Studies in Mice

MRID No.:43397701; 44063901

Discussion of Tumor Data: In both of these studies, DMH was tested up to a limit dose (1000 mg/kg/day). In one study (43397701), a non-significant increase in incidence of lung carcinoma was observed at the high dose in female mice (5/60 mice vs. 1/60 control mice). However, in the second control group, the incidence was reported as 3/60 thus calling into question the treatment-related relevancy of this tumor. In addition to lung tumors at the high dose in females, male mice at the 1000 mg/kg/day dose level were observed with an increased incidence of hepatocellular adenoma (10/60 mice vs. 3/60 mice in the first control group) and carcinoma (4/60 vs. 0/60 in the first control group). However, again, male mice in the second control group showed an incidence of hepatocellular adenoma (11/60) and carcinoma (3/60) that was similar to the high dose incidence. It is not clear why such differences in tumor incidence would occur between two concurrent control groups of mice. It is noted that additional historical control data on tumor incidence in this strain of mouse, obtained from Charles River Laboratories, show a historical range of 0-19% for hepatocellular adenoma and a range of 1.25-11.5% for hepatocellular carcinoma.

In the second study (44063901), no increase in tumorigenicity was observed in treated mice.

Adequacy of the Dose Levels Tested: Dosing was considered adequate based on the use of a limit dose and the lack of excessive toxicity at this dose.

2.2 Classification of Carcinogenic Potential

5,5-dimethylhydantoin is classified as 'not likely' to be a carcinogen based upon the negative evidence for carcinogenicity in both the rat and mouse studies as well as the negative evidence of mutagenicity.

Formaldehyde (a breakdown product of the hydantoins) has previously been classified as a B1 (probable) carcinogen based upon the limited evidence in humans of site-specific respiratory neoplasms and exposure to formaldehyde, and sufficient evidence in animals, which all show squamous cell carcinoma of the nasal cavity following chronic inhalation exposure.

3 MUTAGENICITY

In an Ames Salmonella assay (Accession number 265457), 5,5-dimethylhydantoin (DMH) was tested in S. typhimurium strains TA1535, TA100, TA1538, TA98, and TA1537 in the absence and presence of S9 metabolic activation at concentrations of 100, 500, 2500, 5000, and 10,000 μg/plate. There was neither a cytotoxic or mutagenic response in this assay at any dose level tested in the absence or presence of metabolic activation.

In an in vitro cytogenetics assay using Chinese Hamster Ovary (CHO) cells (Accession number 265457), concentrations of DMH from 200 to 2000 μg/ml showed no evidence of a cytotoxic or clastogenic effect in this study.

In a rat unscheduled DNA synthesis assay (Accession number 265457), seven concentrations of DMH, ranging from 100 to 10,000 μg/ml were tested in primary rat hepatocytes. There was no significant effect of the test material on mean net nuclear grain counts at any of the concentrations tested.

4 FQPA CONSIDERATIONS

4.1 Adequacy of the Data Base

The database for 5,5-dimethylhydantoin is considered adequate for a determination as to potential susceptibility of infants and children. Two studies on reproductive toxicity of dimethylhydantoin are available as well as two developmental toxicity studies.

4.2 Neurotoxicity

There are no neurotoxicity studies available for 5,5-dimethylhydantoin. Evidence of neurotoxicity from the existing database on 5,5-dimethylhydantoin is limited to signs of ataxia and depression in a range-finding developmental toxicity study in rats, in which these signs were observed at a dose of 5000 mg/kg. The HIARC did not consider that these observations were biologically significant given the extremely high dose at which these signs were observed.

4.3 Developmental Toxicity

In a developmental toxicity study in rats (MRID # 42432701), mated female CD rats (25/dose) were administered DMH (99.8% a.i.) by gavage from gestation days 6-15 at dose levels of 0, 100, 300, and 1000 mg/kg/day. There were no effects in maternal rats on mortality or clinical observations at any dose level. Body weight gain was decreased 19% at the high dose during gestation days 9-12. However, a compensatory increase of 16% was noted on gestation days 12-15 for this dose group. There were no treatment-

related effects on gross pathology or cesarean section observations. External, visceral and skeletal malformations occurred at similar incidences in all dose groups or occurred as single events. The Maternal LOAEL is 1000 mg/kg/day based on the transient decrease in body weight gain during gestation days 9-12, and the Maternal NOAEL is 500 mg/kg/day. The Developmental LOAEL was not established; the Developmental NOAEL is $\geq$ 1000 mg/kg/day.

In a developmental toxicity study in rabbits (MRID # 42413101), artificially inseminated New Zealand White rabbits (20/dose) were administered DMH (96-98.7% a.i.) via gavage at dose levels of 0, 100, 500, and 1000 mg/kg/day on gestation days 6-18 inclusive. Decreased body weight gain was observed in maternal rabbits on gestation days 6-12 and 6-18 compared to controls (decreases of greater than 66%). There was no effect in maternal rabbits on mortality, clinical signs, gross pathology findings, or cesarean section observations. Treatment-related anomalies were observed in fetuses at 500 and 1000 mg/kg/day. Adactyly was observed in 4 fetuses from one litter at 1000 mg/kg/day and was outside the historical control range for this anomaly. Litter and fetal incidence of 27th presacral vertebrae was increased at 500 and 1000 mg/kg/day. This effect was considered dose-related and was also observed in the range-finding study. Thus, the developmental toxicity LOAEL is 500 mg/kg/day based on the increased incidence of 27th presacral vertebrae. The Developmental toxicity NOAEL is 100 mg/kg/day.

4.4 Reproductive Toxicity

In a two-generation reproduction study (MRID 43290601), groups of 28 male and 28 female F_0 and F_1 rats were administered 5,5-dimethylhydantoin (0, 2000, 6000, or 20000 ppm) in their diets for 10 weeks before mating and during mating, gestation, and lactation. Calculated doses were 136 and 127, 408 and 379, and 1396 and 1322 mg/kg/day, respectively, for F_0 and F_1 males (premating/postmating periods) and 176 and 158, 516 and 475, and 1775 and 1602 mg/kg/day, respectively, for F_0 and F_1 females (premating periods only).

There was no evidence of systemic toxicity in either F_0 or F_1 male and female rats. Therefore, **a LOEL for systemic toxicity cannot be established; the NOEL is >20,000 ppm.**

No effects were observed on indices of reproductive performance of F_0 or F_1 rats, litter sizes, pup viability, pup survival, or sex ratio. At 20000 ppm, a decrease in pup growth was indicated by statistically significant reductions in body weights (7-8%) and body weight gain (7-13%) of high-dose pups (male and female combined) from day 7 to 21 of lactation. **Therefore, the LOEL for reproductive toxicity is 20,000 ppm and the corresponding NOEL is 6000 ppm.**

This study is classified as acceptable and it satisfies the guideline requirements for a multigeneration reproduction feeding study (83-4). Deficiencies in this study include, (1) a 2- to

5-week break in feeding of test diet to F_1 offspring and (2) no data on pups dying during lactation. The break in feeding the test diet to F_1 offspring is a serious deficiency, which would warrant an "unacceptable" classification except the study showed very low reproductive toxicity (small decreases in pup growth) at doses exceeding 1000 mg/kg/day.

In a second two-generation reproduction toxicity study (MRID # 42462502), male and female CD rats (30/sex/dose/generation) were administered DMH by gavage at doses of 0, 250, 500, or 1000 mg/kg/day for 10-11 weeks per generation. There were no compound-related effects observed in parental animals of either generation. In addition, no compound-related effects on reproduction or fertility were observed at any dose level in either generation of offspring. Based on the results of this study, the NOAEL for both parental and offspring toxicity was 1000 mg/kg/day, and the LOAEL was > 1000 mg/kg/day.

4.5 Additional Information from Literature Sources (*if available*)

Based upon the structural similarity of dimethylhydantoin to diphenylhydantoin (a known teratogenic and carcinogenic agent), concern was expressed by the Agency as to the validity of the use of dimethylhydantoin-containing products, especially for use in pools and spas.

The Agency has considered toxicity data from both diphenylhydantoin and dimethylhydantoin in determining that there is no significant hazard from the use of dimethylhydantoin (memorandum from Robert P. Zendzian to Arturo Castillo, dated October 21, 1983). First, it is evident that the biotransformation and excretion of dimethylhydantoin and diphenylhydantoin differ. Diphenylhydantoin undergoes extensive metabolism of the phenyl group with the production of an arene oxide intermediate (believed responsible for the toxicity of the chemical), while dimethylhydantoin is essentially excreted unchanged. Second, the hazard profile for dimethylhydantoin differs significantly from that of diphenylhydantoin. Dimethylhydantoin lacks the toxicity present with diphenylhydantoin and shows no evidence of carcinogenicity or teratogenicity.

4.6 Determination of Susceptibility

The HIARC has determined that there is no evidence of susceptibility in the available reproductive and developmental toxicity database for 5,5-dimethylhydantoin. Although pup effects (decreased body weight and weight gain) were observed during days 7-21 of lactation in one reproductive toxicity study (MRID 43290601) in the absence of any parental toxicity, the HIARC considered this effect not indicative of susceptibility, based upon the very high dose level at which the effect occurred (1322 mg/kg/day), the minimal nature of the effect, and the likelihood that the effect was due to a greater dose received by pups from ingestion of both milk and feed during the lactational period.

4.7 Recommendation for a Developmental Neurotoxicity Study

A developmental neurotoxicity study is not required for 5,5-dimethylhydantoin.

4.7.1 Evidence that suggest requiring a Developmental Neurotoxicity study:

None

4.7.2 Evidence that **do not** support a need for a Developmental Neurotoxicity study:

The weight of the evidence from the available data on 5,5-dimethylhydantoin indicate no neurotoxic effects of this chemical.

There is no evidence to suggest any positive neurotoxic effects from exposure to 5,5-dimethylhydantoin except at unrealistic exposures.

5.0 HAZARD CHARACTERIZATION

The acute toxicity of dimethylhydantoins is low by the oral and dermal routes of exposure (Toxicity categories III and IV, respectively). Acute lethality by the inhalation route is more significant (Toxicity category II). The dimethylhydantoins are significant eye and skin irritants (Toxicity category I and II respectively). Positive dermal sensitization has also been observed with the dimethylhydantoins.

Non-acute toxicity testing of the dimethylhydantoins (including subchronic, developmental, reproductive, and chronic toxicity testing) all show the presence of non-specific toxicity only at relatively high doses of the test chemical. Developmental and reproductive toxicity testing demonstrate no increase in susceptibility to the toxic effects of DMH with the exception of one study, where an increased fetal and litter incidence of 27 presacral vertebrae was observed at a dose of 500 mg/kg/day, a dose at which there was no significant maternal toxicity observed.

In carcinogenicity testing of the dimethylhydantoins in rats and mice, there is some evidence of target organ toxicity, but no evidence of positive tumorigenicity for the test material.

The data on mutagenicity of dimethylhydantoins show in large part negative responses in the Ames test, chromosome aberration test, in vivo cytogenetics, and unscheduled DNA synthesis test. However, a literature report indicates a positive effect for induction of lethal mutations in Drosophila melanogaster.

Available metabolism data indicate that the dimethylhydantoins are excreted unchanged in the rat However, it is known that methylhydantoins are formaldehyde releasers. Therefore, any risk assessment involving dietary or non-dietary exposure to the methylhydantoins will also necessarily involve calculating risk from formaldehyde exposure.

5 DATA GAPS

The HIARC determined that a 90-day inhalation toxicity study in rats is required because of the concerns for inhalation exposure to formaldehyde as a result of the degradation of hydroxymethyl-5,5-dimethylhydantoin and 1,3-bis(hydroxymethyl-5,5-dimethylhydantoin into free formaldehyde and dimethylhydantoin. Data on the inhalation toxicity of formaldehyde are also relevant for assessing risks posed by inhalation of this chemical from the uses of dimethylhydantoins. The Agency for Toxic Substances and Disease Registry has recently published a Toxicology Profile for Formaldehyde (July, 1999). Minial Risk Levels (MRLs) have been selected for formaldehye from inhalation exposure. Acute, Intermediate, and Chronic MRL's of 0.04 ppm. 0.03 ppm, and 0.008 ppm have been selected for formaldehyde based on human data (acute and chronic MRL's) or animal data (intermediate). These can

be used in assessing risk from inhalation exposure to formaldehyde as a result of its formation from breakdown of dimethylhydantoins.

ACUTE TOXICITY

Acute Toxicity of Dimethylhydantoins

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1	Acute Oral	252096	LD_{50} = 760 mg/kg	III
81-2	Acute Dermal	252096	LD_{50} > 20,000 mg/kg	IV
81-3	Acute Inhalation	43654101	LC_{50} = 0.168 mg/L	II
81-4	Primary Eye Irritation	252096	severe irritant	I
81-5	Primary Skin Irritation	252096	severe skin irritant	II
81-6	Dermal Sensitization	252096	positive sensitizer	
81-8	Acute Neurotoxicity	N/A	no study available	

7.0 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 13-50)	NOAEL= 100 UF = 100	skeletal variations at 500 mg/kg/day	developmental toxicity - rabbit
	Acute RfD = 1 mg/kg		
Chronic Dietary[a] (general population)	NOAEL =300 UF = 100	decreased body weight/weight gain and lymph node hyperplasia	chronic toxicity / carcinogenicity - rats
		Chronic RfD (gen. Pop.)= 3 mg/kg/day	
Chronic Dietary[a] (females 13-50)	NOAEL = 100 UF = 100	**Chronic RfD (females 13-50)** = 1 mg/kg/day	developmental toxicity - rabbit
Incidental Oral, Short-Term	NOAEL=500	decreased body weight gain in maternal rabbits at 1000 mg/kg/day	developmental toxicity - rabbit
Incidental Oral, Intermediate-Term	NOAEL=300	decreased body weight and liver weight at 1000 mg/kg/day	subchronic oral toxicity - rats
Dermal: Short-, Intermediate-, and Long-Term	NOAEL= 390 (HDT)	no systemic toxicity at the highest dose tested.	subchronic dermal toxicity - rats
Inhalation, Short-Term	Oral NOAEL= 100[b]	skeletal effects in offspring at 500 mg/kg/day	developmental toxicity - rabbit

[a]The HIARC selected separate chronic RfDs for females 13-50 and the general population because this was an unusual case where the developmental NOAEL was lower than the lowest NOAEL available for chronic toxicity. The rabbit developmental toxcity study was therefore selected to provide adequate protection for the females 13-50 subpopulation.

[b]a 100% inhalation absorption value is used for route-to-route extrapolation.