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COURTNEY M. PRICE
VICE PRESIDENT
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American Chemistry Council

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July 10, 2003

Ms. Linda Fisher
Acting Administrator
U.S. Environmental Protection Agency
P.O. Box 1473
Merrifield, VA 22116

Re: The American Chemistry Council Brominated Biocides Panel HPV Submission for 5,5-Dimethylhydantoin, CAS No. 77-71-4 (Consortium Number

Dear Ms. Fisher:

The American Chemistry Council (ACC) Brominated Biocides Panel DMH Task Force (Task Force) is pleased to submit the enclosed 5,5-dimethylhydantoin (DMH) Test Plan under the US EPA Voluntary HPV Chemical Challenge Program. The Test Plan includes: 1) summary of available and adequate studies to fulfill HPV SIDS endpoints for DMH; 2) modeling information for DMH; and 3) robust data summaries for DMH on HPV SIDS endpoints.

The Task Force serves as an industry consortium to coordinate activities for DMH under the HPV Program. The Task Force member companies who have voluntarily committed to sponsor DMH under the HPV Chemical Challenge Program include: Ameribrom, Inc.; BioLab, Inc.; and Lonza Inc.

The original commitment to sponsor DMH under the HPV Program was communicated to EPA on November 30, 1999. In subsequent letters of October 17, 2001 and December 13, 2002, the Task Force notified the Agency of an extension in submitting the Test Plan to maintain the proprietary information from becoming publicly available before the Notification deadline under the EU Biocidal Products Directive (BPD). The BPD Notification period closed earlier this year, and therefore the Task Force is now submitting its DMH Test Plan to EPA. DMH data have been used to support halohydantoin product registration in many countries. Currently, EPA is relying on DMH data for halohydantoin Reregistration Eligibility Decision.

The Panel believes that the data presented in this submission are adequate to satisfy the US EPA Voluntary HPV Chemical Challenge Program for DMH, and that no additional testing is required.

This letter and the attached Test Plan are also being sent electronically to the following e-mail addresses:

Oppt.ncic@epa.gov
Chem.rtk@epa.gov

Please feel free to call Has Shah, Manager, DMH Task Force, at 703/741-5637, if you have any questions or need additional information.

Sincerely yours,

Courtney M. Price
Vice President, CHEMSTAR

Enclosure

cc: Brominated Biocides Panel DMH Task Force
Jim Keith

201-14589A

5,5-Dimethylhydantoin (DMH) High Production Volume (HPV) Chemical Challenge

Test Plan

Prepared for:

American Chemistry Council
Brominated Biocides Panel
DMH Task Group

Prepared by:

Toxicology/Regulatory Services, Inc.

July 3, 2003

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5,5-Dimethylhydantoin
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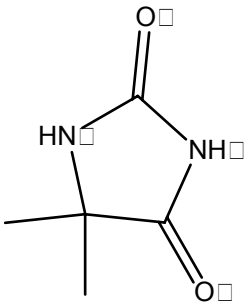
Identity

5,5-Dimethylhydantoin (DMH) is a chemical with the structure:



5,5-Dimethylhydantoin (CAS RN 77-71-4)

Chemical Formula: $C_5H_8N_2O_2$

Molecular Weight: 128.15

Color/Form: White, crystalline solid

Data Availability

5,5-Dimethylhydantoin is a precursor molecule used in the production of FIFRA registered halohydantoin biocides. A substantial database of environmental and toxicology data has been developed for DMH. These data have been accepted to support the FIFRA registration of a number of halohydantoin active ingredients and biocidal products.

The data adequacy for the HPV/SIDS endpoints for DMH is outlined in the following Table 1. Modeling information and results are included in Appendix A and robust summaries for adequate studies are included in Appendix B.

Table 1: Matrix of Available and Adequate Studies to Fulfill HPV/SIDS Endpoints for DMH

Study Category	IUCLID Sections; HPV/SIDS Endpoints	Adequate Study Available
Physical/Chemical Properties	2.1 Melting Point	√ (M)
	2.2 Boiling Point	M
	2.4 Vapor Pressure	M
	2.5 Partition Coefficient (log P_{ow})	√ (M)
	2.6 Water Solubility	√ (M)
Environmental Fate and Pathways	3.1.1 Photodegradation	√ (M)
	3.1.2 Stability in Water	√
	3.3.2 Transport between Environmental Compartments (Fugacity Model)	M
	3.5 Biodegradation	√
Ecotoxicity	4.1 Acute Toxicity to Fish	√ (M)
	4.2 Acute Toxicity to Aquatic Invertebrates	√
	4.3 Toxicity to Aquatic Plants (e.g. Algae)	See Text
	4.5.1 Chronic Toxicity to Fish	√
	4.5.2 Chronic Toxicity to Aquatic Invertebrates	√
Health Effects	5.1.1 Acute Oral Toxicity	√
	5.1.2 Acute Inhalation Toxicity	√
	5.1.3 Acute Dermal Toxicity	√
	5.4 Repeated Dose Toxicity	√
	5.5 Genetic Toxicity *In Vitro*	√
	5.6 Genetic Toxicity *In Vivo*	√
	5.8 Toxicity to Reproduction	√
	5.9 Developmental Toxicity/Teratogenicity	√
	5.10 Absorption and Elimination	√

√ Denotes an adequate study is available and a robust summary has been prepared (Appendix B)
M – Model data exist (see Appendix A and Appendix B)

Physical/Chemical Properties

Modeling procedures and data are presented in Appendix A; robust summaries for model data are included in Appendix B. A measured melting point value (178 ºC) and a modeled value (150

ºC) fulfill the endpoint requirement. No measured boiling point value was available but the endpoint is of minimal value to understanding the fate and effects of DMH, and the modeled value (367 ºC) is adequate to define the endpoint. The modeled value for vapor pressure (1.36 E-006 mm Hg) indicates that DMH is not volatile. A standard reference text indicates DMH is "soluble in water" (Appendix B); the modeled value (4516 mg/l) also indicates that DMH is soluble in water. Octanol/water partition coefficient (K_{ow}) was experimentally determined (Appendix B). The model prediction for log K_{ow} (-0.27) is consistent with the water solubility and in agreement with the measured value log K_{ow} (0.35). Overall, the measured and model data are adequate to support the physical/chemical properties of DMH for the HPV Chemical Challenge Program, and no additional data development is proposed.

Environmental Fate and Ecotoxicity

Model data for atmospheric degradation (photodegradation) and Level III fugacity (transport and distribution) were available for DMH (Appendix A; robust summaries are included in Appendix B). Aqueous photodegradation, hydrolytic stability, and biodegradation have also been evaluated experimentally (Appendix B). DMH is photolytically stable in aqueous solution and hydrolytically stable. DMH is inherently degradable with adequate acclimation time and slowly degraded without acclimation in the biodegradation studies.

Acute and chronic toxicity of DMH to fish and aquatic invertebrates have been extensively studied (Appendix B). DMH is slightly toxic to fish and aquatic invertebrates with LC_{50} and EC_{50} values ranging from approximately 920 to 14,000 mg/l. The ECOSAR model data for fish toxicity (Appendix A and B) indicate a 96-hour LC_{50} value of 1252 mg/l, which is consistent with the measured values. In addition, chronic toxicity to fish and daphnia has been studied (Appendix B). No studies or model data on the toxicity to aquatic plants are available. The lack of specific data for toxicity to aquatic plants is considered inconsequential to meeting the HPV Chemicals Challenge Program goals since DMH is adequately studied for other species, is relatively harmless to aquatic species, and is primarily used as a manufacturing precursor or found as a degradant of halohydantoin biocides eliciting limited environmental exposure potential with FIFRA registered use applications. Further, the US EPA has registered a number of DMH derivatives as biocides based on the available data, recognizing the limited need for data on the toxicity to aquatic plants. Therefore, no additional data development is proposed.

Human Health-Related Data

Extensive evaluation of the acute toxicity, repeated dose toxicity (including chronic toxicity and carcinogenicity), reproductive and developmental toxicity, and genetic toxicity has been conducted for DMH (Appendix B). These data indicate low toxicity and lack of mutagenic, clastogenic, reproductive or carcinogenic effects for DMH. A single occurrence (4 fetuses in one litter) of adactyly and brachydactyly and an increase in incidence of 27 presacral vertebrae was observed in one rabbit developmental toxicity study. The increase of 27 presacral vertebrae is a common variation found in rabbit developmental toxicity studies. In addition, no effects in development were noted in a rabbit developmental toxicity study conducted with a structurally-related hydantoin, 5,5-ethylmethylhydantoin (EMH), or in two rat developmental toxicity studies

conducted with DMH. The human health-related data have been accepted by the EPA for registration of DMH derivatives as biocides. No additional data development is proposed.

Conclusions

Adequate data exist for 5,5-dimethylhydantoin (DMH) to meet the HPV Chemical Challenge Program endpoints. DMH has been extensively studied for potential ecotoxicity and mammalian toxicity. Based on this dataset and the primary use of DMH as a manufacturing precursor and degradant for FIFRA registered halohydantoin biocides with limited human and environmental exposure potentials, no additional data development is proposed.

Appendix A - Modeling Information for DMH

Use of Structure Activity Relationships for DMH

Approaches recommended in the EPA document on the use of structure activity relationship (SAR) in the HPV Chemicals Challenge Program were employed in the assessment of DMH (US EPA, 1999b). Several models were employed to support this review and assessment. The models included several based on structure-activity relationships (SAR), as well as Mackay-type fugacity-based modeling. The SAR models for physical properties were used to estimate melting point, boiling point, vapor pressure octanol-water partition coefficient and water solubility. Other SAR models were used to estimate hydroxyl radical mediated atmospheric photo-oxidation and biodegradation potential. SAR models also were used to obtain conservative estimates of acute toxicity to fish (the model did not provide a value for aquatic invertebrates or plants).

Common Features of the Models

All of the models (except the Mackay-type models) require the input of a molecular structure to perform the calculations. The structure must be entered into the model in the form of a Simplified Molecular Input Line Entry System (SMILES) notation or string. SMILES is a chemical notation system used to represent a molecular structure by a linear string of symbols. The SMILES string allows the program to identify the presence or absence of structural features used by the submodels. The models contain files of structures and SMILES strings for approximately 100,000 compounds, accessible via CAS RNs. SMILES strings cannot be developed for mixtures or chemicals without a single, definable structure.

Estimation of Physical/Chemical Properties

The SAR models for estimating physical properties and abiotic degradation were obtained from Syracuse Research Corporation 2000 (Estimation Programs Interface for Windows, Version 3.10 or EPIWIN v.3.10). The models were used to calculate melting point, boiling point, vapor pressure (submodel MPBPVP), octanol-water partition coefficient (K_{ow}) (submodel KOWWIN) and water solubility (submodel WSKOWWIN). The calculation procedures are described in the program guidance and are adapted from standard procedures based on analysis of key structural features (Meylan and Howard, 1999a, b and c).

Estimation of Environmental Fate Properties

Atmospheric photo-oxidation potential was estimated using the submodel AOPWIN (Meylan and Howard, 2000a). The estimation methods employed by AOPWIN are based on the SAR methods developed by Dr. Roger Atkinson and co-workers (Meylan and Howard, 2000a). The SAR methods rely on structural features of the subject chemical. The model calculates a second-order rate constant with units of cm^3/molecules-sec. Photodegradation based on atmospheric photo-oxidation is in turn based on the rate of reaction (cm^3/molecules-sec) with hydroxyl radicals (HO•), assuming first-order kinetics and an HO• concentration of

1.5 E + 6 molecules/cm^3 and 12 hours of daylight. Pseudo first-order half-lives ($t_{1/2}$) were then calculated as follows: $t_{1/2} = 0.693/[(k_{phot} \times HO\bullet) \times (12\text{-hr}/24\text{-hr})]$.

Estimation of Environmental Distribution

The Level 3 Mackay-type fugacity-based models were obtained from the Trent University's Modeling Center. The specific model used was the generic Equilibrium Concentration model (EQC) Level 3, version 1.01. These models are described in Mackay *et al*. (1996a and b). Fugacity-based modeling is based on the "escaping" tendencies of chemicals from one phase to another. For instance, a Henry's Law constant calculated from water solubility and vapor pressure is used to describe the "escape" of a chemical from water to air or vice versa, as equilibrium between the phases is attained. The key physical properties required as input parameters into the model are melting point, vapor pressure, K_{ow} and water solubility. The model also requires estimates of first-order half-lives in the air, water, soil and sediment. An additional key input parameter is loading of the chemical into the environment.

Estimation of Acute Aquatic Toxicity

Models developed by the US Environmental Protection Agency (EPA) were employed to make estimates of acute toxicity to aquatic organisms, specifically to the fathead minnow (*Pimephales promelas*), a commonly tested fish; a water-column dwelling invertebrate (*Daphnia magna*); and to a commonly tested green alga, *Selenastrum capricornutum*. The models are incorporated in a modeling package called ECOSAR, version 0.99g (US EPA, 2000). ECOSAR may be obtained from the EPA website for the Office of Pollution Prevention and Toxics, Risk Assessment Division. The models calculate inherent toxicity based on structural features and physical properties, mainly the K_{ow} (Meylan and Howard, 1998).

Modeling Information Specific to DMH

The models described above were used for DMH. Estimations of physical/chemical properties (Table A1), environmental fate and distribution, and ecotoxicity (Table A2) were made. The measured physical chemical properties values for melting point (178°C) and octanol-water partition coefficient, log K_{ow} (0.35), were used in the model. Release of DMH to the environment was considered to be 100% to water. The following values were generated from the models:

Table A1: Physical/Chemical Properties Model Data for DMH

Melting Point (°C)	Boiling Point (°C)	Vapor Pressure (mm Hg)	Partition Coefficient (log K_{ow})	Water Solubility (mg/l)
150	366.72	1.36E-06	-0.27	4516

Table A2: Environmental Fate and Ecotoxicity Model Data for DMH*

Photodegradation (cm^3/molecule-sec for k_{phot})	Stability in Water	Transport & Distribution		Acute Tox. to Fish LC_{50} (mg/l)
k_{phot} = 3.06E-12 $t_{1/2}$ = 3.5 days	Model did not estimate	air: < 0.1% water: 99.8% soil: < <0.01% sediment: 0.2%		1252

* ECOSAR did not provide an estimate of daphnid or algae toxicity

References

Mackay, D., A. Di Guardo, S. Paterson, G. Kicsi and C. E. Cowan. 1996a. Assessing the Fate of New and Existing Chemicals: A Five-stage Process. *Environ. Toxicol. Chem*. 15(9): 1618 - 1626.

Mackay, D., A. Di Guardo, S. Paterson and C. E. Cowan. 1996b. Evaluating the Environmental Fate of a Variety of Types of Chemicals Using the EQC Model. *Environ. Toxicol. Chem*. 15(9): 1627 - 1637.

Meylan, W. and P. H. Howard. 1998. User's Guide for the ECOSAR Class Program, Version 0.99d. Syracuse Research Corporation, North Syracuse, NY.

Meylan, W. and P. H. Howard. 1999a. User's Guide for MPBPVP, Version 1.4. Syracuse Research Corporation, North Syracuse, NY.

Meylan, W. and P. H. Howard. 1999b. User's Guide for KOWWIN, Version 1.6. Syracuse Research Corporation, North Syracuse, NY.

Meylan, W. and P. H. Howard. 1999c. User's Guide for WSKOWWIN, Version 1.3. Syracuse Research Corporation, North Syracuse, NY.

Meylan, W. and P. H. Howard. 2000a. User's Guide for AOPWIN, Version 1.9. Syracuse Research Corporation, North Syracuse, NY.

Meylan, W. and P. H. Howard. 2000b. User's Guide for BIOWIN, Version 4.0. Syracuse Research Corporation, North Syracuse, NY.

Syracuse Research Corporation. 2000. Users Guide for Estimation Programs Interface for Windows, Version 3. Syracuse Research Corporation, North Syracuse, NY.
US EPA. Data Evaluation Records (Tabs 1-20): See Appendix B.

US EPA. 1999a. DRAFT #2 Guidance on Developing Robust Summaries. http://www.epa.gov/chemrtk/robsumgd.htm.

US EPA. 2000. ECOSAR Program, Risk Assessment Division (7403). US Environmental Protection Agency, Washington, DC.

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Appendix B

Robust Summaries for DMH

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2.1 MELTING POINT

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	No information provided

Method

Method/Guideline followed:	No information provided
GLP:	NA
Year:	1981
Remarks:	

Results

Melting Point:	178° C
Decomposition:	No information provided
Sublimation:	No information provided
Remarks:	

Conclusions: The endpoint has been adequately characterized by a reputable source. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability:	2D
Remarks:	Reliable with restrictions; information provided in handbook.

References:

Hawley, G. G. 1981. The Condensed Chemical Dictionary, 10th ed. Van Nostrand Reinhold Company, Inc. New York. page 369.

Other Available Reports

Other

Last Changed:	January 23, 2002
Order Number for Sorting:	1a
Remarks:	

2.1 MELTING POINT

Test Substance

Identity: 5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity: NA

Method

Method/Guideline followed: EPIWIN (v 3.10) MPBPVP Submodel v 1.40
GLP: NA
Year: 2003
Remarks: The EPIWIN model was run using the following measured physical chemical properties: melting point = 178°C and octanol-water partition coefficient, Log K_{ow} = 0.35.

Results

Melting Point: 150.34°C
Decomposition: NA
Sublimation: NA
Remarks: Following are the results from the model:

```
MPBPWIN (v1.40) Program Results:
================================
Experimental Database Structure Match:
  Name     :  2,4-IMIDAZOLIDINEDIONE, 5,5-DIMETHYL-
  CAS Num  :  000077-71-4
  Exp MP (deg C):  178
  Exp BP (deg C):  ---
  Exp VP (mm Hg):  ---

SMILES : O=C(NC(C1(=O))(C)C)N1
CHEM   : 2,4-Imidazolidinedione, 5,5-dimethyl-
MOL FOR: C5 H8 N2 O2
MOL WT : 128.13
------------ SUMMARY MPBPWIN v1.40 ---------

Melting Point:  349.84 deg C (Adapted Joback Method)
Melting Point:  100.47 deg C (Gold and Ogle Method)
Mean Melt Pt :  225.15 deg C (Joback; Gold,Ogle Methods)
  Selected MP:  150.34 deg C (Weighted Value)

-------+-----+--------------------+----------+---------
 TYPE  | NUM |  MELT DESCRIPTION  |  COEFF   |  VALUE
-------+-----+--------------------+----------+---------
 Group |  2  |  -CH3              |   -5.10  |  -10.20
 Group |  1  |  >C<   (ring)      |   60.15  |   60.15
 Group |  2  |  -C(=O)NH (ring)   |  240.00  |  480.00
   *   |     |  Equation Constant |          |  122.50
=============+====================+==========+=========
   RESULT    |  MELTING POINT in deg Kelvin  |  652.45
 RESULT-limit|  MELTING POINT in deg Kelvin  |  623.00
             |  MELTING POINT in deg C       |  349.84
-------------------------------------------------------
```

Conclusions: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability: 2

Remarks: Reliable with restrictions; model data.

References:

Meylan W. and P.H. Howard. 1999. User's Guide for MPBPVP, version 1.4; Syracuse Research Corporation, North Syracuse, NY.

Other Available Reports

Other

Last Changed: May 14, 2003

Order Number for Sorting: 56

Remarks:

2.1 BOILING POINT

Test Substance

Identity: 5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity: NA

Method

Method/Guideline followed: EPIWIN (v 3.10) MPBPVP Submodel v 1.40
GLP: NA
Year: 2003
Remarks: The EPIWIN model was run using the following measured physical chemical properties: melting point = 178°C and octanol-water partition coefficient, Log K_{ow} = 0.35.

Results

Boiling Point: 336.72°C
Pressure: NA
Pressure Unit: NA
Decomposition: NA
Remarks: Following are the results from the model:

```
MPBPWIN (v1.40) Program Results:
================================
Experimental Database Structure Match:
  Name     :  2,4-IMIDAZOLIDINEDIONE, 5,5-DIMETHYL-
  CAS Num  :  000077-71-4
  Exp MP (deg C):  178
  Exp BP (deg C):  ---
  Exp VP (mm Hg):  ---

SMILES : O=C(NC(C1(=O))(C)C)N1
CHEM   : 2,4-Imidazolidinedione, 5,5-dimethyl-
MOL FOR: C5 H8 N2 O2
MOL WT : 128.13
------------ SUMMARY MPBPWIN v1.40 ---------

Boiling Point:  366.72 deg C (Adapted Stein and Brown Method)

-------+-----+--------------------+----------+---------
 TYPE  | NUM |  BOIL DESCRIPTION  |  COEFF   |  VALUE
-------+-----+--------------------+----------+---------
 Group |  2  |  -CH3              |   21.98  |   43.96
 Group |  1  |  >C<   (ring)      |   11.12  |   11.12
 Group |  2  |  -C(=O)NH (ring)   |  246.13  |  492.26
   *   |     |  Equation Constant |          |  198.18
=============+====================+==========+=========
RESULT-uncorr|  BOILING POINT in deg Kelvin  |  745.52
RESULT- corr |  BOILING POINT in deg Kelvin  |  639.88
             |  BOILING POINT in deg C       |  366.72
-------------------------------------------------------
```

Conclusions: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability: 2

Remarks: Reliable with restrictions; model data.

References:

Meylan W. and P.H. Howard. 1999. User's Guide for MPBPVP, version 1.4; Syracuse Research Corporation, North Syracuse, NY.

Other Available Reports

Other

Last Changed: May 14, 2003

Order Number for Sorting: 56

Remarks:

2.4 VAPOR PRESSURE

Test Substance

Identity: 5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity: NA

Method

Method/Guideline followed: EPIWIN (v 3.10) MPBPVP Submodel v 1.40
GLP: NA
Year: 2003
Remarks: The EPIWIN model was run using the following measured physical chemical properties: melting point = 178°C and octanol-water partition coefficient, Log K_{ow} = 0.35.

Results

Vapor Pressure:: 1.36 E-006 mm Hg
Temperature: 25°C
Decomposition: NA
Remarks: Following are the results from the model:

```
MPBPWIN (v1.40) Program Results:
================================
Experimental Database Structure Match:
  Name     :  2,4-IMIDAZOLIDINEDIONE, 5,5-DIMETHYL-
  CAS Num  :  000077-71-4
  Exp MP (deg C):  178
  Exp BP (deg C):  ---
  Exp VP (mm Hg):  ---

SMILES : O=C(NC(C1(=O))(C)C)N1
CHEM   : 2,4-Imidazolidinedione, 5,5-dimethyl-
MOL FOR: C5 H8 N2 O2
MOL WT : 128.13
------------ SUMMARY MPBPWIN v1.40 ---------

Vapor Pressure Estimations (25 deg C):
  (Using BP: 366.72 deg C (estimated))
  (Using MP: 178.00 deg C (user entered))
    VP:  5.03E-007 mm Hg (Antoine Method)
    VP:  1.36E-006 mm Hg (Modified Grain Method)
    VP:  3.24E-006 mm Hg (Mackay Method)
  Selected VP:  1.36E-006 mm Hg (Modified Grain Method)
```

Conclusions The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability: 2
Remarks: Reliable with restrictions; model data.

References

Meylan W. and P.H. Howard. 1999. User's Guide for MPBPVP, version 1.4; Syracuse Research Corporation, North Syracuse, NY.

Other Available Reports

Other

Last Changed: May 14, 2003
Order Number for Sorting: 56
Remarks:

2.5 PARTITION COEFFICIENT

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	Not stated

Method

Method:	EPA guidelines for registering pesticides in the US (Federal Register: Volume 43, 29696; July10, 1978, Subdivision D, Product Chemistry 63-11). The method also followed recommendations made by the EPA in the Federal Register (53), March 16, 1979, 16255.
GLP:	Yes
Year:	1987
Remarks:	The octanol-water partition coefficient was determined in four replications. Duplicate 50 and 25 mg portions of 5,5-dimethylhydantoin (DMH) were placed in flasks with 20 ml of phosphate buffer and 100 ml of octanol. The flasks were placed in a shaker bath at 25 ºC and the mixtures were agitated for one hour. The flasks were allowed to remain at 25 ºC for at least 16 hours. The mixtures were centrifuged for five minutes at 16,000 rpm and at a temperature of 25 ºC.

Results

Log P_{ow}:	0.35
Temperature °C:	25 ºC
Remarks:	Accountability of the added DMH gave an average recovery from the four replications of 108%.

Conclusions The Log P_{ow} was determined to be 0.35 at 25°C. (Author of report)

Remarks:	The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch):	1A
Remarks:	Reliable without restriction; Guideline study.

References

Craine, E. M. 1987. The octanol-water partition coefficient of dimethylhydantoin. Project numbers WIL-80192 and WIL-12087. WIL Research Laboratories, Inc., Ashland, OH, US.

Other

Last changed:	January 22, 2002
Order number for sorting:	1
Remarks:	

2.5 PARTITION COEFFICIENT

Test Substance

Identity: 5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity: NA

Method

Method: EPIWIN (v 3.10) KOWWIN Submodel (v 1.66)
GLP: NA
Year: 2003
Remarks: The EPIWIN model was run using the following measured physical chemical properties: melting point = 178°C and octanol-water partition coefficient, Log K_{ow} = 0.35.

Results

Log K_{ow}: -0.27
Temperature °C: NA
Remarks: Following are the results from the model:

```
KOWWIN Program (v1.66) Results:
===============================

                  Log Kow(version 1.66 estimate): -0.27

Experimental Database Structure Match:
  Name     :  2,4-Imidazolidinedione, 5,5-dimethyl-
  CAS Num  :  000077-71-4
  Exp Log P:  -0.48
  Exp Ref  :  Hansch,C et al. (1995)

SMILES : O=C(NC(C1(=O))(C)C)N1
CHEM   : 2,4-Imidazolidinedione, 5,5-dimethyl-
MOL FOR: C5 H8 N2 O2
MOL WT : 128.13
-------+-----+-------------------------------------------+---------+--------
 TYPE  | NUM |        LOGKOW FRAGMENT DESCRIPTION        |  COEFF  |  VALUE
-------+-----+-------------------------------------------+---------+--------
 Frag  |  2  |  -CH3    [aliphatic carbon]               | 0.5473  |  1.0946
 Frag  |  2  |  -NH-    [aliphatic attach]               |-1.4962  | -2.9924
 Frag  |  1  |  -C(=O)N  [aliphatic attach]              |-0.5236  | -0.5236
 Frag  |  1  |  -NC(=O)N-    [urea]                      | 1.0453  |  1.0453
 Frag  |  1  |  -tert Carbon  [3 or more carbon attach]  | 0.2676  |  0.2676
 Factor|  1  |  -N-CO-N-CO-  structure  correction       | 0.6074  |  0.6074
 Const |     |  Equation Constant                        |         |  0.2290
-------+-----+-------------------------------------------+---------+--------
                                                      Log Kow   =  -0.2721
```

Conclusions The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch):	2
Remarks:	Reliable with restrictions; model data.

References

Meylan W. and P.H. Howard. 1999. User's Guide for KOWWIN, version 1.6; Syracuse Research Corporation, North Syracuse, NY

Other

Last changed:	May 14, 2003
Order number for sorting:	56
Remarks:	

2.6 WATER SOLUBILITY

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	No information provided

Method

Method/Guideline followed:	No information provided
GLP:	NA
Year:	1981
Remarks:	

Results

Value:	No information provided
Solubility:	Soluble in water
pH value and concentration:	No information provided
pKa value at 25°C:	No information provided
Remarks:	

Conclusions: The endpoint has been adequately characterized by a reputable source. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability:	2D
Remarks:	Reliable with restrictions; information provided in handbook.

References:

Hawley, G. G. 1981. The Condensed Chemical Dictionary, 10th ed. Van Nostrand Reinhold Company, Inc. New York. page 369.

Other Available Reports

Other

Last Changed:	January 23, 2002
Order Number for Sorting:	1a
Remarks:	

2.6 WATER SOLUBILITY

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	NA

Method

Method/Guideline followed:	EPIWIN (v 310) WSKOWWIN Submodel (V 1.40)
GLP:	NA
Year:	2003
Remarks:	The EPIWIN model was run using the following measured physical chemical properties: melting point = 178°C and octanol-water partition coefficient, Log K_{ow} = 0.35.

Results

Value:	4516 mg/L
Solubility:	Soluble in water
pH value and concentration:	NA
pKa value at 25°C:	NA
Remarks:	Following are the results from the model:

```
Water Sol from Kow (WSKOW v1.40) Results:
=========================================

          Water Sol: 4516 mg/L

Experimental Water Solubility Database Match:
  Name     :  2,4-IMIDAZOLIDINEDIONE, 5,5-DIMETHYL-
  CAS Num  :  000077-71-4
  Exp WSol :  1E+005 mg/L (10 deg C)
  Exp Ref  :  BEILSTEIN

SMILES : O=C(NC(C1(=O))(C)C)N1
CHEM   : 2,4-Imidazolidinedione, 5,5-dimethyl-
MOL FOR: C5 H8 N2 O2
MOL WT : 128.13
--------------- WSKOW v1.40 Results -----------------
Log Kow  (estimated)  :  -0.27
Log Kow (experimental):  -0.48
    Cas No: 000077-71-4
    Name  : 2,4-Imidazolidinedione, 5,5-dimethyl-
    Refer : Hansch,C et al. (1995)
Log Kow used by Water solubility estimates:  0.35 (user entered)

Equation Used to Make Water Sol estimate:
   Log S (mol/L) = 0.693-0.96 log Kow-0.0092(Tm-25)-0.00314 MW +
   Correction

      Melting Pt (Tm) = 178.00 deg C (Use Tm = 25 for all liquids)
```

```
   Correction(s):         Value
   --------------------   -----
    No Applicable Correction Factors

Log Water Solubility  (in moles/L) :  -1.453
Water Solubility at 25 deg C (mg/L):  4516
```

Conclusions

The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability: 2

Remarks: Reliable with restrictions; model data.

References

Meylan W. and P.H. Howard. 1999. User's Guide for WSKOW, version 1.3; Syracuse Research Corporation, North Syracuse, NY

Other Available Reports

Other

Last Changed: May 14, 2003

Order Number for Sorting: 56

Remarks:

3.1.1 PHOTODEGRADATION

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	Non-radiolabeled: > 99.5%; Radiochemical purity: > 98.7%

Method

Method/Guideline followed:	US EPA FIFRA N-161-2 40 CFR Sec. 158.130
Type:	Aqueous photolysis
GLP:	Yes
Year:	1992
Light source:	6500 Watt Xenon arc
Light spectrum:	280 to 790 nm
Relative intensity:	Compared to actual sunlight
Spectrum of substance:	The absorbance spectrum of DMH was measured using a Perkin-Elmer Lambda 3B UV/VIS spectrophotometer.
Remarks:	^{14}C-Dimethylhydantoin (DMH) at a nominal concentration of 10 µg/ml of aqueous buffer at pH 7 was exposed to a xenon arc light source for 30 days in an environmentally controlled chamber at 25 ± 1°C. A test system was prepared that was not exposed to the xenon arc light source. ^{14}C-DMH and potential photolysis products were measured by thin-layer chromatography (TLC)/autoradiography/ liquid scintillation counting. Stability of ^{14}C-DMH in the terminal samples was verified by high-performance liquid chromatography (HPLC).

Results

Concentration of substance:	Nominal = 10µg/ml
Temperature:	25 ± 1 °C
Direct photolysis:	The percentage of total radioactivity recovered as DMH in the Day 30 (terminal) exposed samples was 94.2%. The calculated photolysis rate constant and half-life of DMH were 7.89 X10^{-4} days^{-1} and 878 days and, respectively.
Indirect photolysis:	The percentage of total radioactivity recovered as DMH in the Day 30 (terminal) nonexposed samples was 96.4%. The photolysis rate constant for DMH in the non-exposed test system was not significantly different than zero, which resulted in an indeterminate half-life due to the positive slope of the regression line.
Breakdown products:	None. Parent (^{14}C-DMH) was the only radioactivity zone obtained by TLC.

Remarks: No significant change of pH was observed in the samples over the course of the study. The mean ^{14}C-mass balance was approximately 100% for the exposed and non-exposed test systems. Parent (^{14}C-DMH) compound was the only radioactive component obtained in the test samples when analyzed by TLC and HPLC.

Conclusions

The results of this study demonstrated that DMH was not subject to photodegradation in aqueous media at a pH of 7. Therefore, DMH was stable under these conditions. (Author of report)

Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch): 1A

Remarks: Reliable without restriction; guideline study.

References

Schmidt, J. M. and W. A. Stansbrey. 1992. Determination of the aqueous photolysis rate of dimethylhydantoin. Project number 39509. ABC Laboratories, Inc., Columbia, MO, US.

Other

Last changed: January 22, 2002

Order number for sorting: 2

Remarks:

3.1.1 PHOTODEGRADATION

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	Radiochemical purity: = 98.0%

Method

Method/guideline followed:	US EPA FIFRA N-161-2 40 CFR Sec. 158.130
Type:	Photodegradation in pH-7 buffer solution
GLP:	Yes
Year:	1987
Light source:	Xenon Arc Light System
Light spectrum:	300 to 700 nm
Relative intensity:	One-half the intensity of the sun
Spectrum of substance:	The spectral irradiance of the source was measured with a LiCor LI-1800® spectral radiometer.
Remarks:	The 30-day photolysis test was conducted in pH-7 buffered solutions of ^{14}C-5,5-dimethylhydantoin. Both photosensitized and non-photosensitized systems were evaluated. Half of the samples were wrapped in aluminum foil for dark controls. The other half were placed on the photolysis apparatus and exposed to the output of the Xenon arc lamp. At the sample times of 0, 1, 3, 7, 14, 21 and 30 days, duplicate exposed and dark samples were collected. The samples were stored at 4 ºC prior to the assay step. Rate constants and half-lives were determined based on the test substance remaining in solution.

Results

Concentration of substance:	253.9 µg/ml
Temperature °C:	Not stated
Direct photolysis:	Described below
Indirect photolysis:	Described below
Breakdown products:	No
Remarks:	All samples showed a negligible decrease in percent of activity existing as parent compound with increasing exposure time. The rate constant for the sensitized, exposed system was determined to be -0.000302 days^{-1}, which gave a half-life of 2295 days. For the non-sensitized, exposed system, a rate constant of -0.000330 days^{-1} was found, which gave a half-life of 2100 days under the test conditions. The dark samples for the sensitized system had a rate constant of -0.000617 days^{-1} ($t_{1/2}$ = 1123 days) while the non-sensitized system gave a rate constant and half-life of -0.000458 days^{-1} and 1513 days, respectively. The corrected rate constants for the exposed were not determined due to the poor model fit of the test data. The rate constants and half-lives

calculated from the data did not reflect the actual decomposition rate of the test substance in aqueous solution.

Conclusions

Given the stability of the test substance, under the conditions of this test, the data indicated that photolytic decomposition of the test substance in aqueous solution would not contribute significantly to its decomposition in the environment. (Author of report)

Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch): 1A

Remarks: Reliable without restriction; guideline study

References

Carpenter, M. 1987. Determination of photodegradation of 5,5-dimethylhydantoin in pH 7 buffer solution. Project number 35178. Analytical Bio-Chemistry Laboratories, Inc., Columbia, MO, US.

Other

Last changed: January 22, 2002

Order number for sorting: 2a

Remarks:

3.1.1 PHOTODEGRADATION

Test Substance

Identity: 5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity: NA

Method

Method/guideline followed: EPIWIN (v 3.10) AOPWIN submodel (v 1.90)
Type: NA
GLP: NA
Year: 2003
Remarks: The EPIWIN model was run using the following measured physical chemical properties: melting point = 178°C and octanol-water partition coefficient, Log K_{ow} = 0.35.

Results

Concentration of substance: NA
Temperature °C: NA
Direct photolysis: NA
Indirect photolysis: NA
Breakdown products: NA
Remarks: Overall OH Rate Constant (k_{phot}) = 3.06E-12 cm^3/molecule-sec
$t_{1/2}$ = 3.5 days (12-hr day; 1.5E6 OH/cm3)
Following is the output from the model:

```
AOP Program (v1.90) Results:
============================
SMILES : O=C(NC(C1(=O))(C)C)N1
CHEM   : 2,4-Imidazolidinedione, 5,5-dimethyl-
MOL FOR: C5 H8 N2 O2
MOL WT : 128.13
---------- SUMMARY (AOP v1.90): HYDROXYL RADICALS ----------
Hydrogen Abstraction       =   1.0608 E-12 cm3/molecule-sec
**Reaction with N, S and -OH =   2.0000 E-12 cm3/molecule-sec
Addition to Triple Bonds   =   0.0000 E-12 cm3/molecule-sec
Addition to Olefinic Bonds =   0.0000 E-12 cm3/molecule-sec
Addition to Aromatic Rings =   0.0000 E-12 cm3/molecule-sec
Addition to Fused Rings    =   0.0000 E-12 cm3/molecule-sec

   OVERALL OH Rate Constant =   3.0608 E-12 cm3/molecule-sec
   HALF-LIFE =     3.495 Days (12-hr day; 1.5E6 OH/cm3)
   HALF-LIFE =    41.934 Hrs
........  ** Designates Estimation(s) Using ASSUMED Value(s)
---------- SUMMARY (AOP v1.90): OZONE REACTION -------------

               ******  NO OZONE REACTION ESTIMATION ******
               (ONLY Olefins and Acetylenes are Estimated)

Experimental Database:  NO Structure Matches
```

Conclusions: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch): 2

Remarks: Reliable with restrictions; model data

References: Meylan W. and P. H. Howard. 1999. User's Guide for AOPWIN, Version 1.9; Syracuse Research Corporation, North Syracuse, NY

Other

Last changed: May 14, 2003

Order number for sorting: 56

Remarks:

3.1.2 STABILITY IN WATER

Test Substance

Identity: 5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity: Radiochemical purity: >98.7%

Method

Method/Guideline followed: US EPA FIFRA N-161-1 40 CFR Sec. 158.130
Type: Hydrolysis as a Function of pH at 25 °C
GLP: Yes
Year: 1992
Remarks: The effect of pH on the hydrolysis of ^{14}C-dimethylhydantoin (DMH) was determined in a 30-day hydrolysis study.

Results

Nominal: 10 µg/ml
Measured value: 10.5 to 10.2 µg/ml at pH 7 (TRIS) and
10.6 to 10.2 µg/ml at pH 7 (HEPES)
Degradation %: Remaining ^{14}C-DMH (as percent of initial measured dose):

Day	pH 7 (TRIS)	pH 7 (HEPES)
Day 0	100	100
Day 1	98.1	100
Day 3	97.2	100
Day 7	97.2	99.0
Day 14	100	100
Day 21	98.1	98.1
Day 30	96.2	97.1

Half-life: 3194 days for pH 7 (TRIS) and
1715 days for pH 7 (HEPES)
Breakdown products: ^{14}C-DMH accounted for more than 90% of the radioactivity and no hydrolysis products accounting for up to 10% of the radioactivity were observed.
Remarks: The parent (^{14}C-DMH) compound did not significantly hydrolyze in the pH range of 5 to 9 as determined by thin-layer chromatography and high-performance liquid chromatography. Half-lives were not calculated for the pH 5 and pH 9 systems as positive slopes were obtained based on the linear regression analysis of the data.

Conclusions: The parent compound (^{14}C-DMH) did not hydrolyze in aqueous media at the pH of 5 and 9 and at a pH of 7, hydrolysis of DMH was minimal, resulting in very long half-lives. (Author of report)
Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch):	1A
Remarks:	Reliable without restriction; guideline study.

References

Schmidt, J. M. and W. A. Stansbrey. 1992. Hydrolysis of dimethylhydantoin as a function of pH at 25 °C. Project number 39508. ABC Laboratories, Inc., Columbia, MO, US.

Other

Last changed:	January 22, 2002
Order number for sorting:	3
Remarks:	

3.1.2 STABILITY IN WATER

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	Radiochemical purity: = 98.3%

Method

Method/Guideline followed:	Not stated
Type:	Hydrolysis as a function of pH at 25°C
GLP:	Yes
Year:	1987
Remarks:	The hydrolysis test was conducted with the test substance in four aqueous buffered solutions, pH 5, pH 7-A, pH 7-B and pH 9 at a nominal test concentration of 10 µg/ml. Quantification and characterization of the test substance were by reverse phase thin layer chromatography and liquid scintillation counting analysis. The pH 5, pH 7-A (tris), pH 7-B (phosphate) and pH 9 buffered test systems were conducted for 30 days.

Results

Nominal:	10 µg/ml
Measured value:	Not stated
Half-life:	842, 760, 1070 and 182 days at pH 5, pH 7-A, pH 7-B and pH 9, respectively, at 25 ± 1 ºC
Degradation %:	Not stated
Breakdown products:	Not stated
Remarks:	The hydrolysis was minimal in all four test systems. The rate constants of the test substance at pH 5, pH 7-A, pH 7-B and pH 9 were -0.0008229/day, -0.0009121/day, -0.0006477/day and -0.003809/day, respectively. The ^{14}C-mass accountability in the pH 5, pH 7-A, pH 7-B and pH 9 test systems was 97.8%, 101%, 99.6% and 97.0%, respectively.

Conclusions	The estimated half-lives calculated for the pH 5, pH 7-A and pH 7-B test systems indicate that the test substance does not hydrolyze significantly within 30 days under the conditions of this test. The correlation and rate constant calculated for the pH 9 test system, however, indicate that the half-life of 182 days is a reliable approximation for that test system. (Author of report)
Remarks:	The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch):	1A
Remarks:	Reliable without restriction; guideline study.

References

Daly, D. 1987. Hydrolysis as a function of pH at 25 °C with ^{14}C-5,5-dimethylhydantoin. Project number 35181. Analytical Bio-Chemistry Laboratories, Inc., Columbia, MO, US.

Other

Last changed: January 22, 2002
Order number for sorting: 3a
Remarks:

3.3.2 TRANSPORTATION BETWEEN ENVIRONMENTAL COMPARTMENTS (FUGACITY MODEL)

Test Substance

Identity: 5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity: NA

Method

Method/Guideline followed: Equilibrium Concentration Model (EQC) Level III (V 1.01 Calculation according to Mackay, Level III
Media: Water, air, soil and sediment (model run with emissions to water = 1000 kg/hr and emissions to air, soil and sediment = 0 kg/hr each)
GLP: NA
Year: 2003
Remarks: The EPIWIN model was run using the following physical chemical properties: melting point = 178°C and octanol-water partition coefficient, Log K_{ow} = 0.35.

Results

Remarks: Following are the results from the model:

```
Level III Fugacity Model (Full-Output):
========================================
  Chem Name   : 2,4-Imidazolidinedione, 5,5-dimethyl-
  Molecular Wt: 128.13
  Henry's LC  : 2.77e-009 atm-m3/mole (Henrywin program)
  Vapor Press : 0.00145 mm Hg  (Mpbpwin program)
  Liquid VP   : 0.0471 mm Hg  (super-cooled)
  Melting Pt  : 178 deg C (user-entered)
  Log Kow     : 0.35  (user-entered)
  Soil Koc    : 0.918  (calc by model)

           Mass Amount    Half-Life    Emissions
            (percent)        (hr)       (kg/hr)
   Air       3.14e-006       83.9         0
   Water     99.8            900          1000
   Soil      0.00161         900          0
   Sediment  0.188           3.6e+003     0

             Fugacity    Reaction    Advection   Reaction    Advection
              (atm)      (kg/hr)      (kg/hr)    (percent)   (percent)
   Air       3.39e-017    0.000147    0.000178    1.47e-005   1.78e-005
   Water     6.11e-014    435         565         43.5        56.5
   Soil      3.4e-017     0.00703     0           0.000703    0
   Sediment  5.62e-014    0.205       0.0213      0.0205      0.00213

   Persistence Time: 566 hr
   Reaction Time:    1.3e+003 hr
   Advection Time:   1e+003 hr
   Percent Reacted:  43.5
   Percent Advected: 56.5
```

```
Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):
   Air:      83.88
   Water:    900
   Soil:     900
   Sediment: 3600
     Biowin estimate: 2.704  (weeks-months)

Advection Times (hr):
   Air:      100
   Water:    1000
   Sediment: 5e+004
```

Conclusions

Mass Amount (percent):
Air: < 0.01
Water: 99.8
Soil: < 0.01
Sediment: 0.2

Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch): 2
Remarks: Reliable with restrictions; model data

References

Mackay, D., A. DiGuardo, S. Paterson and C. E. Cowan. 1996. Evaluating the Environmental Fate of a Variety of Types of Chemicals Using the EQC Model. Environ. Toxicol. Chem. 15(9): 1627-1637

Other

Last changed: May 14, 2003
Order number for sorting: 56
Remarks:

3.5 BIODEGRADATION

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	100%

Method

Method/Guideline followed:	US EPA 40 CFR 796.3340. September 27, 1985. "Inherent Biodegradability: Modified SCAS Test"
Test type:	Aerobic
GLP:	Yes
Year:	1986
Contact time:	42 days
Inoculum:	Activated sludge from Colerain Twp., and/or O'Bannon Creek
Remarks:	5,5-Dimethylhydantoin (DMH) was measured for inherent biodegradability using the modified SCAS test method. Throughout the study, the temperature was maintained at a range of 20.5 to 24.0°C.

Results

Degradation:	101.3%
Results:	From test day 18 until the completion of the study on test day 42, average percent removals were at levels greater than 95%.
Kinetic:	Mean percent removal of DMH over time: Day 1 = 27.5% Day 2 = 3.0% Day 3 to 8 = no removal Day 11 = 4.5% Day 14 = 50.0% Day 16 = 92.3% Day 18 to 42 ranged from 95.8 to 109.3%
Breakdown products:	None stated
Remarks:	An exposure period of approximately 16 days was necessary to acclimate the activated sludge to 5,5-DMH. On test days 1 and 2, some carbon removal was observed (27.5 and 3.0% mean percent removal, respectively). However, from test day 3 through 10, negative percent removals were observed which ranged from –1.0% to –12.0%, which indicated no biodegradability of 5,5-DMH. Beginning on test day 11 to test day 18, an acclimation phase occurred where average percent removals began to increase from 4.5% to 101.3%.

Conclusions

5,5-DMH may be classified as ultimately biodegradable according to the test guideline, providing a sufficient acclimation period occurs. (Author of report)

Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch): 1A

Remarks: Reliable without restriction; guideline study.

References

Mulberry, G. K. 1986. Evaluation of biodegradation using the modified SCAS test method. Study number 86-1449-11. Hill Top Research, Inc., Miamiville, OH, US.

Other

Last changed: January 22, 2002

Order number for sorting: 4

Remarks:

3.5 BIODEGRADATION

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	Not stated

Method

Method/Guideline followed:	Not stated
Test type:	Aerobic
GLP:	No
Year:	1980
Contact time:	19 days (after a 2 week acclimation period)
Inoculum:	Activated sludge (non-nitrate fortified, obtained from the Nine Springs Sewage Treatment Plant in Madison, Wisconsin)
Remarks:	After a two-week acclimation period, 25 ppm of ^{14}C-dimethylhydantoin (DMH) was added to duplicate fermenters containing 500 ml of activated sludge. During the acclimation period, a third fermenter served as a control for plate counting data and was not amended with DMH. This fermenter was discarded at initiation of the biodegradation test. Samples were collected at 30 minutes, 1, 3, 6 and 24 hours and at 2, 3, 4, 6, 8, 10, 14 and 19 days after test initiation. Chemical analysis by HPLC and radiochemical analysis were conducted.

Results

Degradation:	94% after 19 days
Results:	DMH degrades rapidly with no obvious toxic effects upon the organisms.
Kinetic:	Not stated.
Breakdown products:	Described below
Remarks:	A gradual increase in microbial population over the 2-week acclimation period, with no apparent differences between the control and the treated fermenters, indicated that the bacterial populations were not measurably reduced in the presence of DMH. Within 24 hours after test initiation, the level of DMH in the incubation mixture, as measured by HPLC, decreased from about 20 ppm to an average of 5 ppm, a 75% loss. In the same period, however, radioactivity in the mixture showed only a 19% loss; this was explained by the release of metabolites into solution and subsequent absorption by the particulate matter. After three days, DMH concentration in the mixture was <1 ppm, and radioactivity had decreased to 48% of its original level, showing that metabolites ultimately were leaving the system as carbon dioxide. By 19 days, 94% of the radioactivity had been recovered as carbon dioxide. Only trace amounts of radioactivity were found as volatiles other than carbon dioxide, and these appeared to be due to aerosols from the incubation mixture. When the results were

corrected for known leakages of carbon dioxide in the apparatus, a carbon balance was maintained. Replicate fermenter assemblies produced comparable data.

Conclusions

Under the conditions of this test, DMH degrades rapidly with no obvious toxic effects upon the organisms. (Author of report)

Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch): 1B

Remarks: Reliable without restriction; comparable to guideline study.

References

Raltech Scientific Services. 1980. Degradation of dimethylhydantoin by activated sludge. Raltech Scientific Services, Ralston Purina Company, Madison, WI, US.

Other

Last changed: January 22, 2002

Order number for sorting: 5

Remarks:

3.5 Biodegradation

Test Substance

Identity: 5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity: 100%

Method

Method/Guideline followed: US EPA TSCA Test Guidelines 40 CFR 796.3240. September 27, 1985.
Test type: Aerobic
GLP: Yes
Year: 1986
Contact time: 28 days
Inoculum: A mixed composite of inoculum, 100 ml each of: Soil inoculum (from flood plain between the Little Miami River and Hill Top Research); secondary effluent (activated sludge from the O'Bannon Creek Sewage Treatment Plant); and surface water (from O'Bannon Creek).
Remarks: 5,5-Dimethylhydantoin (DMH) was measured for ready biodegradability using the OECD screening method. Throughout the study, the temperature was maintained at a range of 20.5 to 24.0 °C. Sodium benzoate was used as the reference compound in the study.

Results

Degradation: 10.1% by Day 28
Results: The mean percent carbon removal ranged from 4.5 to 10.1% from days 7 to 28.
Kinetic: Mean percent carbon removal over time:

Compound	Test Day				
	7	14	21	27	28
Sodium benzoate	94.3	90.0	100.6	97.6	100.8
DMH	7.3	4.5	10.1	5.6	9.5

Breakdown products: None stated
Remarks: Since the EPA criteria for ready biodegradability is ≥ 70% DOC removal, it can be concluded that
5,5-DMH at 20 mg carbon/liter cannot be classified as "readily biodegradable" using the modified OECD screening method. It should be noted, that due to the nature of the test system, the chance for adaptation and acclimation is minimal since the sole source of carbon and energy for the microorganisms is the test compound. Therefore, since a low level of biodegradation was

found in this study, it does not necessarily mean that the compound in not biodegradable under actual environmental conditions.

Conclusions

5,5-DMH at 20 mg carbon/liter cannot be classified as "readily biodegradable" using the modified OECD screening method. (Author of report)

Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch): 1A

Remarks: Reliable without restriction; guideline study.

References

Mulberry, G. K. 1986. Evaluation of biodegradation using the modified OECD screening method. Study number 86-1450-11. Hill Top Research, Inc., Miamiville, OH, US.

Other

Last changed: January 22, 2002

Order number for sorting: 54

Remarks:

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	97.1%

Method

Method/Guideline followed:	US EPA, Series 72 of Pesticide Assessment Guidelines, FIFRA Subdivision E Hazard Evaluation: Wildlife and Aquatic Organisms, EPA 540/9-82-024, October 1982 and ASTM Standard E 729-88, Standard Practice for Conducting Acute Toxicity Tests with Fishes, Macroinvertebrates, and Amphibians, American Society for Testing and Materials, 1988
Type:	Static
GLP:	Yes
Year:	1991
Species/Strain/Supplier:	Rainbow trout (*Oncorhyncus mykiss*)/Troutlodge, Inc., McMillin, WA
Analytical monitoring:	Yes
Exposure period:	96 hours
Statistical methods:	None
Remarks:	Ten juvenile rainbow trout were exposed to the test substance at nominal test concentrations of 0 (reconstituted freshwater) and 972.2 mg dimethylhydantoin (DMH)/l for 96 hours under static conditions. The test substance was tested in triplicate, while the control was tested in duplicate. A stock solution of the test substance was prepared by sonicating DMH in reconstituted freshwater. The dilution water was soft, reconstituted freshwater, which generally had a hardness of approximately 40 to 48 mg/l as $CaCO_3$, the alkalinity of approximately 30 to 35 mg/l as $CaCO_3$ and a pH of approximately 7.3 to 7.5. The mean wet weight and mean standard length of the fish were 0.24 g (range = 0.19 - 0.31 g) and 26 mm (range = 23 - 28 mm), respectively. Ambient room light was used to illuminate the test systems. Test chambers were 25 liter aquaria filled with 15 liters of test solution. The depth of the test solution in each test chamber was approximately 17 cm. Hardness, alkalinity, pH and conductivity of the control water at the beginning to the test were measured as 36 mg/l as $CaCO_3$, 24 mg/l $CaCO_3$, 7.4 and 170 µmhos/cm, respectively. Daily measurements of dissolved oxygen and pH of the control and test solutions ranged from 9.2 to 10.4 mg/l and 7.2 to 7.5, respectively. Temperature measurements made at the beginning and end of the test ranged from approximately 12.2 to 12.4 ºC. Observations of mortality and treatment-related effects were made at 20, 24, 48, 72 and 96 hours.

Results

Nominal concentrations (mg/l): 0 and 1000 mg/l
Measured concentrations (mg/l): 0 and 972.2 mg/l
Unit: mg/l
Element value: 96-hour LC_{50} > 972.2 mg/l
Statistical results: None
Remarks: Cumulative mortality was as follows:

Dose level (mg/l)	Time (hours)				
	20	24	48	72	96
0	0/20	0/20	0/20	0/20	0/20
972.2	0/30	0/30	0/30	0/30	0/30

All fish were normal in appearance and behavior throughout the test period. The no mortality concentration and no observed effect concentration both were 972.2 mg/l.

Conclusions

The 96-hour LC_{50} for DMH was determined to be greater than 972.2 mg/l. (Author of report)

Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch): 1A
Remarks: Reliable without restriction; guideline study.

References

Murphy, D. 1992. A 96-hour static acute toxicity test with the rainbow trout (*Oncorhynchus mykiss*). Project number 298A-102. Wildlife International Ltd., Easton, MD, US.

Other

Last changed: January 22, 2002
Order number for sorting: 6a
Remarks:

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	97.1%

Method

Method/Guideline followed:	US EPA, Series 72 of Pesticide Assessment Guidelines, FIFRA Subdivision E Hazard Evaluation: Wildlife and Aquatic Organisms, EPA 540/9-82-024, October 1982 and ASTM Standard E 729-88, Standard Practice for Conducting Acute Toxicity Tests with Fishes, Macroinvertebrates, and Amphibians, American Society for Testing and Materials, 1988
Type:	Static
GLP:	Yes
Year:	1991
Species/Strain/Supplier:	Fathead minnow (*Pimephales promelas*)/Wildlife International Ltd. cultures
Analytical monitoring:	Yes
Exposure period:	96 hours
Statistical methods:	None
Remarks:	Ten juvenile fathead minnows per concentration were exposed to mean measured test concentrations of 0 (reconstituted freshwater) and 1085 mg dimethylhydantoin (DMH)/l for 96 hours under static conditions. The test substance was tested in triplicate, while the control was tested in duplicate. A stock solution of the test substance was prepared by sonicating DMH in reconstituted freshwater. The dilution water was soft, reconstituted freshwater, which generally had a hardness of approximately 40 to 48 mg/l as $CaCO_3$, the alkalinity of approximately 30 to 35 mg/l $CaCO_3$ and a pH of approximately 7.3 to 7.5. The mean wet weight and mean standard length of the fish were 0.29 g (range = 0.20 - 0.45 g) and 25 mm (range = 22 - 29 mm), respectively. Ambient room light was used to illuminate the test systems. Test chambers were 25 liter aquaria filled with 15 liters of test solution. The depth of the test solution in each test chamber was approximately 20 cm. Hardness, alkalinity, pH and conductivity of the control water at the beginning of the test were measured as 52 mg/l as $CaCO_3$, 28 mg/l $CaCO_3$, 7.6 and 260 µmhos/cm, respectively. The control and test solutions had daily measurements of dissolved oxygen ranging from 6.6 to 8.4 mg/l and pH between 7.2 and 7.6. Temperature measurements made at the beginning and end of the test ranged from approximately 23.2 to 25.2 ºC. Observations of mortality and treatment-related effects were made at 1.5, 24, 48, 72 and 96 hours.

Results

Nominal concentrations (mg/l): 0 and 1000 mg/l
Measured concentrations (mg/l): 0 and 1085 mg/l
Unit: mg/l
Element value: 96-hour LC_{50} > 1085 mg/l
Statistical results: None
Remarks: Cumulative mortality was as follows:

Dose level (mg/l)	Time (hours)				
	1.5	24	48	72	96
0	0/20	0/20	0/20	0/20	0/20
1085	0/30	0/30	0/30	0/30	0/30

All fish were normal in appearance and behavior throughout the test period. The no mortality concentration and no observed effect concentration both were 1085 mg/l.

Conclusions

The 96-hour LC_{50} for DMH was determined to be greater than 1085 mg/l. (Author of report)

Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch): 1A
Remarks: Reliable without restriction; guideline study.

References

Murphy, D. and G. J. Smith. 1992. A 96-hour static acute toxicity test with the fathead minnow (*Pimephales promelas*). Project number 298A-103. Wildlife International Ltd., Easton, MD, US.

Other

Last changed: January 22, 2002
Order number for sorting: 6b
Remarks:

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	97.1%

Method

Method/Guideline followed:	US EPA, Series 72 of Pesticide Assessment Guidelines, FIFRA Subdivision E Hazard Evaluation: Wildlife and Aquatic Organisms, EPA 540/9-82-024, October 1982 and ASTM Standard E 729-88, Standard Practice for Conducting Acute Toxicity Tests with Fishes, Macroinvertebrates, and Amphibians, American Society for Testing and Materials, 1988
Type:	Static
GLP:	Yes
Year:	1991
Species/Strain/Supplier:	Sheepshead minnow (*Cyprinodon variegatus*)/Wildlife International Ltd. cultures
Analytical monitoring:	Yes
Exposure period:	96 hours
Statistical methods:	None
Remarks:	Ten juvenile sheepshead minnows per concentration were exposed to mean measured test concentrations of 0 (saltwater) and 1006 mg dimethylhydantoin (DMH)/l for 96 hours under static conditions. The test substance was tested in triplicate, while the control was tested in duplicate. A stock solution of the test substance was prepared by sonicating DMH in saltwater. The dilution water was saltwater collected at Indian River Inlet, Delaware, and had a mean salinity of 25% and a pH of 8.1. The mean wet weight and mean standard length of the fish were 0.27 g (range = 0.16 to 0.50 g) and 18 mm (range = 15 to 22 mm), respectively. Ambient room light was used to illuminate the test systems. Test chambers were 25 liter aquaria filled with 15 liters of test solution. The depth of the test solution in each test chamber was approximately 17 cm. The control water at the beginning to the test had a salinity of 25% and a pH of 8.1. Daily measurements of dissolved oxygen and pH of the control and test solutions ranged from 6.2 to 7.6 mg/l and 7.6 to 8.2, respectively. Temperature measurements made at the beginning and end of the test ranged from approximately 20.4 to 21.7 ºC. Observations of mortality and treatment-related effects were made at 24, 48, 72 and 96 hours.

Results

Nominal concentrations (mg/l): 0 and 1000 mg/l
Measured concentrations (mg/l): 0 and 1006 mg/l
Unit: mg/l
Element value: 96-hour LC_{50} > 1006 mg/l
Statistical results: None
Remarks: Cumulative mortality was as follows:

Dose level (mg/l)	Time (hours)			
	24	48	72	96
0	0/20	0/20	0/20	0/20
1006	0/30	0/30	0/30	0/30

All fish were normal in appearance and behavior throughout the test period. The no mortality concentration and no observed effect concentration both were 1006 mg/l.

Conclusions

The 96-hour LC_{50} for DMH was determined to be greater than 1006 mg/l. (Author of report)

Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch): 1A
Remarks: Reliable without restriction; guideline study.

References

Murphy, D and G. J. Smith. 1992. A 96-hour static acute toxicity test with the sheepshead minnow (*Cyprinodon variegatus*). Project number 298A-104. Wildlife International Ltd., Easton, MD, US.

Other

Last changed: January 22, 2002
Order number for sorting: 6c
Remarks:

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	97.1%

Method

Method/Guideline followed:	US EPA, Series 72 of Pesticide Assessment Guidelines, FIFRA Subdivision E Hazard Evaluation: Wildlife and Aquatic Organisms, EPA 540/9-82-024, October 1982 and ASTM Standard E 729-88, Standard Practice for Conducting Acute Toxicity Tests with Fishes, Macroinvertebrates, and Amphibians, American Society for Testing and Materials, 1988
Type:	Static
GLP:	Yes
Year:	1991
Species/Strain/Supplier:	Bluegill sunfish (*Lepomis macrochirus*)/Northeastern Biologists, Inc., Rhinebeck, NY
Analytical monitoring:	Yes
Exposure period:	96 hours
Statistical methods:	None
Remarks:	Ten juvenile bluegill sunfish per concentration were exposed to mean measured test concentrations of 0 (reconstituted freshwater) and 1017 mg dimethylhydantoin (DMH)/l for 96 hours under static conditions. The test substance was tested in triplicate, while the control was tested in duplicate. A stock solution of the test substance was prepared by sonicating DMH in reconstituted freshwater. The dilution water was soft, reconstituted freshwater, which generally had a hardness of approximately 40 to 48 mg/l as $CaCO_3$, the alkalinity of approximately 30 to 35 mg/l $CaCO_3$ and a pH of 7.3 to 7.5. The mean wet weight and mean standard length of the fish were 0.45 g (range = 0.32 to 0.66 g) and 23 mm (range = 21 to 26 mm), respectively. Ambient room light was used to illuminate the test systems. Test chambers were 25 liter aquaria filled with 15 liters of test solution. The depth of the test solution in each test chamber was approximately 20 cm. Hardness, alkalinity, pH and conductivity of the control water at the beginning to the test were measured as 48 mg/l as $CaCO_3$, 26 mg/l $CaCO_3$, 7.7 and 240 µmhos/cm, respectively. The control and test solutions had daily measurements of dissolved oxygen from 6.4 to 8.6 mg/l and pH of 7.2 to 7.7. Temperature measurements made at the beginning and end of the test ranged from approximately 21.4 to 22.2 ºC. Observations of mortality and treatment-related effects were made at 2, 24, 48, 72 and 96 hours.

Results

Nominal concentrations (mg/l):	0 and 1000 mg/l

Measured concentrations (mg/l): 0 and 1017 mg/l
Unit: mg/l
Element value: 96-hour LC_{50} > 1017 mg/l
Statistical results: None
Remarks: Cumulative mortality was as follows:

Dose level (mg/l)	Time (hours)				
	2	24	48	72	96
0	0/20	0/20	0/20	0/20	0/20
1017	0/30	0/30	0/30	0/30	0/30

All fish were normal in appearance and behavior throughout the test period. The no mortality concentration and no observed effect concentration both were 1017 mg/l.

Conclusions

The 96-hour LC_{50} for DMH was determined to be greater than 1017 mg/l. (Author of report)

Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch): 1A
Remarks: Reliable without restriction; guideline study.

References

Murphy, D and G. J. Smith. 1992. A 96-hour static acute toxicity test with the bluegill (*Lepomis macrochirus*). Project number 298A-105. Wildlife International Ltd., Easton, MD, US.

Other

Last changed: January 22, 2002
Order number for sorting: 6d
Remarks:

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	Not stated

Method

Method/Guideline followed:	Registration of Pesticides in the United States, proposed rules published by EPA in Federal Register, Vol. 43, No. 132, July 10, 1978
Type:	Static
GLP:	No
Year:	1980
Species/Strain/Supplier:	Fathead minnow (*Pimephales promelas*)/Kurtz's Fish Hatchery near Elverson, PA
Analytical monitoring:	None
Exposure period:	96 hours
Statistical methods:	Litchfield-Wilcoxon
Remarks:	Ten juvenile fathead minnows/group were exposed to the test substance at dose levels of 0, 5000, 10000, 12500, 15000 and 20000 mg/l for 96 hours under static conditions. The test was conducted in duplicate. Fish averaged 0.51 g/fish and ranged from 21 to 31 mm total length. Water was dechlorinated Pittsburgh (West Penn Water Company) tap water. Pretreatment included activated carbon filters, and UV light. This treated water was used in the test animal culture/acclimation tanks and for preparation of stock solutions and test media. The test chambers used were 10 liter stainless steel tanks. Fish were monitored daily for mortality. Test animal behavior was observed and recorded throughout the test period. Surviving fish were sacrificed, weighed and measured at the end of the test. Temperature was measure daily for all dose levels and was found to be in the range of 17.3 to 17.9 ºC. Dissolved oxygen and pH were measured daily for all dose levels except 10,000 and 15,000 mg/l, and were found to be in the ranges of 6.2 to 9.0 mg/l and 6.2 to 6.8, respectively. Alkalinity, hardness and conductivity were measured at 0 and 96 hours for the 5,000 and 12,500 mg/l groups, and at 24 hours for the 20,000 mg/l group and were found to be in the ranges of 27 to 31 mg/l as $CaCO_3$, 98 to 110 mg/l as $CaCO_3$ and 245 to 270 umhos, respectively.

Results

Nominal concentrations (mg/l): 0, 5000, 10000, 12500, 15000 and 20000 mg/l
Measured concentrations (mg/l): Not measured
Unit: mg/l
Element value: 96-hour LC_{50} = 14,200 mg/l
(95% Confidence Limits = 13,200 to 15,300 mg/l)
Statistical results: Slope of line, fitted to mortality data plotted on log-probit paper = 1.13
Remarks: Cumulative mortalities were as follows:

	Time (hours)				
Dose level (mg/l)	0	24	48	72	96
0	0/20	0/20	0/20	0/20	0/20
5,000	0/20	0/20	0/20	0/20	0/20
10,000	0/20	0/20	0/20	0/20	0/20
12,500	0/20	3/20	3/20	3/20	3/20
15,000	0/20	11/20	13/20	14/20	14/20
20,000	0/20	20/20	20/20	20/20	20/20

Conclusions

The 96-hour LC_{50} for DMH was determined to be 14,200 mg/l. (Author of report)
Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch): 1A
Remarks: Reliable without restriction; guideline study.

References

Horne, J. D., R. D. Groover, M. Afzal, B. D. Lorenz, R. L. Shema and B. R. Oblad. 1980. 96-hour static bioassays using two Great Lakes Chemical Corporation compounds with three marine and three freshwater species. NUS Corporation, Northern Environmental Services Division, Pittsburgh, PA and Southern Environmental Services Division, Clear Lake, TX, US.

Other

Last changed: January 22, 2002
Order number for sorting: 7
Remarks:

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	Not stated

Method

Method/Guideline followed:	Registration of Pesticides in the United States, proposed rules published by EPA in Federal Register, Vol. 43, No. 132, July 10, 1978
Type:	Static
GLP:	No
Year:	1980
Species/Strain/Supplier:	Sheepshead minnow (*Cyprinodon variegates*)/spawned and reared at NUS Corporation's laboratory
Analytical monitoring:	None
Exposure period:	96 hours
Statistical methods:	Straight-line interpolation procedure described in Standard methods, 14th ed., APHA, 1975
Remarks:	Ten sheepshead minnows/group were exposed to the test substance at dose levels of 0, 1800, 2700, 4200, 6500 and 10,000 mg/l for 96 hours under static conditions. The test was conducted in duplicate. Fish were 45 ± 2 days old, averaged 0.13 g/fish, and ranged from 10 to 26 mm total length. Salt water consisted of a synthetic sea salt dissolved in deionized water and was used in the test animal culture/acclimation tanks and for preparation of stock solutions and test media. The test aquaria used were 1-gallon wide mouth jars. Fish were monitored daily for mortality. Test animal behavior was observed and recorded throughout the test period. Surviving fish were sacrificed, weighed and measured at the end of the test. Temperature, dissolved oxygen and salinity were measured daily and were found to be in the ranges of 20 to 26 ºC, 2.2 to 7.6 mg/l and 20 to 31 ppt, respectively.

Results

Nominal concentrations (mg/l):	0, 1800, 2700, 4200, 6500 and 10,000 mg/l
Measured concentrations (mg/l):	Not measured
Unit:	mg/l
Element value:	96-hour LC_{50} = 8100 mg/l
Statistical results:	The 95% confidence limits could not be determined using the analytical procedures employed.

Remarks: Cumulative mortalities were as follows:

Dose level (mg/l)	Time (hours)				
	0	24	48	72	96
0	0/20	0/20	0/20	0/20	0/20
1800	0/20	0/20	0/20	0/20	0/20
2700	0/20	0/20	0/20	0/20	0/20
4200	0/20	0/20	0/20	0/20	0/20
6500	0/20	0/20	0/20	0/20	0/20
10,000	0/20	1/20	6/20	18/20	20/20

Conclusions

The 96-hour LC_{50} for DMH was determined to be 8100 mg/l. (Author of report)

Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch): 1A

Remarks: Reliable without restriction; guideline study.

References

Horne, J. D., R. D. Groover, M. Afzal, B. D. Lorenz, R. L. Shema and B. R. Oblad. 1980. 96-hour static bioassays using two Great Lakes Chemical Corporation compounds with three marine and three freshwater species. NUS Corporation, Northern Environmental Services Division, Pittsburgh, PA and Southern Environmental Services Division, Clear Lake, TX, US.

Other

Last changed: January 22, 2002

Order number for sorting: 7

Remarks:

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	Not stated

Method

Method/Guideline followed:	Registration of Pesticides in the United States, proposed rules published by EPA in Federal Register, Vol. 43, No. 132, July 10, 1978
Type:	Static
GLP:	No
Year:	1980
Species/Strain/Supplier:	Rainbow trout *(Salmo gairdneri)/*from a commercial hatchery near Elverson, PA
Analytical monitoring:	None
Exposure period:	96 hours
Statistical methods:	Litchfield-Wilcoxon
Remarks:	Ten juvenile rainbow trout/group were exposed to the test substance at dose levels of 0, 5000, 10000, 12500, 15000 and 25000 mg/l for 96 hours under static conditions. The test was conducted in duplicate. Fish averaged 2.18 g/fish and ranged from 32 to 58 mm total length. Water was dechlorinated Pittsburgh (West Penn Water Company) tap water. Pretreatment included activated carbon filters, and UV light. This treated water was used in the test animal culture/acclimation tanks and for preparation of stock solutions and test media. The test chambers used were 18.9 liter glass containers. Fish were monitored daily for mortality. Test animal behavior was observed and recorded throughout the test period. Surviving fish were sacrificed, weighed and measured at the end of the test. Temperature was measured daily for all dose levels and was found to be in the range of 9.2 to 10.9 ºC. Dissolved oxygen and pH were measured daily for all dose levels except 10,000 and 15,000 mg/l, and were found to be in the ranges of 2.2 to 10.6 mg/l and 6.2 to 6.8, respectively. Alkalinity, hardness and conductivity were measured at 0 and 96 hours for the 5,000 and 12,500 mg/l groups, and at 72 hours for the 25,000 mg/l group, and were found to be in the ranges of 28 to 33 mg/l as $CaCO_3$, 102 to 116 mg/l as $CaCO_3$ and 200 to 280 umhos, respectively.

Results

Nominal concentrations (mg/l): 0, 5000, 10000, 12500, 15000 and 25000 mg/l
Measured concentrations (mg/l): Not measured
Unit: mg/l
Element value: 96-hour LC_{50} = 12,700 mg/l
(95% Confidence Limits = 11,300 to 14,200 mg/l)
Statistical results: Slope of line, fitted to mortality data plotted on log-probit paper = 1.20
Remarks: Cumulative mortalities were as follows:

	Time (hours)				
Dose level (mg/l)	0	24	48	72	96
0	0/20	0/20	0/20	0/20	0/20
5,000	0/20	0/20	0/20	0/20	0/20
10,000	0/20	0/20	0/20	0/20	2/20
12,500	0/20	0/20	0/20	1/20	8/20
15,000	0/20	0/20	3/20	11/20	17/20
25,000	0/20	9/20	17/20	20/20	20/20

Conclusions

The 96-hour LC_{50} for DMH was determined to be 12,700 mg/l. (Author of report)
Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch): 1A
Remarks: Reliable without restriction; guideline study.

References

Horne, J. D., R. D. Groover, M. Afzal, B. D. Lorenz, R. L. Shema and B. R. Oblad. 1980. 96-hour static bioassays using two Great Lakes Chemical Corporation compounds with three marine and three freshwater species. NUS Corporation, Northern Environmental Services Division, Pittsburgh, PA and Southern Environmental Services Division, Clear Lake, TX, US.

Other

Last changed: January 22, 2002
Order number for sorting: 7
Remarks:

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	NA

Method

Method/Guideline followed:	EPIWIN (v 3.10) ECOSAR Submodel (V 0.99g)
Type:	NA
GLP:	NA
Year:	2003
Species/Strain/Supplier:	Fish
Analytical monitoring:	NA
Exposure period:	96-hour
Statistical methods:	NA
Remarks:	The EPIWIN model was run using the following measured physical chemical properties: melting point = 178°C and octanol-water partition coefficient, Log K_{ow} = 0.35.

Results

Nominal concentrations (mg/l):	NA
Measured concentrations (mg/l):	NA
Unit:	mg/l
Element value:	96-hour LC_{50} = 1252 mg/l
Statistical results:	NA
Remarks:	Following are the results from the model:

Conclusions	The 96-hour LC_{50} for DMH was calculated as 1252 mg/l.
Remarks:	The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch):	2
Remarks:	Reliable with restrictions; model data.

References	US EPA. 2000. ECOSAR Program, Risk Assessment Division (7403). US Environmental Protection Agency, Washington, DC.

Other

Last changed:	May 20, 2003
Order number for sorting:	56
Remarks:	

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	Not stated

Method

Method/Guideline followed:	Registration of Pesticides in the United States, proposed rules published by EPA in Federal Register, Vol. 43, No. 132, July 10, 1978
Test type:	Static
GLP:	No
Year:	1980
Analytical procedures:	None
Species/Strain:	American oyster (*Crassostrea virginica*)/from a commercial lease-bed operator near Smith Point, TX
Test details:	Static
Statistical methods:	Litchfield-Wilcoxon
Remarks:	Ten American oysters/group were exposed to the test substance at dose levels of 0, 10400, 12250, 14500, 17000 and 20000 mg/l for 96 hours under static conditions. The test was conducted in duplicate. Individual oysters averaged 1.5 to 3.0 inches (largest shell dimension) and the average wet-tissue weight was 3.8 g. Salt water consisted of a synthetic sea salt dissolved in deionized water and was used in the test animal culture/acclimation tanks and for preparation of stock solutions and test media. The test aquaria used were 10-gallon aquaria. Oysters were monitored daily for mortality. Test animal behavior was observed and recorded throughout the test period. Surviving oysters were sacrificed, weighed and measured at the end of the test. Temperature, dissolved oxygen and salinity were measured daily and were found to be in the ranges of 20 to 24 ºC, 5.3 to 7.1 mg/l and 20 to 38 ppt, respectively.

Results

Nominal concentrations (mg/l):	0, 10400, 12250, 14500, 17000 and 20000 mg/l
Measured concentrations (mg/l):	Not measured
Unit:	mg/l
LC_{50} (96-hour):	13,300 mg/l (95% Confidence Limits = 10,300 to 17,500 mg/l)

Remarks: Cumulative mortalities were as follows:

Dose level (mg/l)	Time (hours)				
	0	24	48	72	96
0	0/20	0/20	0/20	0/20	0/20
10,400	0/20	0/20	0/20	1/20	4/20
12,250	0/20	0/20	3/20	4/20	8/20
14,500	0/20	1/20	5/20	10/20	15/20
17,000	0/20	3/20	11/20	13/20	15/20
20,000	0/20	0/20	6/20	11/20	11/20

Conclusions

The 96-hour LC_{50} for DMH was determined to be 13,300 mg/l. (Author of report)

Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch): 1A

Remarks: Reliable without restriction; guideline study.

References

Horne, J. D., R. D. Groover, M. Afzal, B. D. Lorenz, R. L. Shema and B. R. Oblad. 1980. 96-hour static bioassays using two Great Lakes Chemical Corporation compounds with three marine and three freshwater species. NUS Corporation, Northern Environmental Services Division, Pittsburgh, PA and Southern Environmental Services Division, Clear Lake, TX, US.

Other

Last changed: January 22, 2002

Order number for sorting: 7

Remarks:

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	Not stated

Method

Method/Guideline followed:	Registration of Pesticides in the United States, proposed rules published by EPA in Federal Register, Vol. 43, No. 132, July 10, 1978
Test type:	Static
GLP:	No
Year:	1980
Analytical procedures:	None
Species/Strain:	Water flea (*Daphnia magna*)/from Wards Natural Science Estab., Inc.
Test details:	Static
Statistical methods:	Litchfield-Wilcoxon
Remarks:	*Daphnia* females' brood were pipetted into 250 ml beakers containing the test substance at dose levels of 0, 3000, 5000, 7000, 10000 and 15000 mg/l until ten test organisms were added to each beaker. *Daphnia* were exposed to the test substance for 48 hours under static conditions. The test was conducted in duplicate. First instars were used in the test. Water was dechlorinated Pittsburgh (West Penn Water Company) tap water. Pretreatment included activated carbon filters, and UV light. This treated water was used in the test animal culture/acclimation tanks and for preparation of stock solutions and test media. The test chambers used were 25 ml glass beakers. *Daphnia* were monitored daily for mortality. Test animal behavior was observed and recorded throughout the test period. Surviving *Daphnia* were sacrificed, weighed and measured at the end of the test. Temperature, dissolved oxygen and salinity were measured daily and were found to be in the ranges of 22 to 26 ºC, 1.4 to 7.5 mg/l and 20 to 28 ppt, respectively.

Results

Nominal concentrations (mg/l):	0, 3000, 5000, 7000, 10000 and 15000 mg/l
Measured concentrations (mg/l):	Not measured
Unit:	mg/l
LC_{50} (48-hour):	6200 mg/l (95% Confidence Limits = 5300 to 7300 mg/l)

Remarks: Cumulative mortalities were as follows:

Dose level (mg/l)	Time (hours)				
	0	12	24	36	48
0	0/20	0/20	0/20	0/20	0/20
3,000	0/20	0/20	0/20	0/20	0/20
5,000	0/20	0/20	1/20	6/20	7/20
7,000	0/20	0/20	5/20	9/20	11/20
10,000	0/20	9/20	12/20	17/20	20/20
15,000	0/20	20/20	20/20	20/20	20/20

Conclusions

The 48-hour LC_{50} for DMH was determined to be 6200 mg/l. (Author of report)

Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch): 1A

Remarks: Reliable without restriction; guideline study.

References

Horne, J. D., R. D. Groover, M. Afzal, B. D. Lorenz, R. L. Shema and B. R. Oblad. 1980. 96-hour static bioassays using two Great Lakes Chemical Corporation compounds with three marine and three freshwater species. NUS Corporation, Northern Environmental Services Division, Pittsburgh, PA and Southern Environmental Services Division, Clear Lake, TX, US.

Other

Last changed: January 22, 2002

Order number for sorting: 7

Remarks:

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	Not stated

Method

Method/Guideline followed:	Methods for acute toxicity tests with fish, macroinvertebrates and amphibians, EPA-600/3-75-009, April 1975; Bioassay procedures for the ocean disposal permit program, EPA-600/9-78-010, March 1978; Methods for measuring the acute toxicity of effluents to aquatic organisms, EPA-600/4-78-012, Revised July 1978; and Standard methods, 14th ed., APHA, 1975.
Test type:	Static
GLP:	No
Year:	1980
Analytical procedures:	None
Species/Strain:	Grass shrimp (*Palaemonetes pugio*)/from Dickinson Bayou, TX
Test details:	Static
Statistical methods:	Litchfield-Wilcoxon
Remarks:	Ten grass shrimp/group were exposed to the test substance at dose levels of 0, 760, 1170, 1800, 2700, 4200, 6500 and 10,000 mg/l for 96 hours under static conditions. The test was conducted in duplicate. Shrimp averaged 0.18 g/individual and ranged from 17 to 38 mm total length (rostrum to telson). Salt water consisted of a synthetic sea salt dissolved in deionized water and was used in the test animal culture/acclimation tanks and for preparation of stock solutions and test media. The test aquaria used were 1-gallon wide mouth jars. Shrimp were monitored daily for mortality. Test animal behavior was observed and recorded throughout the test period. Surviving shrimp were sacrificed, weighed and measured at the end of the test. Temperature, dissolved oxygen and salinity were measured daily and were found to be in the ranges of 22 to 26ºC, 1.4 to 7.5 mg/l and 20 to 28 ppt, respectively.

Results

Nominal concentrations (mg/l):	0, 760, 1170, 1800, 2700, 4200, 6500 and 10,000 mg/l
Measured concentrations (mg/l):	Not measured
Unit:	mg/l
LC_{50} (96-hour):	1300 mg/l (95% Confidence Limits = 1100 to 1600 mg/l)

Remarks: Cumulative mortalities were as follows:

Dose level (mg/l)	Time (hours)				
	0	24	48	72	96
0	0/20	0/20	0/20	1/20	1/20
760	0/20	0/20	1/20	1/20	3/20
1170	0/20	0/20	1/20	5/20	7/20
1800	0/20	7/20	14/20	15/20	16/20
2700	0/20	11/20	18/20	18/20	20/20
4200	0/20	17/20	20/20	20/20	20/20
6500	0/20	19/20	20/20	20/20	20/20
10,000	0/20	20/20	20/20	20/20	20/20

Conclusions

The 96-hour LC_{50} for DMH was determined to be 1300 mg/l. (Author of report)

Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch): 1A

Remarks: Reliable without restriction; guideline study.

References

Horne, J. D., R. D. Groover, M. Afzal, B. D. Lorenz, R. L. Shema and B. R. Oblad. 1980. 96-hour static bioassays using two Great Lakes Chemical Corporation compounds with three marine and three freshwater species. NUS Corporation, Northern Environmental Services Division, Pittsburgh, PA and Southern Environmental Services Division, Clear Lake, TX, US.

Other

Last changed: January 22, 2002

Order number for sorting: 7

Remarks:

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	Non-radiolabeled: = 97.1; Radiochemical purity: = 98.5%

Method

Method/Guideline followed:	US EPA, Series 72 of Pesticide Assessment Guidelines, FIFRA Subdivision E Hazard Evaluation: Wildlife and Aquatic Organisms, EPA 540/9-82-024, October 1982 and ASTM Standard E 729-88, Standard Practice for Conducting Acute Toxicity Tests with Fishes, Macroinvertebrates, and Amphibians, American Society for Testing and Materials, 1988
Test type:	Static
GLP:	Yes
Year:	1991
Analytical procedures:	Yes
Species/Strain:	Saltwater mysid (*Mysidopsis bahia*)
Test details:	Static
Statistical methods:	None
Remarks:	Ten juvenile saltwater mysids per concentration were exposed to mean measured test concentrations of 0 (saltwater) and 921.7 mg dimethylhydantoin (DMH)/l for 96 hours under static conditions. The test substance was tested in triplicate, while the control was tested in duplicate. Mysids that were less than 24 hours old were obtained from Wildlife International Ltd. cultures, Easton, MD. A stock solution of the test substance was prepared by sonicating DMH in saltwater. The dilution water was saltwater collected at Indian River Inlet, Delaware, and had a mean salinity and pH of 25% and 8.0, respectively. Ambient room light from fluorescent tubes was used to illuminate the test systems. The light intensity during the experiment was approximately 70 footcandles at the surface of the water and the photoperiod was 16 hours light/8 hours dark. Test chambers were 2-liter glass beakers filled with 1.2 liters of test solution. The depth of the test solution in each test chamber was approximately 10.5 cm. Salinity and pH of the control water at the beginning to the test were measured as 25% and 8.2, respectively. Daily measurements of dissolved oxygen and pH of the control and test solutions ranged from 4.8 to 6.8 mg/l and 7.6 to 8.2, respectively. Temperature measurements made at the beginning and end of the test ranged from approximately 25.2 to 25.9 ºC. Observations of mortality and treatment-related effects were made at 20, 24, 48, 72 and 96 hours. Samples of the test solution were analyzed to verify concentrations of the test substance by radioactivity.

Results

Nominal concentrations (mg/l): 0 and 1000 mg/l
Measured concentrations (mg/l): 0 and 921.7 mg/l
Unit: mg/l
LC_{50} (96-hour): > 921.7 mg/l
Remarks: Cumulative mortality was as follows:

Dose level (mg/l)	Time (hours)				
	20	24	48	72	96
0	0/20	0/20	0/20	0/20	0/20
921.7	0/30	0/30	8/30	8/30	9/30

All surviving mysids were normal in appearance and behavior throughout the test period.

Conclusions

The 96-hour LC_{50} for DMH was determined to be greater than 921.7 mg/l. (Author of report)

Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch): 1A
Remarks: Reliable without restriction; guideline study.

References

Murphy, D and G. J. Smith. 1992. A 96-hour static acute toxicity test with the saltwater mysid (*Mysidopsis bahia*). Project number 298A-106. Wildlife International Ltd., Easton, MD, US.

Other

Last changed: January 22, 2002
Order number for sorting: 8a
Remarks:

4.5.1 CHRONIC TOXICITY TO FISH

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	Non-radiolabeled: > 99.9%; Radiochemical purity: = 98.5%

Method

Method/Guideline followed:	US EPA FIFRA Subdivision E, Series 72-4
Type:	Flow-through
GLP:	Yes
Year:	1992-1993
Species/Strain/Supplier:	*Pimephales promelas* (Fathead minnow)/Wildlife International Ltd. cultures
Endpoint:	Length of fish, and wet and dry weight of fish
Analytical monitoring:	Yes
Exposure period:	5-day hatching period and 28-day post hatching period
Statistical methods:	Discrete-variable data (e.g., hatching success and survival) were transformed using the arc-sine-square root transformation prior to any statistical analysis of the data. Bartlett's test for homogeneity of variances and the Chi-square test for normality was performed followed by an analysis of variance for post hatch survival. The hatching success data passed the Chi-square test but failed the Bartlett's test; therefore, a Kruskal Wallis test was performed. Continuous variable data: Bartlett's test for homogeneity of variances failed, so a nonparametric Mann-Whitney test was performed.
Remarks:	Dilution water used in the test was freshwater obtained from a well 45 meters deep on the Wildlife International Ltd. site. The well water was characterized as medium-hard water. Dilution water chemistry parameters were measured during 28 day test period with the following results: conductivity ranged from 350 to 360 µmhos/cm, hardness ranged from 140 to 144 mg/l as $CaCO_3$, alkalinity ranged from 182 to 190 mg/l as $CaCO_3$, pH ranged from 7.6 to 7.9, dissolved oxygen content ranged from 7.0 to 8.3 mg/L and temperature ranged from 24.6 to 25.0 °C. The test chambers were 9-liter glass aquaria filled with approximately 7.5 liters of test solution. The depth of the test water in the test chambers was approximately 16.8 cm. Forty fathead minnow embryos (approximately 4.5 to 22-hours old) per replicate (two replicates at each concentration) were exposed to mean measured test concentrations of 0, 6.8, 14, 29, 55 and 116 ppm dimethylhydantoin (DMH). Observations of mortality and other signs of toxicity were made twice daily during the embryo exposure period. After hatching, larvae were observed daily. Samples of the test solution were analyzed to verify concentrations of the test substance by radioactivity.

Results

Nominal concentrations (ppm):	0, 7.5, 15, 30, 60 and 120 ppm
Measured concentrations (ppm):	0, 6.8, 14, 29, 55 and 116 ppm
Unit:	ppm
Statistical results:	See below
NOEC	14 ppm
LOEC	29 ppm
Remarks:	There were no treatment-related effects upon mean hatching success or on the survival of fathead minnow larvae during the 28-day post hatch exposure period at any concentration of DMH tested. Based upon the hatching success and survival data, the NOEC was 116 ppm and the LOEC was >116 ppm. The mean length of the fish in the 0, 6.8, 14, 29, 55 and 116 ppm groups at study termination were 18.3, 17.8, 18.7, 17.8, 17.6 and 17.9 cm, respectively. The mean wet weight of the fish in the 0, 6.8, 14, 29, 55 and 116 ppm groups at study termination were 66.5, 67.8, 72.4, 65.2, 62.0 and 65.5 mg, respectively, and the mean dry weight of the fish in the 0, 6.8, 14, 29, 55 and 116 ppm groups at study termination were 14.1, 14.2, 14.2, 12.5, 11.4 and 11.8 mg, respectively. There were no statistically significant differences in the mean total length or mean wet weight of fish exposed to any concentration of DMH. However, fish dry weights were significantly decreased in the 29, 55 and 116 ppm treatment groups when compared to the control group. This reduction appeared to be treatment related.

Conclusions

Based on measurements of length, wet weight and dry weight of fathead minnows, the NOEC and LOEC of DMH were 14 and 29 ppm, respectively. The maximum acceptable toxicant concentration was 20 ppm DMH. (Author of report)

Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch):	1A
Remarks:	Reliable without restriction; guideline study.

References

Holmes, C. M and J. P. Swigert. 1993. An early life-stage toxicity test with 5,5-dimethylhydantoin in the Fathead minnow (*Pimephales promelas*). Project number 289A-111. Wildlife International Ltd., Easton, MD, US.

Other

Last changed: January 22, 2002
Order number for sorting: 6
Remarks:

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	Non-radiolabeled: > 99.9%; Radiochemical purity: = 98.5%

Method

Method/Guideline followed:	US EPA FIFRA Subdivision E, Series 72-4 and OECD guideline 202
Test type:	Flow-through
GLP:	Yes
Year:	1992-1993
Analytical procedures:	Yes
Species/Strain:	*Daphnia magna*
Endpoint:	Survival, growth and reproduction
Exposure period:	21 days
Statistical methods:	Survival data were analyzed using the Mann-Whitney test. Reproduction, length, and dry weight data were tested for normality and homogeneity using the Chi-square test and Bartlett's test for homogeneity of variances, respectively, followed by a t-test when appropriate.
Remarks:	Dilution water used in the test was freshwater obtained from a well 45 meters deep on the Wildlife International Ltd. site. The well water was characterized as medium-hard water. Dilution water chemistry parameters were measured during 21-day test period with the following results: conductivity ranged from 330 to 335 µmhos/cm, hardness ranged from 132 to 136 mg/l as $CaCO_3$, alkalinity ranged from 182 to 184 mg/l as $CaCO_3$, pH ranged from 7.8 to 8.1, dissolved oxygen content ranged from 7.8 to 8.7 mg/L and temperature ranged from 19.7 to 20 °C. The test compartments were constructed from 300 ml glass beakers having a diameter of approximately 6.5 cm and a height of approximately 12 cm. A total of 22 *Daphnia* per concentration were exposed to mean measured test concentrations of 0, 15.7, 25.3, 42.2, 70.9 and 116 ppm dimethylhydantoin (DMH) for 21 days. *Daphnia* were less than 24 hours old at test initiation. All daphnia were observed for survival, and the criteria for death included the following: absence of heartbeat, white opaque coloration, lack of movement of appendages and lack of response to gentle prodding. At the end of the test, the length and dry weight of each surviving first-generation daphnid were measured. Samples of the test solution were analyzed to verify concentrations of the test substance by radioactivity.

Results

Nominal concentrations (ppm):	0, 15.6, 25.9, 43.2, 72.0 and 120 ppm
Measured concentrations (ppm):	0, 15.7, 25.3, 42.2, 70.9 and 116 ppm
Unit:	ppm
NOEC:	70.9 ppm
LOEC:	116 ppm
Remarks:	Mortality of the daphnids in the control group was 9% (2 of 22). Mortality of the daphnids in the 15.7, 25.3, 42.2 and 70.9 ppm groups ranged from 5 to 14% (1 to 3 of 22) and was considered similar to that of the control group. Mortality of the daphnids in the 116 ppm group was 55% (12 of 22) and was statistically different from the control group. Based on survival and clinical observations data, the NOEC for DMH was 70.9 ppm and the LOEC for DMH was 116 ppm. Mean neonatal production in the 0, 15.7, 25.3, 42.2, 70.9 and 116 ppm groups was 69, 104, 80, 85, 94 and 58 neonates per daphnid, respectively. Although the number of neonates per daphnid in the 116 ppm group was lower than any other treated group, it was not statistically different from the control group and therefore was not considered to be treatment-related. When compared to the control group, there were no significant decreases in the length or dry weight of daphnids at any of the concentrations of DMH tested.

Conclusions

	Based on neonate production and measurements of length and dry weight the NOEC for DMH was 116 ppm and the LOEC for DMH was >116 ppm. The maximum acceptable toxicant concentration was 90.7 ppm DMH. (Author of report)
Remarks:	The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch):	1A
Remarks:	Reliable without restriction; guideline study.

References

Zelinka, E. A., C. M. Holmes and J. P. Swigert. 1993. A flow-through life-cycle toxicity test with 5,5-dimethylhydantoin in the cladoceran (*Daphnia magna*). Project number 289A-110. Wildlife International Ltd., Easton, MD, US.

Other

Last changed:	January 22, 2002
Order number for sorting:	8
Remarks:	

5.1.1 ACUTE ORAL TOXICITY

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	Not stated

Method

Method/guideline followed:	Not stated
Type:	Oral LD_{50}
GLP:	Yes
Year:	1979-1980
Species/Strain:	Rat/Sprague-Dawley
Sex:	Male and female
No. of animals per sex per dose:	5
Vehicle:	Not stated
Route of administration:	Gavage
Remarks:	Ten young adult rats (five males and five females) were administered the test substance via gavage at a dose level of 5,000 mg/kg. Males and females weighed 151 to 159 g and 131 to 146 g, respectively, and were fasted for approximately 16 hours prior to dosing. Rats were observed for signs of toxicity and mortality at frequent intervals during the day of dosing, and twice daily thereafter for a total of 14 days. Body weights were taken on days 0, 7 and 14. At the end of the 14-day observation period, surviving rats were sacrificed and gross necropsies were performed.

Results

Value:	LD_{50} > 5,000 mg/kg
Number of deaths:	0/10
Remarks:	No signs of toxicity were observed in any of the males throughout the study. On the day of dosing, two females were observed to be slightly to moderately lethargic and slight lacrimation was noted, which subsided by day 1. The females were observed to be normal throughout the remainder of the study.

Conclusions	The acute oral LD_{50} for DMH was determined to be greater than 5,000 mg/kg. (Author of report)
Remarks:	The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch):	1B
Remarks:	Reliable without restriction; comparable to guideline study.

References

Mayhew, D. A. 1980. Acute oral toxicity in rats. Project number WIL-79298. WIL Research Laboratories, Inc., Cincinnati, OH, US.

Other

Last changed:	January 22, 2002
Order number for sorting:	10
Remarks:	

5.1.2 ACUTE INHALATION TOXICITY

Test Substance

Identity:	Dantoin DMH (CAS RN 77-71-4; 5,5-Dimethylhydantoin)
Purity:	Not stated

Method

Method/guideline followed:	Not stated
Type:	Acute inhalation toxicity
GLP:	No
Year:	1978
Species/Strain:	Rat/strain not specified
Sex:	Male and female
No. of animals per sex per dose:	5
Vehicle:	Not stated
Route of administration:	Inhalation
Remarks:	A 1-hour exposure at a nominal exposure concentration of 14.68 mg/l. At approximately 30 minutes into the exposure period, the dust feed mechanism jammed and the exposure was suspended for five minutes while the dust feed was cleared. The animals were observed at 15-minute intervals throughout the exposure period, upon removal from the exposure chamber, hourly for four hours post-exposure, and daily thereafter for 14 days. Body weights were recorded on Day 0 (prior to exposure), 1, 2, 4, 7 and 14. On day 14 all animals were killed and gross necropsy examinations were performed.

Results

Value:	LC_{50} > 14.68 mg/l
Number of deaths:	0/10
Remarks:	Labored breathing was observed in one animal at 53 minutes of exposure. Signs observed in the animals upon removal were yellow staining of the anogenital fur (7 of 10 rats), red and mucoid nasal discharge (2 of 10 rats), and dry rales (1 of 10 rats). All signs, except dry rales, subsided by 4 hours post-exposure. Observation over the 14-day post-exposure period included dry rales (7 of 10 rats) red and mucoid nasal discharge (5 of 10 rats) and chromodacryorrhea (1 of 10 rats). One female lost weight post-exposure and did not regain her original day 0 body weight. All other animals gained weight during the 14-day observation period. Necropsy examinations revealed lung discoloration in five of ten rats and liver discoloration in three of ten rats.
Conclusions	Signs of possible immediate and residual toxicity were observed in test animals exposed to the test substance for a 1-hour exposure at a nominal exposure concentration of 14.68 mg/l. (Author of report)

Remarks: The acute inhalation LC_{50} was not provided. This study is included to provide additional information on the acute toxicity of the test substance. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch): 2D

Remarks: Reliable with restrictions; data are reliable but report lacks details

References

Thackars, J. W. and W. E. Rinehard. 1978. An acute inhalation toxicity study of dantoin DMH in the rat. Project number 77-1978. Bio/dynamics Inc., East Millstone, New Jersey, US.

Other

Last changed: January 22, 2002

Order number for sorting: 12

Remarks:

5.1.3 Acute Dermal Toxicity

Test Substance

Identity:	Dantoin DMH (CAS RN 77-71-4; 5,5-Dimethylhydantoin)
Purity:	Not stated

Method

Method/guideline followed:	Federal Hazardous Substances Control Act (FHSA), 16 CFR 1500.40
Type:	LD_{50} limit test
GLP:	No
Year:	1979
Species/Strain:	New Zealand White
Sex:	Male and female
No. of animals per sex per dose:	3
Vehicle:	None
Route of administration:	Dermal
Remarks:	The weight range for the rabbits used in this study was 2.5 to 3.5 kg. The skin of half of the rabbits (one male and two females) was abraded. A single dermal dose of 20,000 mg/kg was applied to the clipped skin, covered with gauze and a plastic sleeve to ensure contact of the test material for a 24-hour period. Following the 24-hour exposure period, the sleeves and gauze wrappings were removed and the animals were observed for mortality, skin response and general behavior for 14 days. Body weights were recorded at initiation and termination of the study.

Results

Value:	LD_{50} > 20,000 mg/kg
Number of deaths:	Abraded skin: 0/3 Intact skin: 0/3
Remarks:	A slight decrease in body weight was observed in one abraded animal and failure to gain weight was exhibited by two non-abraded animals. Well-defined erythema and very slight edema were observed at 24 hours post dose in three animals (1 abraded female and 2 non-abraded males). The remaining three animals (1 abraded female, 1 abraded male and 1 non-abraded female) exhibited very slight erythema. In-life signs observed within 24 hours of dosing included decreased motor activity and ataxia. Other signs exhibited sporadically throughout the study included fecal staining/soft stool, nasal discharge, ocular discharge, collar removed by animal, piloerection, increased motor activity and aggressive behavior.

Conclusions The acute dermal LD_{50} for DMH was determined to be greater than 20,000 mg/kg. (Author of report)

Remarks:	The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch):	1a
Remarks:	Reliable without restriction; guideline study.

References

Auletta, C. S. 1979. Acute dermal toxicity study in rabbits. Project number 4737-77. Bio/dynamics Inc., East Millstone, New Jersey, US.

Other

Last changed:	January 22, 2002
Order number for sorting:	13
Remarks:	

5.1.3 ACUTE DERMAL TOXICITY

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	Not stated

Method

Method/guideline followed:	Not stated
Type:	Dermal LD_{50}
GLP:	Yes
Year:	1979-1980
Species/Strain:	Rabbit/New Zealand White
Sex:	Male and female
No. of animals per sex per dose:	4
Vehicle:	Physiological saline
Route of administration:	Dermal
Remarks:	Eight albino rabbits (four males and four females) were administered the test substance dermally at a dose level of 3000 mg/kg. Rabbits were 10 to 13 weeks old and weighed 2.75 to 3.35 kg. Twenty-four hours prior to the application of the test substance the hair was clipped from the back and flanks of each rabbit. The exposure sites of two rabbits (one male and one female) were lightly abraded. The exposure area was occluded. The rabbits were exposed to the test substance for 24 hours. All rabbits were observed for systemic toxicity and skin irritation for 14 days following the 24-hour exposure period. Body weights were recorded for each rabbit before dosing and at 7 and 14 days post dose. At the end of the 14-day observation period, all rabbits were killed and gross necropsies were performed.

Results

Value:	$LD_{50} > 3000$ mg/kg
Number of deaths:	0/8
Remarks:	Slight erythema was noted in one female rabbit for the first two days following the exposure period. No other irritation was noted throughout the study. During the first two or three days of the observation period, most of the rabbits exhibited a creamy nasal discharge, these signs reappeared intermittently throughout the remainder of the observation period. Watery eye discharge was noted daily in one female rabbit. A gross necropsy revealed no significant gross pathological findings in any of the rabbits.

Conclusions The acute dermal LD_{50} for DMH was determined to be greater than 3000 mg/kg. (Author of report)

Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch): 1B

Remarks: Reliable without restriction; comparable to guideline study.

References

Mayhew, D. A. 1980. Acute percutaneous toxicity study in rabbits. Project number WIL-79298. WIL Research Laboratories, Inc., Cincinnati, OH, US.

Other

Last changed: January 22, 2002

Order number for sorting: 14

Remarks:

5.4 REPEATED DOSE TOXICITY

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	Not stated
Remarks:	Test substance considered to be 100% pure for dose calculations.

Method

Method/Guideline followed:	FIFRA, Section 82-1 and TSCA Part 798, Subpart C, 798.2650 and OECD 407
Test type:	Oral
GLP:	Yes
Year:	1989
Species:	Mouse
Strain:	CD®-1
Route of administration:	Oral feed
Duration of test:	28 days
Doses/concentration levels:	0, 1000, 5000, 10000 and 50000 ppm
Sex:	Male and female
Exposure period:	28 days
Frequency of treatment:	Continuous
Control group and treatment:	Yes, basal diet
Postexposure observation period:	None
Statistical methods:	One-way analysis of variance, followed by Dunnett's Test
Remarks:	Groups of mice (five males and five females) were administered the test substance in the diet at concentrations of 1000, 5000, 10000 and 50000 ppm for a period of four weeks. A concurrent control group was administered the basal diet alone. Mice were approximately 43 days old at study initiation. All mice were observed twice daily for mortality and signs of overt toxicity. Detailed physical examinations, individual body weights and food consumption were recorded weekly. The following clinical pathology parameters were evaluated for all mice after 28 consecutive days of test substance administration: hematology (including differential white blood cell count, platelet estimate, red blood cell morphology, white cell estimate and hemoglobin estimate) and serum chemistry (including urea nitrogen, creatinine, total bilirubin, aspartate aminotransferase, alanine aminotransferase and serum alkaline phosphatase). Clinical necropsy examinations were performed at the scheduled sacrifice and the following organs were weighed: brain, kidneys, liver, ovaries and testes. A microscopic examination was conducted on the following tissues from mice in the control and 50,000 ppm groups: adrenals, bone with marrow, brain, duodenum, gallbladder, heart, kidneys, liver, lungs, ovaries with oviducts, peripheral sciatic nerve, pituitary, spinal cord, spleen, stomach, testes with epididymides, thyroid and all gross lesions. Evaluation

of tissues for the 1000, 5000 and 10,000 ppm groups was limited to kidneys and liver.

Results

NOAEL (NOEL): NOAEL = 50,000 ppm
LOAEL (LOEL): None
Actual dose received: (mg/kg/day)

	1000 ppm	5000 ppm	10,000 ppm	50,000 ppm
Males	172 to 185	900 to 984	1592 to 1756	14254 to 9106
Females	244 to 317	1167 to 1319	2549 to 3366	13829 to 16726

Toxic response/effects: Described below
Statistical results: Described below
Remarks: All animals survived to the scheduled sacrifice. No compound-related effect was apparent at any dose level on survival, clinical observations, body weight data, food consumption, hematology parameters, macroscopic or microscopic necropsy findings, or organ weight data. In the serum chemistry parameters, mean serum alkaline phosphatase was statistically significantly increased in the 50,000 ppm group females. However, based on the apparent wide range of biological variability in serum alkaline phosphatase values exhibited in the control group, and the limited sample size in this study, this increase may not be toxicologically meaningful.

Conclusions Systemic toxicity was not apparent at any dose level. The only potential effect of DMH administered for 28 days to mice was increased serum alkaline phosphatase in the female mice at 50,000 ppm. (Author of report)
Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch): 1A
Remarks: Reliable without restriction; guideline study.

References

Naas, D. J. 1991. 28-day dietary study in mice with DMH. Study number WIL-12164. WIL Research Laboratories, Inc., Ashland, OH, US.

Other

Last changed: January 22, 2002
Order number for sorting: 15
Remarks:

5.4 REPEATED DOSE TOXICITY

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	Not stated

Method

Method/Guideline followed:	Not stated
Test type:	Oral
GLP:	Yes
Year:	1982
Species:	Rat
Strain:	CD® Sprague-Dawley
Route of administration:	Oral gavage
Duration of test:	4 weeks
Doses/concentration levels:	2500, 5000, 9000 or 12,500 mg/kg/day
Sex:	Male and female
Exposure period:	4 weeks
Frequency of treatment:	Once daily
Control group and treatment:	Yes, 0.5% methylcellulose
Postexposure observation period:	None
Statistical methods:	Not stated
Remarks:	Groups of rats (five males and five females) were administered the test substance in 0.5% methylcellulose via oral gavage at concentrations of 2500, 5000, 9000 or 12,500 mg/kg once daily for a period of four weeks. A concurrent control group was administered 0.5% methylcellulose alone. Individual doses were adjusted weekly following body weight measurement. All rats were observed twice daily for general appearance, behavior, toxic signs, morbidity or mortality. Individual body weights and food consumption were recorded weekly.

Results

NOAEL (NOEL):	NOEL = 5000 mg/kg/day
LOAEL (LOEL):	LOEL = 9000 mg/kg/day
Actual dose received:	2500, 5000, 9000 or 12,500 mg/kg
Toxic response/effects:	Described below
Statistical results:	Described below
Remarks:	One female rat in the high dose group was found dead on day 1 and one female rat in the high dose group was sacrificed moribund. Marked distension of the stomach was noted at the gross necropsy of these two rats. A low incidence of lethargy and salivation were noted at the two high dose levels and appeared to be test-substance related. Transient effects were noted on body weights and food consumption in high dose rats during the first two weeks of dosing. At study termination a gross necropsy revealed a uterus filled with fluid in two high dose females; otherwise, no apparent findings

related to the test substance were noted. Doses of 2000, 5000 and 10,000 mg/kg were recommended for use in the subsequent 90-day oral dosing study.

Conclusions

The oral NOEL for DMH in this four-week dose range-finding study was 5000 mg/kg/day. (Author of report)

Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch): 1B

Remarks: Reliable without restriction; comparable to guideline study.

References

Mayhew, D. A. 1982. Four week range-finding oral gavage study in rats with dimethylhydantoin (DMH). Project number WIL-81164. WIL Research Laboratories, Inc., Cincinnati, OH, US.

Other

Last changed: January 22, 2002

Order number for sorting: 16

Remarks:

5.4 REPEATED DOSE TOXICITY

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	Not stated

Method

Method/Guideline followed:	Not stated
Test type:	Oral
GLP:	Yes
Year:	1992
Species:	Beagle dog
Strain:	Not stated
Route of administration:	Oral (capsule)
Duration of test:	4 Weeks
Doses/concentration levels:	250, 500, 1000 and 2000 mg/kg/day
Sex:	Male and female
Exposure period:	4 Weeks
Frequency of treatment:	Daily
Control group and treatment:	Yes, empty capsule
Postexposure observation period:	None
Statistical methods:	None
Remarks:	Groups of dogs (two males and two females) were administered the test substance in capsule form at concentrations of 250, 500, 1000 and 2000 mg/kg/day, five days per week, for a period of four weeks. A concurrent control group received the same number of capsules (empty) as the high dose group on a comparable regimen. Dogs were approximately six to seven months old at study initiation. All dogs were observed twice daily for mortality and moribundity. Clinical examinations were performed at the time of dosing, one hour following dosing and three hours following dosing. Individual body weights were recorded weekly. Food consumption was recorded daily and reported weekly. Hematology, serum chemistry and urinalysis evaluations were conducted prior to study initiation and prior to study termination. Complete necropsies were performed and the following organs were weighed: adrenals, brain, kidneys, liver, ovaries and testes. Bone marrow smears were made from the rib of each dog at the scheduled sacrifice. A microscopic examination was conducted on the following tissues from dogs in the control and 2000 mg/kg/day groups: adrenals, aorta, bone with marrow, brain, eyes with optic nerve, gallbladder, gastrointestinal tract, heart, kidneys, liver, lungs, lymph node, ovaries with mesovarium, pancreas, peripheral sciatic nerve, pituitary, prostate, salivary gland, skeletal muscle, skin with mammary gland, spinal cord, spleen, testes with epididymides, thymus, thyroid glands, tongue, trachea, urinary bladder, uterus with vagina and all gross lesions. Evaluation of

tissues from the 250, 500 and 1000 mg/kg/day groups was limited to lungs, liver, kidneys, testes and gross lesions.

Results

NOAEL (NOEL):	Male NOEL = 1000 mg/kg/day Female NOEL = 2000 mg/kg/day
LOAEL (LOEL):	Male LOEL = 2000 mg/kg/day
Actual dose received:	250, 500, 1000 and 2000 mg/kg/day
Toxic response/effects:	Described below
Statistical results:	None
Remarks:	All animals survived to the scheduled necropsy. No treatment-related clinical findings were observed in the 250, 500 and 1000 mg/kg/day group males and females or in the 2000 mg/kg/day group females. Post dosing observations of bilateral ptosis and ataxia in one male in the 2000 mg/kg/day group were possibly related to treatment since similar findings were not observed in the other dosage groups. Body weight and food consumption data in the treated groups were comparable to the control group. No test substance-related effect was apparent on hematology, serum chemistry or urinalysis values. No treatment-related macroscopic or microscopic lesions were observed at the scheduled necropsy. The absolute and relative testes/epididymides weights were remarkably lower in the 2000 mg/kg/day group males when compared to the control group. There was no microscopic indication of testicular dysfunction associated with these testes weight decreases. The significance of this effect was unclear. No remarkable differences in organ weights (absolute or relative to final body weight) were observed in the 2000 mg/kg/day group females or in the 250, 500 and 1000 mg/kg/day group males and females. Doses recommended for use in the conduct of the subsequent 13-week oral (capsule) study were 250, 500 and 1000 mg/kg/day.

Conclusions

The oral NOEL for DMH in this four-week dose range-finding study was 1000 and 2000 mg/kg/day for male and female dogs, respectively. (Author of report)

Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch):	1B
Remarks:	Reliable without restriction; comparable to guideline study.

References

Naas, D. J. 1991. 28-day oral (capsule) study in beagle dogs with DMH. Study number WIL-12234. WIL Research Laboratories, Inc., Ashland, OH, US.

Other

Last changed:	January 22, 2002
Order number for sorting:	17
Remarks:	

5.4 REPEATED DOSE TOXICITY

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	Not stated

Method

Method/Guideline followed:	Not stated
Test type:	Oral
GLP:	Yes
Year:	1982
Species:	Rat
Strain:	CD® Sprague-Dawley
Route of administration:	Oral gavage
Duration of test:	90 days
Doses/concentration levels:	2000, 5000 and 10,000 mg/kg/day
Sex:	Male and female
Exposure period:	90 days
Frequency of treatment:	Once daily
Control group and treatment:	Yes, 0.5% methylcellulose
Postexposure observation period:	None
Statistical methods:	Dunnett's test
Remarks:	Groups of rats (20 males and 20 females) were administered the test substance via oral gavage at concentrations of 2000, 5000 and 10,000 mg/kg once daily for a period of at least 90 days. A concurrent control group was administered 0.5% methylcellulose alone. Rats were approximately seven weeks old at study initiation. All rats were observed twice daily for behavioral changes, general health, activity, appearance, signs of toxicity and mortality. Detailed physical examinations, individual body weights and food consumption were recorded weekly. The following clinical pathology parameters were evaluated for selected rats: hematology, serum chemistry and urinalysis. Clinical necropsy examinations were performed at the scheduled sacrifice and the following organs were weighed: brain, kidneys, liver, heart and gonads. A microscopic examination was conducted on the following tissues from rats from the control and high dose groups: adrenals, aorta, bone with marrow, brain, cecum, epididymis, esophagus, eyes, heart, intestines, kidneys, liver, lungs, lymph node, mammary gland, ovaries, pancreas, pituitary, prostate, salivary gland, sciatic nerve, seminal vesicles, skeletal muscle, skin, spinal cord, spleen, stomach, testes, thymus, thyroids, trachea, urinary bladder, uterus, vagina and all gross lesions. In the low and mid dose groups, the heart, kidneys, liver and lesions were evaluated.

Results

NOAEL (NOEL):	NOAEL = 2000 mg/kg/day
LOAEL (LOEL):	LOAEL = 5000 mg/kg/day
Actual dose received:	2000, 5000 and 10,000 mg/kg/day
Toxic response/effects:	Described below
Statistical results:	None
Remarks:	Four mortalities were noted during the study: One high dose male was sacrificed moribund on day 86 due to chronic pyelonephritis predisposing to bacteremia and one mid dose female was sacrificed moribund on day 64 with evidence of renal pelvic urolithiasis producing hydronephrosis; two rats, a control female and a high dose female, were found dead on days 11 and 84 with evidence of dosing trauma. Following at least 90 days of exposure to the test substance histopathologic changes were noted in the kidney. There was an increased incidence of renal pelvic urolithiasis primarily in mid dose male rats, which was accompanied by chronic interstitial nephritis. These same findings were present in low and high dose rats. Urolithiasis also was noted in mid dose females. These histopathologic changes were accompanied by a dose-related increase in the kidney weights in male rats and in mid and high dose females. Clinical pathology changes consistent with the histopathology changes were noted; alkaline phosphatase levels were increased in high dose rats at weeks four and 12 and urea nitrogen levels were increased in high dose rats at week 12. A slight increase in the incidence of protein and red blood cells in the urine was noted macroscopically and microscopically in mid and high dose groups and were consistent with the kidney pathology changes. Other changes were noted in serum chemistries, however, there were no apparent histopathologic changes to explain them: cholesterol levels were increased in high dose males weeks 4 and 12; albumin levels were increased in high dose females weeks 4 and 12; and aspartate aminotransferase levels were increased in high dose males at week 12 and in high dose females at weeks 4 and 12. The only hematology parameter significantly altered was a decrease in platelet count in mid and high dose males and high dose females at week 4, which persisted in the males at week 12. Clinical observations included a dose-related incidence of white granular material in the urogenital area and/or urine stains, which were related to the high dose levels of material and the kidney pathologic changes. There was a slight decrease (7 to 10%) in mean body weights in high dose males from week 7 throughout the study. Mean food consumption was increased in high dose females from week 5 through the end of the study with the exception of week 9. Food consumption also was sporadically increased in mid dose females throughout the study.

Conclusions

The oral NOAEL for DMH in this 90-day study was 2000 mg/kg/day. (Author of report)

Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch): 1B

Remarks: Reliable without restriction; comparable to guideline study.

References

Mayhew, D. A. 1982. 90-day oral gavage study in rats dosed with dimethylhydantoin (DMH). Project number WIL-81165. WIL Research Laboratories, Inc., Cincinnati, OH, US.

Other

Last changed: January 22, 2002

Order number for sorting: 20

Remarks:

5.4 REPEATED DOSE TOXICITY

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	99%

Method

Method/Guideline followed:	Not stated
Test type:	Oral
GLP:	Yes
Year:	1984
Species:	Rat
Strain:	COBS® CD®
Route of administration:	Oral gavage
Duration of test:	90 days
Doses/concentration levels:	250, 500, 1000 and 2000 mg/kg/day
Sex:	Male and female
Exposure period:	90 days
Frequency of treatment:	Once daily
Control group and treatment:	Yes, 1.0% aqueous methylcellulose
Postexposure observation period:	None
Statistical methods:	One-way analysis of variance, followed by Dunnett's Test
Remarks:	Groups of rats (20 males and 20 females) were administered the test substance via oral gavage at concentrations of 250, 500, 1000 and 2000 mg/kg/day for a period of at least 90 days. A concurrent vehicle control group, also composed of 20 male and 20 female rats, received 1.0% aqueous methylcellulose on a comparable regimen at 20 ml/kg/day. The animals were observed twice daily for signs of overt toxicity. Detailed physical examinations, individual body weights and food consumption were recorded weekly. Clinical laboratory studies, including hematology, serum chemistry and urinalysis, were conducted prior to study initiation, after six weeks of treatment and at study termination (week 13) on selected rats. Complete necropsy examinations were performed on all rats at study termination and the following organ weights were obtained: brain, heart, kidneys, liver, ovaries and testes. A microscopic examination was conducted on the following tissues from rats in the control and high dose groups: adrenals, aorta, bone with marrow, brain, eyes with optic nerve, gastrointestinal tract, heart, kidneys, liver, lungs, lymph node, ovaries, pancreas, peripheral sciatic nerve, pituitary, prostate, salivary gland, seminal vesicles, skeletal muscle, skin with mammary gland, spinal cord, spleen, testes, thymus, thyroids, trachea, urinary bladder, uterus, vagina and all gross lesions. Evaluation of tissues in the 250, 500 and 1000 mg/kg/day groups was limited to kidneys, liver, lungs and gross lesions.

Results

NOAEL (NOEL):	NOEL = 2000 mg/kg/day
LOAEL (LOEL):	None
Actual dose received:	250, 500, 1000 and 2000 mg/kg/day
Toxic response/effects:	Described below
Statistical results:	Described below
Remarks:	No deaths occurred during the study period. The incidence and duration of hair loss on the forepaws and forelegs was increased in the 2000 mg/kg/day group males and slightly increased in the 500 and 1000 mg/kg/day group males. Hair loss in females from all treated groups was comparable to that observed in females from the control group. No treatment-related effects in body weights, food consumption, clinical laboratory parameters, ophthalmoscopic, macroscopic or microscopic examinations, or organ weights were apparent in any treated groups. The differences noted in this study were considered to occur spontaneously in rats of this strain and age and could not be attributed to treatment with the test substance.

Conclusions

Based on the results of this study, repeated oral gavage administration of DMH for 90 days does not result in systemic toxicity in the rat at dosages as high as 2000 mg/kg/day. (ACC Brominated Biocides Panel, DMH Task Group)

Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch):	1B
Remarks:	Reliable without restriction; comparable to guideline study.

References

Laveglia, J. 1985. 90-day study in rats with 5,5-dimethylhydantoin. Project number WIL-12034. WIL Research Laboratories, Inc., Ashland, OH, US.

Other

Last changed:	January 22, 2002
Order number for sorting:	21
Remarks:	

5.4 REPEATED DOSE TOXICITY

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	Not stated
Remarks:	The test substance was considered to be 100% pure for dose calculations.

Method

Method/Guideline followed:	US EPA FIFRA Section 82-1 and OECD 408
Test type:	Oral
GLP:	Yes
Year:	1989
Species:	Mouse
Strain:	CD®-1
Route of administration:	Oral feed
Duration of test:	13 weeks
Doses/concentration levels:	5000, 20000 and 50000 ppm
Sex:	Male and female
Exposure period:	13 weeks
Frequency of treatment:	Continuous
Control group and treatment:	Yes, basal diet
Postexposure observation period:	None
Statistical methods:	One-way analysis of variance, followed by Dunnett's Test
Remarks:	Groups of mice (20 males and 20 females) were administered the test substance in the diet at concentrations of 5000, 20000 and 50000 ppm for a period of 13 weeks. A concurrent control group was administered the basal diet alone. Mice were approximately 44 days old at study initiation. All mice were observed twice daily for mortality and signs of overt toxicity. Detailed physical examinations, individual body weights and food consumption were recorded weekly. The following clinical pathology parameters were evaluated for surviving mice at study termination: hematology (including differential white blood cell count; platelet count; total leukocyte count; erythrocyte count; hemoglobin; hematocrit; and mean corpuscular volume, hemoglobin and hemoglobin concentration) and serum chemistry (including urea nitrogen, creatinine, total bilirubin, aspartate aminotransferase, alanine aminotransferase and serum alkaline phosphatase). Ophthalmological examinations were performed before the study began and prior to study termination (week 12). Clinical necropsy examinations were performed at the scheduled sacrifice and the following organs were weighed: adrenals, brain, kidneys, liver, ovaries and testes. A microscopic examination was conducted on the following tissues from mice in the control and 50,000 ppm groups: adrenals, aorta, bone with marrow, brain, eyes with optic nerve, gallbladder, gastrointestinal tract, heart, kidneys, liver,

lungs, lymph node, mammary gland, ovaries with oviducts, pancreas, peripheral sciatic nerve, pituitary, prostate, salivary gland, seminal vesicles, skeletal muscle, skin, spinal cord, spleen, testes, thymus, thyroid glands, trachea, urinary bladder, uterus, vagina and all gross lesions. Evaluation of tissues from the 5000 and 20,000 ppm groups was limited to lungs, kidneys, liver, gross lesions and, in females, the adrenal glands.

Results

NOAEL (NOEL): NOEL = 20,000 ppm
LOAEL (LOEL): LOAEL = 50,000 ppm
Actual dose received: (mg/kg/day)

	5000 ppm	**20,000 ppm**	**50,000 ppm**
Male	686 to 1033	2799 to 4324	7178 to 11426
Female	917 to 1213	3565 to 5109	9254 to 14348

Toxic response/effects: Described below
Statistical results: Described below
Remarks: One female in the 20,000 ppm group died during study week 8. No overt clinical findings were noted for this female prior to death. Necropsy findings did not suggest that this death was treatment-related. No treatment-related effect was apparent at any dose level on survival, clinical observations, body weight data, food consumption, necropsy findings, ophthalmological findings, organ weight data, hematology parameters or serum chemistry parameters. An apparent test substance-related microscopic change of the adrenal gland(s) occurred in the high dose females; these glands appeared to be a target organ in this study. This change consisted of deposition of lipid material, an age-related change in female mice. It was considered to be related to the test substance only in that the severity of the lipid deposition was generally increased for the 50,000 ppm females. The overall incidence of this microscopic change was similar in the control and all treated groups.

Conclusions The oral NOEL for DMH in this 13-week study was 20,000 ppm. (Author of report)
Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch): 1A
Remarks: Reliable without restriction; guideline study.

References

Naas, D. J. 1991. 90-day dietary study in mice with DMH. Project number WIL-12186. WIL Research Laboratories, Inc., Ashland, OH, US.

Other

Last changed: January 22, 2002
Order number for sorting: 22
Remarks:

5.4 REPEATED DOSE TOXICITY

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	Not stated

Method

Method/Guideline followed:	US EPA FIFRA Section 82-1 and OECD 409
Test type:	Oral
GLP:	Yes
Year:	1991
Species:	Beagle dog
Strain:	Not stated
Route of administration:	Oral (capsule)
Duration of test:	13 weeks
Doses/concentration levels:	250, 500 and 1000 mg/kg/day
Sex:	Male and female
Exposure period:	13 weeks
Frequency of treatment:	Daily
Control group and treatment:	Yes, empty capsule
Postexposure observation period:	4 Weeks
Statistical methods:	One-way analysis of variance, followed by Dunnett's Test
Remarks:	Groups of dogs (six males and six females) were administered the test substance in capsule form at concentrations of 250, 500 and 1000 mg/kg/day, daily, for a period of 13 weeks. A concurrent control group received the same number of capsules (empty) as the high dose group on a comparable regimen. At the end of the 13-week dosing period, four males and four females from each group were necropsied. The remaining animals in each group continued on study for a four-week recovery period but were not dosed. Dogs were approximately five to six months old at study initiation. All dogs were observed twice daily for mortality and moribundity. Detailed physical examinations were conducted on all dogs weekly. Clinical examinations were performed daily at the time of dosing, one hour following dosing and three hours following dosing during the treatment period and daily during the recovery period. Individual body weights were recorded weekly. Food consumption was recorded daily and reported weekly. Hematology, serum chemistry and urinalysis evaluations were conducted prior to study initiation, during the sixth and thirteenth weeks of dosing (weeks 5 and 12) and near the end of the recovery period (week 16). Ocular examinations were conducted prior to study initiation, during week 12 and during the 4th week of recovery (week 17). Complete necropsies were performed on all dogs and the following organs were weighed: adrenals, brain, kidneys, heart, lungs with trachea, liver, ovaries, testes with epididymides and thyroid/parathyroid. Bone marrow smears were

made from the rib of each dog at the scheduled necropsies. A microscopic examination was conducted on the following tissues from all dogs at the scheduled necropsies: adrenals, aorta, bone with marrow, bone marrow smear, brain, eyes with optic nerve, femur with joint, gallbladder, gastrointestinal tract, heart, kidneys, liver, lungs, lymph node, ovaries with mesovarium, pancreas, peripheral sciatic nerve, pituitary, prostate, salivary glands, skeletal muscle, skin with mammary gland, spinal cord, spleen, testes with epididymides, thymus, thyroid glands, trachea, urinary bladder, uterus with vagina and all gross lesions.

Results

NOAEL (NOEL):	Male and female NOEL = 1000 mg/kg/day
LOAEL (LOEL):	None
Actual dose received:	250, 500 and 1000 mg/kg/day
Toxic response/effects:	Described below
Statistical results:	Described below
Remarks:	Definitive test All animals survive to the scheduled necropsy. No adverse effects on the clinical condition of the animals, body weight gain, food consumption, clinical pathologic parameters (hematology, serum chemistry and urinalysis) or organ weight data were observed. Ocular examinations and macroscopic and microscopic examinations of selected tissues revealed no lesions that could be attributed to the test substance.

Conclusions

Based on the results of this study, repeated oral (capsule) administration of DMH for 13 weeks does not result in systemic toxicity in the dog at dosages as high as 1000 mg/kg/day. (ACC Brominated Biocides Panel, DMH Task Group)

Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch):	1A
Remarks:	Reliable without restriction; guideline study.

References

Naas, D. J. 1992. 13-week oral (capsule) study in dogs with DMH. Study number WIL-12244. WIL Research Laboratories, Inc., Ashland, OH, US.

Other

Last changed:	January 22, 2002
Order number for sorting:	23
Remarks:	

5.4 REPEATED DOSE TOXICITY

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	99.5%

Method

Method/Guideline followed:	US EPA Guidelines for Pesticide Assessment, Subdivision F, Section 82-1, November 1984 and OECD Guidelines, Section 408, 1981.
Test type:	Oral
GLP:	Yes
Year:	1991
Species:	Rat
Strain:	CRl: CDBR (Sprague-Dawley)
Route of administration:	Oral gavage
Duration of test:	13 weeks
Doses/concentration levels:	100, 300 and 1000 mg/kg/day
Sex:	Male and female
Exposure period:	13 weeks
Frequency of treatment:	5 Days/week
Control group and treatment:	Yes, reverse osmosis water
Post exposure observation period:	None
Statistical methods:	Bartlett's test was performed to determine if the dose groups had equal variances. For parametric procedures, a standard one way analysis of variance (ANOVA) followed by Dunnett's test, if appropriate, were performed. In addition, a standard regression analysis for linear response in the dose groups and linear lack of fit were performed. For nonparametric procedures, the test of equality of means was performed using the Kruskal-Wallis test, followed by a Dunn's Summed Rank test if appropriate. In addition, Jonckheere's test for monotonic trend in the dose response was performed.
Remarks:	Based on the results of a range-finding test, 15 rats/sex/group were administered 5,5-dimethylhydantoin (DMH) via oral gavage at dose levels of 100, 300 and 1000 mg/kg/day at a dose volume of 10 ml/kg five days/week for 13 weeks. There was no adjustment made for percent purity. Fifteen rats/sex in a control group were treated similarly with reverse osmosis water, the vehicle used in this study. Male and female rats approximately 7 weeks of age at dose initiation were used on study. Detailed clinical examinations including palpation for masses were conducted weekly. In addition, careful cage side observations were made daily during the test period. Ophthalmic examinations were performed prior to study initiation and during the final week of the study. Body weights and food consumption were recorded weekly during the

test period. Necropsies were performed, and selected organs and tissues were collected and weighed. Clinical laboratory studies (hematology and serum chemistry) were performed on the first 10 surviving animals/sex/group at terminal sacrifice. Microscopic examinations were performed on a complete set of tissues from the high dose and control animals (10 animals/sex/group) and on a limited set of tissues from the animals in the mid and low dose groups.

Range-finding test:

The test substance was administered at concentrations of 200, 500, 1000 and 2000 mg/kg/day via gavage, seven days per week for two weeks to five rats/sex/group. A control group received the vehicle, reverse osmosis water, only. There were no deaths that were considered to be treatment-related. There were clinical observations that were considered to be treatment-related. Also, there were no statistically significant differences in body weights or food consumption noted during the study. There were no statistically significant differences in any of the hematology parameters in the male rats. There were statistically significant differences noted in the female rats; however, none were considered to be biologically significant. Analysis of the mean serum chemistry values revealed several dose-related trends, but all findings were slight and not considered to be biologically significant. Examination of the mean organ and relative organ weights revealed a dose-related increase in male adrenal weights, with the high dose male values being significantly increased over that of the controls. There were no statistically significant differences among the female organ or relative organ weights. There were no necropsy findings in those rats that survived until scheduled sacrifice that were considered to be treatment-related. Postmortem examination of the rats that succumbed prior to study termination revealed abnormalities of the trachea, lungs and/or esophagus indicative of a dosing accident. No treatment-related microscopic changes were observed in any of the male or female rats given 2000 mg/kg/day of the test substance.

Results

NOAEL (NOEL):	NOAEL = 1000 mg/kg/day
LOAEL (LOEL):	Not applicable
Actual dose received:	100, 300 and 1000 mg/kg/day
Toxic response/effects:	Described below
Statistical results:	See below
Remarks:	Two animals died during the study period. One animal was euthanized due to a broken snout and the other died spontaneously due to dosing trauma. The mean body weight and food consumption values of the male animals in the high dose group were depressed relative to the controls during most of the treatment period. On an absolute body weight basis, this

difference from the control was as high as approximately 8% on study day 63. While a relationship to treatment cannot be ruled out, the fact that an opposite effect (i.e. higher mean body weights relative to the control) was observed in the high dose female rats, renders the relationship of this finding to treatment in the high dose male rats somewhat questionable. The mean absolute and relative liver weights for male rats in the high dose group also were depressed relative to the controls. As was the case with body weight, an opposite trend for liver weights was noted in female rats in the high dose group. No clinical or microscopic changes were noted to support a relationship to treatment with either the decreases or increases in liver weights. The decreased body weights in males and increased body weights in females in the high dose group probably had some influence on these organ weight changes. No findings indicative of treatment-related effects were noted in the data collected on clinical signs, ophthalmology, or clinical and anatomic pathology.

Conclusions

The results of this 13-week oral gavage study indicate that DMH has little or no potential to produce toxic effects when administered to rats at dosages as high as 1000 mg/kg/day. (Author of report)

Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch): 1A

Remarks: Reliable without restriction; guideline study.

References

Federici, T. M. 1991. 90-day subchronic oral toxicity study in rats with dimethylhydantoin. Project number 169070. Exxon Biomedical Sciences, Inc., East Millstone, New Jersey, US.

Federici, T. M. 1991. 14-day rangefinding study in rats with dimethylhydantoin (MRD-90-690). Project number 169071. Exxon Biomedical Sciences, Inc., East Millstone, New Jersey, US.

Other

Last changed: January 22, 2002

Order number for sorting: 24 and 25

Remarks:

5.4 REPEATED DOSE TOXICITY

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	99.8-99.9%

Method

Method/Guideline followed:	US EPA FIFRA Subdivision F, Section 82-3and OECD Guideline No. 411.
Test type:	Dermal
GLP:	Yes
Year:	1992
Species:	Rat
Strain:	CD®
Route of administration:	Dermal
Duration of test:	13 weeks
Doses/concentration levels:	39, 130 and 390 mg/kg/day
Sex:	Male and female
Exposure period:	13 weeks
Frequency of treatment:	6 Hours/day for 5 days/week
Control group and treatment:	Yes, 3.0 ml/kg Milli-Q® filtered water
Post exposure observation period:	None
Statistical methods:	Quantitative continuous variables were intercompared for the three treatment groups and control group by use of Levene's test for equality of variances, analysis of variance (ANOVA) and t-tests. Nonparametric data were statistically evaluated using the Kruskal-Wallis test, followed by the Mann-Whitney U test when appropriate. Frequency data were compared using Fisher's Exact Test.
Remarks:	Fifteen rats/sex/group were administered the test substance via dermal application with a saturated aqueous solution of 5,5-dimethylhydantoin (DMH) (13%) at dose volumes of 0.3, 1.0 and 3.0 ml/kg/day, six hours/day (occluded), five days/week for 13 weeks. Fifteen rats/sex in a control group were treated similarly with 3.0 ml/kg/day Milli-Q® filtered water, the vehicle used in this study. Dose levels were selected based on the maximum aqueous solubility of DMH (13%) and the maximum dose volume that could be administered in the test system. Male and female rats, were approximately 32 days old when received, were used on study. Animals were acclimated to the testing facility for approximately three weeks prior to test substance administration. Animals were observed for mortality and signs of overt toxicity twice each day. Detailed observations, with special attention to the skin of the dose site were performed on each animal weekly and just prior to sacrifice. Ophthalmic examinations were performed prior to the first exposure and following the sixty-third

exposure. Body weights were collected weekly the morning prior to the first dose and weekly thereafter. Fasting body weights were collected just prior to sacrifice. Food consumption was recorded weekly. Prior to sacrifice, blood from all surviving animals was obtained for hematology and clinical chemistry determinations. Complete necropsies were performed for all animals on the study and selected organs from all surviving animals were weighed at terminal necropsy. Histopathology was conducted on a full set of tissues and organs from all animals in the control and high dose groups and on a subset of organs from the mid and low dose groups.

Results

NOAEL (NOEL):	NOEL = at least 390 mg/kg/day
LOAEL (LOEL):	Not applicable
Actual dose received:	39, 130 and 390 mg/kg/day
Toxic response/effects:	Described below
Statistical results:	No treatment-related statistical significances were noted in the parameters evaluated.
Remarks:	No clinical signs of toxicity or effects on any of the parameters evaluated were found.

Conclusions

Based on the results of this study, repeated dermal exposure to saturated aqueous solutions of DMH does not result in systemic toxicity or skin irritation in the CD® rat. (Author of report)

Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch):	1A
Remarks:	Reliable without restriction; guideline study.

References

Chun, J. S. and K. A. Loughran. 1994. Ninety-day dermal toxicity study with 5,5-dimethylhydantoin (DMH) in CD® rats. Project number 92N1016. Bushy Run Research Center, Union Carbide Chemicals and Plastics Company Inc., Export, PA, US.

Other

Last changed:	January 22, 2002
Order number for sorting:	26
Remarks:	

5.4 REPEATED DOSE TOXICITY

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	98.9%

Method

Method/Guideline followed:	US EPA Pesticide Assessment Guidelines, Subdivision F, November 1984.
Test type:	Oral
GLP:	Yes
Year:	1992
Species:	Dog
Strain:	Purebred beagle
Route of administration:	Oral (feed)
Duration of test:	12 Months
Doses/concentration levels:	4000, 12000 and 40000 ppm
Sex:	Male and female
Exposure period:	12 Months
Frequency of treatment:	3 hours/day
Control group and treatment:	Yes, basal diet
Post exposure observation period:	None
Statistical methods:	Parametric parameters (i.e. body weights, food consumption, etc.) were analyzed using one-way analysis of variance (ANOVA) and Bartlett's test for homogeneity of variance, Dunnett's t-test or Welch t-test with a Bonferroni correction when appropriate. Non-parametric data were analyzed by the rank transformation methods described by Conover and Iman.
Remarks:	Based on the results of a range-finding test, four dogs/sex/group were administered DMH at constant concentrations of 4000, 12000 and 40000 ppm for a three-hour period each day for 12 months. Four dogs/sex in a control group were treated similarly with the basal diet used to prepare the DMH-treated diets. Dietary concentrations were selected based on preliminary toxicity studies that showed that dietary concentrations of 40,000 ppm were well tolerated by the beagle dog. This dietary concentration is equivalent to 1 g of DMH/kg body weight/day and is considered to be the limit dose for chronic feeding studies in dogs. Male and female beagle dogs approximately 5 months of age when received were used on study. Animals were acclimated to the testing facility for approximately 4 weeks prior to test substance administration. Animals were observed for mortality, morbidity and signs of overt toxicity at least twice daily. A detailed clinical examination was performed on each dog weekly, and body weights and food consumption also were recorded weekly. An ophthalmic examination was performed on each animal pretest and prior to study termination. A physical

examination was conducted on each animal pretest, at 3, 6 and 9 months of study, and prior to study termination. Clinical pathology evaluations, including hematology, serum biochemistry and urinalysis, were conducted on all animals prior to study initiation, and at 6 and 12 months of study. A thorough postmortem examination was conducted on all animals at study termination. A complete set of all major tissues and organs was harvested and selected organs were weighted.

Two-week palatability study:

Dimethylhydantoin (DMH) was offered *ad libitum* in the diet to groups of two beagle dogs (one male one female) at concentrations of 0, 5000, 10000, 20000 and 40000 ppm for two weeks. Control dogs received the basal diet alone. All dogs survived to study termination. There were no clear treatment-related clinical signs of toxicity, changes in body weight or food consumption. Based on the results of this study, diets containing 40,000 ppm DMH are palatable to beagle dogs.

Range-finding test:

DMH was offered *ad libitum* in the diet for a period of eight weeks to groups of two male and two female beagle dogs at concentrations of 0, 1200, 4000, 12000 and 40000 ppm. Control dogs received the basal diet alone. These dietary concentrations were selected based on the results of preliminary palatability studies conducted in dogs. All dogs survived to study termination. There were no clinical signs of toxicity or changes in body weight, hematology, clinical chemistry, organ weights, gross or microscopic pathology that were attributed to treatment with the test substance. In addition, there were no toxicologically significant changes in food consumption.

Results

NOAEL (NOEL):	NOEL = 12,000 ppm
Actual dose received:	120, 342 and 1506 mg/kg/day/day for male dogs in the 4000, 12000 and 40000 ppm groups, respectively. 121, 414 and 1352 mg/kg/day/day for female dogs in the 4000, 12000 and 40000 ppm groups, respectively.
Toxic response/effects:	Described below
Statistical results:	Statistically significant increases in the absolute adrenal weights (relative to body weight and relative to brain weight) in male dogs
Remarks:	Treatment-related effects were limited to small decreases in body weight (not statistically significant), increases in absolute and relative adrenal weights and mild hypertrophy of the adrenal cortex for males in the 40,000 ppm treatment group and small decreases in body weight for females in the 40,000 ppm treatment group. There were no treatment-related effects observed for males or females in the other treatment groups. There were no treatment-related effects on food consumption measurements,

ophthalmologic examinations, or hematology, biochemistry, urinalysis and macroscopic evaluations.

Conclusions

The oral NOEL for DMH in this 12-month study in dogs was 12,000 ppm. (Author of report)

Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch): 1A

Remarks: Reliable without restriction; guideline study.

References

Goldenthal, E. I. 1995. Evaluation of dimethylhydantoin (DMH) in a one-year chronic dietary toxicity study in dogs. Project number 647-004. International Research and Development Corporation, Mattawan, MI, US.

Goldenthal, E. I. 1996. Evaluation of dimethylhydantoin in an eight-week dietary toxicity study in dogs. Project number 647-002. International Research and Development Corporation, Mattawan, MI, US.

Goldenthal, E. I. 1996. Evaluation of dimethylhydantoin in a two-week palatability study in dogs. Project number 647-001. International Research and Development Corporation, Mattawan, MI, US.

Other

Last changed: January 22, 2002

Order number for sorting: 27, 27a and 28

Remarks:

5.4 REPEATED DOSE TOXICITY

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	99.8%

Method

Method/Guideline followed:	US EPA FIFRA Subdivision F, Section 83-2, November 1984 and OECD Guideline No. 451, May 12, 1981.
Test type:	Oral
GLP:	Yes
Year:	1991
Species:	Mouse
Strain:	CD-1®
Route of administration:	Oral (feed)
Duration of test:	78 Weeks
Doses/concentration levels:	100, 300 and 1000 mg/kg/day
Sex:	Male and female
Exposure period:	78 Weeks
Frequency of treatment:	Daily
Control group and treatment:	Yes, basal diet
Post exposure observation period:	None
Statistical methods:	Quantitative continuous variables were intercompared for the three treatment groups and control group by use of Levene's test for equality of variances, analysis of variance (ANOVA) and t-tests. Nonparametric data were statistically evaluated using the Kruskal-Wallis test, followed by the Mann-Whitney U test when appropriate. Frequency data were compared using Fisher's Exact Test.
Remarks:	Based on the results of a range-finding test, sixty mice/sex/group were administered 5,5-dimethylhydantoin (DMH) in the diet at dosages of 100, 300 and 1000 mg/kg/day for at least 78 weeks. Two concurrent control groups comprising sixty mice/sex were treated similarly with the basal diet used to prepare the DMH-treated diets. Males and females approximately 31 days of age when received were used on study. Animals were acclimated to the testing facility for approximately three weeks prior to test substance administration. Animals were observed twice each day for mortality and signs of overt toxicity. Detailed clinical observations, including examinations for palpable masses, were conducted weekly throughout the study. Body weights and food consumption were measured weekly for the first 14 weeks of the study and every other week thereafter. Hematology was evaluated on ten animals/sex from the high dose and control groups at 12 months and on ten animals/sex from all groups at 18 months. Complete necropsies were performed for all animals on the study and selected organs from all surviving animals were

weighed at terminal necropsy. Histopathology was conducted on a full set of tissues and organs from all animals in the control and high dose groups.

Range-finding test:

Ten mice per sex per group were administered the test substance in the diet at concentrations of 0, 1000, 3500 and 7000 mg/kg/day for 28 days. There were no treatment-related effects observed in clinical observations, body weight, food consumption or histopathology. The NOEL for males and females was 1247 and 1676 mg/kg/day, respectively.

Results

NOAEL (NOEL):	NOEL = 300 mg/kg/day for toxicity and 1000 mg/kg/day for oncogenicity.
LOAEL (LOEL):	LOEL = 1000 mg/kg/day for toxicity
Actual dose received:	Ranged from 87 to 110, 245 to 343 and 849 to 1108 mg/kg/day for the male mice in the 100, 300 and 1000 mg/kg/day groups, respectively. Ranged from 84 to 119, 257 to 344 and 860 to 1075 mg/kg/day for the female mice in the 100, 300 and 1000 mg/kg/day groups, respectively.
Toxic response/effects:	Described below
Statistical results:	Described below
Remarks:	A slight, treatment-related decrease in the mean absolute body weight and body weight gain was observed in male mice from the 1000 mg/kg/day dose group. No other treatment-related effects were observed for animals in the 1000 mg/kg/day dose group, and no treatment-related effects were observed for animals in the 100 or 300 mg/kg/day groups for any parameter evaluated. In addition, pairwise comparisons and/or life table analyses did not reveal any treatment-related effects on survival, tumor incidence or time to tumor. The test substance was not considered to be oncogenic in this strain of mice under the condition of this study. Based upon the decreased body weights in male mice from the 1000 mg/kg/day dose group, the no-observed-effect level of DMH was considered to be 300 mg/kg/day. The NOEL for oncogenicity was at least 1000 mg/kg/day.

Conclusions

Based upon the decreased body weights in male mice from the 1000 mg/kg/day dose group, the NOEL of DMH under the conditions of this study was considered to be 300 mg/kg/day. The NOEL for oncogenicity was at least 1000 mg/kg/day. (Author of report)

Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch): 1A

Remarks: Reliable without restriction; guideline study.

References

Hermansky, S. J. and K. A. Loughran. 1994. Chronic dietary oncogenicity study with 5,5-dimethylhydantoin (DMH) in CD-1® mice. Project number 91N0112. Bushy Run Research Center, Union Carbide Corporation, Export, PA.

Hermansky, S. J. and C. L. Benson. 1995. Twenty-eight day dietary dose range-finding study with 5,5-dimethylhydantoin (DMH) in CD-1® mice. Project number 91N0054. Bushy Run Research Center, Union Carbide Corporation, Export, PA, US.

Other

Last changed: January 22, 2002

Order number for sorting: 29 and 30

Remarks:

5.4 REPEATED DOSE TOXICITY

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	99.8%

Method

Method/Guideline followed:	US EPA FIFRA Subdivision F, Section 83-5 and OECD 453
Test type:	Oral
GLP:	Yes
Year:	1991
Species:	Rat
Strain:	CD®
Route of administration:	Oral (feed)
Duration of test:	104 Weeks
Doses/concentration levels:	100, 300 and 1000 mg/kg/day
Sex:	Male and female
Exposure period:	104 Weeks
Frequency of treatment:	Daily
Control group and treatment:	Yes, basal diet
Post exposure observation period:	None
Statistical methods:	Quantitative continuous variables were intercompared by use of Levene's test for equality of variances, analysis of variance and t-tests. Nonparametric data were statistically evaluated using the Kruskal-Wallis test followed by the Mann-Whitney U test. Incidental tumor analyses were performed using computer software developed by the National Toxicology Program.
Remarks:	Based on the results of a range-finding test, sixty rats/sex/group were administered 5,5-dimethylhydantoin (DMH) in the diet at dosages of 100, 300 and 1000 mg/kg/day for at least 104 weeks. Two concurrent control groups comprising sixty rats/sex were treated similarly with the basal diet used to prepare the DMH-treated diets. Animals were observed twice each day for mortality and signs of overt toxicity. Detailed clinical observations, including examinations for palpable masses, were conducted weekly throughout the study. Body weights and food consumption were measured weekly for the first 14 weeks of the study and every other week thereafter. Ophthalmology examinations were conducted prior to study initiation and final sacrifice. Hematology, clinical chemistry and urinalysis were evaluated on 15 animals/sex/group at 6, 12, 18 and 24 months. Complete necropsies were performed for all animals on the study and selected organs from all surviving animals were weighed at terminal necropsy. Histopathology was conducted on a full set of tissues and organs from all animals in the control and high dose groups. In addition, the lungs, liver, kidneys, pituitary gland,

mammary gland and all gross lesions were processed and examined histologically for the animals in the low and mid dose groups.

Range-finding test:
Rats were exposed to the test substance in the diet for 14 days to determine the palatability of the test substance and the potential for the test substance to produce overt toxicity when administered in the diet. Dietary concentrations of 0, 7000, 14000 and 20000 ppm were evaluated in groups of ten rats per sex. There were no treatment-related effects observed in clinical observations, body weight, food consumption or necropsy.

Results

NOAEL (NOEL): NOAEL for systemic toxicity = 1000 mg/kg/day
NOEL for oncogenicity = 1000 mg/kg/day

LOAEL (LOEL): LOAEL > 1000 mg/kg/day

Actual dose received: (mg/kg/day)

	100 mg/kg/day	**300 mg/kg/day**	**1000 mg/kg/day**
Males	88.9 to 112.2	265.3 to 342.5	896.9 to 1132.4
Females	90.9 to 117.6	269.0 to 347.7	908.8 to 1147.9

Toxic response/effects: Described below

Statistical results: Described below

Remarks: No treatment-related effects on parameters of clinical signs, food consumption, clinical pathology, organ weights, and gross or microscopic pathology were observed for animals in any dose group. Slight decreases in the mean absolute body weight were observed in the 1000 mg/kg/day dose group of both sexes during the last two to three months of the study. Slight decreases in survival rates also were observed in the 1000 mg/kg/day dose group of both sexes. The body weight effects may have been secondary to reduced animal survival, since it is typical for animals to lose body weight prior to death. Furthermore, while decrease in survival was confirmed statistically in the high dose male rats through life table analyses, the mean survival time for the high dose group of both sexes was within the range of historical controls for CD® rats at the testing laboratory and the overall survival for this strain of rats was decreasing over the past several year prior to the conduct of this study. Therefore, the relationship of DMH treatment to both the decrease in survival as well as the decrease in body weight in the high dose group animals was uncertain.

Conclusions

Based upon the equivocal decreases in body weight and survival for animals in the high dose group, the no-observed-adverse-effect level of DMH was considered to be 1000 mg/kg/day. The NOEL for oncogenicity was at least 1000 mg/kg/day. Reproductive organs were examined meeting SIDS/HPV requirements for reproductive screening. (ACC Brominated Biocides Panel, DMH Task Group)

Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch): 1A

Remarks: Reliable without restriction; guideline study.

References

Hermansky, S. J. and C. L. Benson. 1994. Chronic dietary toxicity/oncogenicity study with 5,5-dimethylhydantoin (DMH) in rats. Project number 91N0113. Bushy Run Research Center, Union Carbide Corporation, Export, PA, US.

Hermansky, S. J. and C. L. Benson. 1995. Fourteen-day dietary palatability and dose range-finding study with 5,5-dimethylhydantoin (DMH) in CD® rats. Project number 91N0053. Bushy Run Research Center, Union Carbide Corporation, Export, PA, US.

Other

Last changed: January 22, 2002

Order number for sorting: 31 and 32

Remarks:

5.4 REPEATED DOSE TOXICITY

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	Not stated

Method

Method/Guideline followed:	TSCA test guidelines
Test type:	Oral
GLP:	Yes
Year:	1986
Species:	Rat
Strain:	Not stated
Route of administration:	Oral gavage
Duration of test:	90 days
Doses/concentration levels:	1000 mg/kg/day
Sex:	Male and female
Exposure period:	90 days
Frequency of treatment:	5 Days per week
Control group and treatment:	Yes, water
Postexposure observation period:	None
Statistical methods:	Not stated
Remarks:	Groups of rats (15 males and 15 females) were administered an aqueous formulation of the test substance via oral gavage at a concentration of 1000 mg/kg body weight, once a day, five days a week, for 90 days. A concurrent control group was administered the water alone. Prior to dosing, a group of ten male and ten female animals were sacrificed for hematological and serum biochemistries analyses. In addition, ophthalmoscopic examination was conducted on five male and five female rats from each experimental group. Rats were observed once a day for mortality and signs of toxicity. Body weights were recorded weekly. Thirty days after start of the dosing, five male and five female rats from each group were sacrificed, and samples of blood taken by cardiac puncture were analyzed from hematology and serum biochemistries. Prior to terminal sacrifice, ophthalmological examination was conduced on five male and five female rats from each experimental group. All surviving rats were sacrificed 90 days after the dosing stared, and subjected to a complete gross necropsy, and histopathological examination. Samples of blood were collected by cardiac puncture from five male and five female rats from the group treated with the test substance, and six male and six female rats from the control group.

Results

NOAEL (NOEL):	NOEL = 1000 mg/kg/day
LOAEL (LOEL):	Not applicable
Actual dose received:	Not stated
Toxic response/effects:	Described below
Statistical results:	Described below
Remarks:	All rats survived to scheduled sacrifice. There were no significant clinical observations that could be attributed to treatment. Body weight curves of rats dosed with the test substance were similar to control rats, within each sex. There were few statistical effects on organ weights, including the following: male rats treated with the test substance had smaller livers, and females had heavier spleens. Since these observations were not supported by clinical, biochemical or histopathological evidence, it was concluded that they were the result of normal weight variation. Other differences in organ weights were attributed to differences in animal size. No ocular lesions were observed in any rat. Statistically significant differences in clinical chemistry were not considered to be treatment-related. Also, there were no histopathologic findings that were considered to be treatment-related.

Conclusions

Based on the results of this study, repeated oral gavage administration of DMH for 90 days does not result in systemic toxicity in the rat at a dose of 1000 mg/kg/day. (ACC Brominated Biocides Panel, DMH Task Group)

Remarks: Only a single dose used. Data included to show no toxicity at 1000 mg/kg/day. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch):	1A
Remarks:	Reliable without restriction; guideline study

References

Salinas, J. A. 1986. 90-day repeated dose oral toxicity study on EMH and DMH in rats. Study number T86M0023G. Findley Research, Inc., Fall River, MA, US.

Other

Last changed:	January 22, 2002
Order number for sorting:	33
Remarks:	

5.4 REPEATED DOSE TOXICITY

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	Not stated
Remarks:	The test substance was considered to be 100% pure for dose calculations.

Method

Method/Guideline followed:	US EPA FIFRA Section 83-5 and OECD 451
Test type:	Oral
GLP:	Yes
Year:	1992
Species:	Rat
Strain:	Crl:CD®BR
Route of administration:	Oral feed
Duration of test:	24 Months
Doses/concentration levels:	100, 320 and 1000 mg/kg/day
Sex:	Male and female
Exposure period:	24 Months
Frequency of treatment:	Continuous
Control group and treatment:	Yes, basal diet
Postexposure observation period:	None
Statistical methods:	One-way analysis of variance, followed by Dunnett's Test; Fisher's Exact Test
Remarks:	Groups of rats (100 males and 100 females) were administered the test substance in the diet at concentrations of 100, 320 and 1000 mg/kg/day for a period of 24 months. A concurrent control group was administered the basal diet alone. Within each treatment group, 20 males and 20 females were assigned to a chronic subgroup and the remaining 80 males and 80 females were assigned to an oncogenicity subgroup. Rats were approximately six weeks old at study initiation. The chronic subgroup was necropsied following 53 weeks of test substance administration. The oncogenicity subgroup was necropsied following a minimum of 104 weeks of dosing. Parameters evaluated included clinical observations, body weights and food consumption. At approximately 3, 6, 12, 18 and 24 months, clinical pathologic parameters, including hematology, serum chemistry and urinalysis were evaluated in selected animals from all groups. Ophthalmological examinations were performed on all rats before the study began and during study weeks 51 and 103. Necropsies were performed on all rats that died, were euthanized *in extremis* and on all surviving rats at the scheduled necropsies. The following organs were weighed: adrenals, brain, heart, kidneys, liver, ovaries and testes. A microscopic examination was conducted on the following tissues from rats that died, were

euthanized *in extremis* and in all rats from the control and 1000 mg/kg/day groups: adrenals, aorta, bone with marrow, brain, clitoral gland, eyes with optic nerve, femur, gastrointestinal tract, heart, kidneys, liver, lungs, lymph nodes, mammary gland, ovaries with oviducts, pancreas, peripheral sciatic nerve, pituitary, preputial gland, prostate, salivary gland, seminal vesicles, skeletal muscle, skin, spinal cord, spleen, testes with epididymides, thymus, thyroids, trachea, urinary bladder, uterus, vagina and all gross lesions. Examination of tissues from the 100 and 320 mg/kg/day groups was limited to adrenals, kidneys, liver, lungs, pituitary gland, masses and gross lesions suspected of being treatment-related.

Results

NOAEL (NOEL):	NOAEL > 1000 mg/kg/day NOEL for systemic toxicity = 100 mg/kg/day NOEL for oncogenicity > 1000 mg/kg/day
LOAEL (LOEL):	LOEL = 320 mg/kg/day
Actual dose received:	100, 320 and 1000 mg/kg/day
Toxic response/effects:	Described below
Statistical results:	Described below
Remarks:	Twelve-month (52 weeks) survival in the chronic subgroup was 97.5% for males, 100% for females and 98.8% overall (males and females combined). Twelve-month survival in the oncogenicity subgroup was 99.0% for males, 96.9% for females and 98.0% overall. Twenty-four-month (104 and 105 weeks) survival in the oncogenicity subgroup was 37.8% for males, 47.8% for females and 42.8% overall. The only clinical sign suggestive of a test substance-related effect was yellow matting (both wet and dried) in the urogenital region at dose levels of 320 and 1000 mg/kg/day. This sign was observed in a dose- and time-related manner. However, lack of a toxicologically significant correlate associated with this clinical sign suggested that it was not an adverse effect. No treatment-related effects were noted in palpable mass data. There were no treatment-related effects seen in mean body weights and mean body weight changes. Increase food consumption means occurred occasionally in the 320 mg/kg/day group rats and often in the 1000 mg/kg/day group rats. The increased food consumption probably was due to the increasing concentration of the test substance (which was presume to have no nutritive value) in the diet. Thus, it was not considered to be a primary effect of the test substance. There also were no treatment-related effects on hematology, serum chemistry or urinalysis. No ophthalmological lesions indicative of a toxic effect were observed. No test substance-related macroscopic or microscopic lesions were seen. No treatment-related effects were observed in organ weights (absolute and relative) or histology.

Conclusions

Based on the clinical sign of yellow matting in the urogenital region observed in the 320 and 1000 mg/kg/day dose groups, the NOEL for systemic toxicity of DMH under the conditions of this study was considered to be 100 mg/kg/day. This clinical sign was not considered to be adverse due to lack of any toxicologically significant effect; therefore, the NOAEL for toxicity was at least 1000 mg/kg/day. The NOEL for oncogenicity was at least 1000 mg/kg/day. (Author of report)

Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch): 1A

Remarks: Reliable without restriction; guideline study.

References

Naas, D. J. 1996. Combined 24-month toxicity/oncogenicity study in rats with DMH. Project number WIL-12258. WIL Research Laboratories, Inc., Ashland, OH, US.

Other

Last changed: January 22, 2002

Order number for sorting: 34

Remarks:

5.4 REPEATED DOSE TOXICITY

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	99.9%

Method

Method/Guideline followed:	US EPA FIFRA Section 83-1
Test type:	Oral
GLP:	Yes
Year:	1992
Species:	Dog
Strain:	Outbred beagle
Route of administration:	Oral (capsule)
Duration of test:	1 Year
Doses/concentration levels:	250, 500 and 1000 mg/kg/day
Sex:	Male and female
Exposure period:	1 Year
Frequency of treatment:	Daily
Control group and treatment:	Yes, empty capsule
Postexposure observation period:	None
Statistical methods:	One-way analysis of variance, followed by Dunnett's Test
Remarks:	Groups of dogs (four males and four females) were administered the test substance in capsule form at concentrations of 250, 500 and 1000 mg/kg once daily for a period of 52 consecutive weeks. A concurrent control group received the same number of capsules (empty) on a comparable regimen. Dogs were approximately five to six months old at study initiation. All dogs were observed twice daily for mortality and signs of overt toxicity. Detailed physical examinations were performed weekly. Individual body weights were recorded weekly. Food consumption was recorded daily and reported weekly. Hematology, serum chemistry and urinalysis evaluations were conducted prior to the initiation of dosing and during study weeks 11 (12 for urinalysis), 25 and 51. Ocular examinations also were conducted once prior to the initiation of dosing and during study weeks 12, 25 and 51. A complete necropsy was performed on all dogs at study termination (week 52) and the following organs were weighed: adrenals, brain, heart, kidneys, liver, ovaries, lungs with trachea, testes with epididymides and thyroids with parathyroids. A microscopic examination was conducted on the following tissues from all dogs sacrificed at study termination: adrenals, aorta, bone with marrow, bone marrow smear, brain, eyes with optic nerve, femur, gallbladder, gastrointestinal tract, heart, kidneys, liver, lungs, lymph node, ovaries with mesovarium, pancreas, peripheral sciatic nerve, pituitary, prostate, salivary gland, skeletal muscle, skin with mammary gland, spinal cord, spleen, testes with epididymides,

thymus, thyroid glands, trachea, urinary bladder, uterus with vagina and all gross lesions.

Results

NOAEL (NOEL):	NOEL = 1000 mg/kg/day
LOAEL (LOEL):	None
Actual dose received:	250, 500 and 1000 mg/kg/day
Toxic response/effects:	Described below
Statistical results:	Described below
Remarks:	All dogs survived to the scheduled necropsy. No test substance-related clinical signs were observed. Body weight and food consumption were unaffected by test substance administration throughout the study. No treatment-related effects were observed on hematology, serum chemistry or urinalysis parameters. No ocular lesions indicative of a toxic effect were observed. No macroscopic or microscopic lesions related to test substance administration were noted. Mean absolute and relative organ weights in the treated groups were unaffected.

Conclusions

Based on the results of this study, repeated oral (capsule) administration of DMH for one year does not result in systemic toxicity in the dog at dosages as high as 1000 mg/kg/day. (ACC Brominated Biocides Panel, DMH Task Group)

Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch):	1A
Remarks:	Reliable without restriction; guideline study.

References

Chengelis, C. P. 1995. One-year oral toxicity study in dogs with DMH. Project number WIL-12274. WIL Research Laboratories, Inc., Ashland, OH, US.

Other

Last changed:	January 22, 2002
Order number for sorting:	35
Remarks:	

5.4 REPEATED DOSE TOXICITY

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	Not stated

Method

Method/Guideline followed:	US EPA FIFRA Section 82-1 and OECD Health Effects Test Guidelines adopted May 12, 1981
Test type:	Oral
GLP:	Yes
Year:	1992
Species:	Mouse
Strain:	Crl:CD-1® (ICR)BR
Route of administration:	Oral feed
Duration of test:	18 Months
Doses/concentration levels:	100, 320 and 1000 mg/kg/day
Sex:	Male and female
Exposure period:	18 Months
Frequency of treatment:	Continuous
Control group and treatment:	Yes, basal diet
Postexposure observation period:	Not stated
Statistical methods:	One-way analysis of variance, followed by Dunnett's Test; Fisher's Exact Test
Remarks:	Groups of mice (80 males and 80 females) were administered the test substance in the diet at concentrations of 100, 320 and 1000 mg/kg/day for a period of at least 78 weeks. A concurrent control group was administered the basal diet alone. Mice were approximately six weeks old at study initiation. At weekly intervals animals were given a physical examination that included clinical observations and palpation for masses. Body weights and food consumption were measured weekly and test substance consumption was calculated. At study weeks 52 and 79, blood smears were evaluated from all surviving control and 1000 mg/kg/day mice for differential leukocyte count determinations. In addition, blood samples were taken from mice euthanized *in extremis* for determination of leukocyte differential counts. Necropsies were performed on all mice that died or were euthanized *in extremis* and on all surviving mice at study termination. The following organs were weighed: brain, heart, kidneys, liver, ovaries and testes. A microscopic examination was conducted on the following tissues from mice in the control and 1000 mg/kg/day groups: adrenals, aorta, bone with marrow, brain, clitoral gland, eyes with optic nerve, femur, gallbladder, gastrointestinal tract, heart, kidneys, liver, lungs, lymph nodes, mammary gland, ovaries with oviducts, pancreas, peripheral sciatic nerve, pituitary, preputial gland, prostate, salivary gland, seminal

vesicles, skeletal muscle, skin, spinal cord, spleen, testes with epididymides, thymus, thyroids, trachea, urinary bladder, uterus with vagina and all gross lesions. Evaluation of tissues for the 100 and 320 mg/kg/day groups was limited to adrenals, kidneys, liver, lungs, masses and all gross lesions suspected of being treatment-related.

Results

NOAEL (NOEL):	NOEL = 1000 mg/kg/day
LOAEL (LOEL):	None
Actual dose received:	100, 320 and 1000 mg/kg/day
Toxic response/effects:	Described below
Statistical results:	Described below
Remarks:	The numbers of mice surviving for 18 months were 64/80, 53/80, 65/80 and 54/80 for males and 65/80, 64/80, 59/80 and 64/80 for females in the control, 100, 320 and 1000 mg/kg/day groups, respectively. The overall survival during the study was 76% and was not affected by treatment with the test substance, i.e. mortality data were not found to be statistically significant when compared to the control group. No treatment-related clinical signs of toxicity were observed at any dose level at the daily or weekly examinations. No treatment-related effects were seen in palpable mass data.

Conclusions

Based on the results of this study, repeated administration of DMH in the feed for 18 months does not result in systemic toxicity in the mouse at dosages as high as 1000 mg/kg/day. (ACC Brominated Biocides Panel, DMH Task Group)

Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch):	1A
Remarks:	Reliable without restriction; guideline study

References

Naas, D. J. 1996. 18-Month dietary oncogenicity study in mice with DMH. Project number WIL-12257. WIL Research Laboratories, Inc., Ashland, OH, US.

Other

Last changed:	January 22, 2002
Order number for sorting:	35a
Remarks:	

5.5 GENETIC TOXICITY *IN VITRO*

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	Not stated

Method

Method/guideline followed:	Not stated
Type:	Mammalian cell forward mutation assay
System of testing:	Non bacterial
GLP:	Yes
Year:	1982
Species/strain:	L5178Y heterozygous $TK^{+/-}$ mouse lymphoma cells
Metabolic activation:	With and without S-9 activation; 4 ml of S-9 used where applicable
Concentrations tested:	82, 117, 168, 240, 343, 490, 700 and 1000 µg/ml
Statistical methods:	Not stated
Remarks:	L5178Y heterozygous $TK^{+/-}$ mouse lymphoma cells were treated with the test substance at concentrations of 82, 117, 168, 240, 343, 490, 700 and 1000 µg/ml in the presence and absence of metabolic activation. Cell culture medium was used as the solvent control. Ethylmethane sulfonate (620 µg/ml) was used as the positive control without metabolic activation. 3-Methylcholanthrene (1 µg/ml) was used as the positive control with metabolic activation. The following criteria were used to evaluation the assay: 1. A test chemical was considered positive if a dose-related response was obtained in which the mutation frequencies at two or more test concentrations were at least two-fold higher than the mutation frequency of the solvent control. 2. Mutation frequencies must have been at levels of 1% or greater cell survival.

Results

Result:	The test substance tested at eight concentrations ranging from 82 to 1000 µg/ml in the presence and in the absence of metabolic activation did not cause increases in forward mutations at the TK locus in L5178Y mouse lymphoma cells.
Cytotoxic concentration:	No cytotoxicity seen in dose levels as high as 1000 µg/ml
Genotoxic effects:	Negative
Statistical results:	Not stated
Remarks:	Positive and negative controls in this assay confirmed the sensitivity of the test system species.

Conclusions The test substance was not mutagenic in this assay at concentrations as high as 1000 µg/ml. (ACC Brominated Biocides Panel, DMH Task Group)

Remarks:	The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch):	1B
Remarks:	Reliable without restriction; comparable to guideline study.

References

Farrow, M. G. 1982. Mouse lymphoma forward mutation assay. Report number 224-102. Hazleton Laboratories America, Inc., Vienna, VA, US.

Other

Last changed:	January 22, 2002
Order number for sorting:	36
Remarks:	

5.5 GENETIC TOXICITY *IN VITRO*

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	Not stated

Method

Method/guideline followed:	Not stated
Type:	Cell transformation assay
System of testing:	Mammalian
GLP:	Yes
Year:	1982
Species/strain:	C3H/10T ½ (clone 8) cells
Metabolic activation:	With S-9 activation
Concentrations tested:	10, 30, 100, 300 and 1000 µg/ml
Statistical methods:	Described below
Remarks:	C3H/10T ½ (clone 8) cells were treated with the test substance in Basal Modified Eagle's Medium (BME) at concentrations of 10, 30, 100, 300 and 1000 µg/ml in the presence of metabolic activation. BME also was used as the solvent control. Cyclophosphamid (CP) was used as the positive control. For the test, ten transformation cultures were prepared for the assay and ten cultures were prepared for the parallel cytotoxicity test. Twenty replicates were prepared for the transformation phase of testing for the positive and negative controls. After 13 days of incubation, the number of colonies on the test and control plates was counted and cytotoxicity from each dose was determined. The transformation series was continued for an additional 21 days. Throughout the incubation period, the cells were replenished with culture medium every four to seven days. At the conclusion of incubation, each plate was individually examined for the presence of Type III foci. Type III foci were defined as discrete darkened dense areas of crisscrossed cells growing on a lightly stained monolayer of normal nondividing cells. The foci were counted, recorded and calculations were performed. For the assay to be considered valid, the following criteria must be met: 1. The positive control must produce a significantly greater number ($p < 0.01$) of morphologically transformed foci than the solvent control. Probability is calculated using Fisher's Exact Method for Comparing Two Proportions. 2. At least three doses of the test substance in the transformation series must be analyzable. If the above criteria were met, and a statistically significant increase ($p < 0.01$) in the frequency of transformed foci occurred in a dose-related response at two or more dose levels, a test substance was considered to have a positive effect.

Results

Result:	No significant increase in the frequency of morphologically transformed foci resulted from exposure of C3H/10T ½ (clone 8) cells to five graded doses of the test substance ranging from 10 to 1000 µg/ml.
Cytotoxic concentration:	No cytotoxicity was observed in dose levels as high as 1000 µg/ml
Genotoxic effects:	Negative
Statistical results:	Described above.
Remarks:	

Conclusions

Under the conditions of this study, DMH was not genotoxic or cytotoxic at concentrations as high as 1000 µg/ml. (ACC Brominated Biocides Panel, DMH Task Group)

Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch):	2A
Remarks:	Reliable with restrictions; acceptable, well-documented study report which meets basic scientific principles.

References

Farrow, M. G. 1983. Cell transformation assay dimethylhydantoin with metabolic activation. Report number 224-104. Hazleton Laboratories America, Inc., Vienna, VA, US.

Other

Last changed:	January 22, 2002
Order number for sorting:	37
Remarks:	

5.5 GENETIC TOXICITY *IN VITRO*

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	Not stated

Method

Method/guideline followed:	Not stated
Type:	Cell transformation assay
System of testing:	Bacterial
GLP:	Yes
Year:	1982
Species/strain:	C3H/10T ½ (clone 8) cells
Metabolic activation:	None
Concentrations tested:	10, 30, 100, 300 and 1000 µg/ml
Statistical methods:	Described below
Remarks:	C3H/10T ½ (clone 8) cells were treated with the test substance in Basal Modified Eagle's Medium (BME) at concentrations of 10, 30, 100, 300 and 1000 µg/ml in the absence of metabolic activation. BME also was used as the solvent control. Benzo(a)pyrene was used as the positive control. For the test, ten transformation cultures were prepared for the assay and ten cultures were prepared for the parallel cytotoxicity test. Twenty replicates were prepared for the transformation phase of testing for the positive and negative controls. After 11 days of incubation, the number of colonies on the test and control plates was counted and cytotoxicity from each dose was determined. The transformation series was continued for an additional 23 days. Throughout the incubation period, the cells were replenished with culture medium every four to seven days. At the conclusion of incubation, each plate was individually examined for the presence of Type III foci. Type III foci were defined as discrete darkened dense areas of crisscrossed cells growing on a lightly stained monolayer of normal nondividing cells. The foci were counted, recorded and calculations were performed. For the assay to be considered valid, the following criteria must be met: 1. The positive control must produce a significantly greater number ($p < 0.01$) of morphologically transformed foci than the solvent control. Probability is calculated using Fisher's Exact Method for Comparing Two Proportions. 2. At least three doses of the test substance in the transformation series must be analyzable. If the above criteria were met, and a statistically significant increase ($p < 0.01$) in the frequency of transformed foci occurred in a dose-related response at two or more dose levels, a test substance was considered to have a positive effect.

Results

Result:	No significant increase in the frequency of morphologically transformed foci resulted from exposure of C3H/10T ½ (clone 8) cells to five graded doses of the test substance ranging from 10 to 1000 µg/ml.
Cytotoxic concentration:	No cytotoxicity was observed at dose levels as high as 1000 µg/ml
Genotoxic effects:	Negative
Statistical results:	Described above.
Remarks:	

Conclusions

Under the conditions of this study, DMH was not genotoxic or cytotoxic at concentrations as high as 1000 µg/ml. (ACC Brominated Biocides Panel, DMH Task Group)

Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch):	2A
Remarks:	Reliable with restrictions; acceptable, well-documented study report which meets basic scientific principles.

References

Farrow, M. G. 1983. Cell transformation assay dimethylhydantoin without metabolic activation. Report number 224-104. Hazleton Laboratories America, Inc., Vienna, VA, US.

Other

Last changed:	January 22, 2002
Order number for sorting:	37a
Remarks:	

5.5 GENETIC TOXICITY *IN VITRO*

Test Substance

Identity:	Dimethyl hydantoin 40-683 635658 (CAS RN 77-71-4; 5,5-Dimethylhydantoin)
Purity:	Not stated

Method

Method/guideline followed:	Not stated
Type:	Reverse mutation assay
System of testing:	Bacterial
GLP:	No
Year:	1978
Species/Strain:	*Salmonella typhimurium* strains TA-1535, TA-1537, TA-1538, TA-98, TA-100 and *Saccharomyces* D4.
Metabolic activation:	With and without S-9 activation; S-9 mix obtained from the liver of Aroclor 1254-induced rats.
Concentrations tested:	0.1, 1.0, 10.0, 100 and 500 µg per plate
Statistical methods:	None
Remarks:	The plate incorporation method was utilized for this assay. The solvent was distilled water. Positive controls were EMS (at 10 µl/plate for nonactivation assays with TA-1535, TA-100 and D4), QM (at 10 µg/plate for nonactivation assays with TA-1537), NF (at 10 µg/plate for nonactivation assays with TA-1538 and TA-98), ANTH (at 2.5 µg/plate for activation assays with all *Salmonella typhimurium* strains) and DMNA (at 100 micromoles/plate for activation assays with D4). Criteria for evaluation of the assay: A compound was considered mutagenic when it produced a positive dose response in strains TA-1535, TA-1537 and TA-1538 over three concentrations with the lowest increase equal to twice the solvent control value. A compound was considered mutagenic when it produced a positive dose response over three concentrations with the highest increase equal to twice the solvent control value for TA-100 and two to three times the solvent control values for strains TA-98 and D4.

Results

Result:	The test substance showed no evidence of mutagenic activity when tested in this bacterial system in the presence and absence of a liver activation system.
Cytotoxic concentration:	None
Genotoxic effects:	Negative
Statistical results:	None performed
Remarks:	

Conclusions When tested at dose levels up to 500 µg/plate dimethyl hydantoin 40-683 635658 was not mutagenic in this bacterial test system. (Author of report)

Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch): 2B

Remarks: Reliable with restrictions; Basic data given, comparable to guidelines/standards.

References

Jagannath, D. R. 1978. Mutagenicity evaluation of dimethyl hydantoin 40-683 635658 in the Ames *Salmonella*/microsome plate test. Project number 20838. Litton Bionetics, Inc., Greenwich, CT, US.

Other

Last changed: January 22, 2002

Order number for sorting: 38

Remarks:

5.5 GENETIC TOXICITY *IN VITRO*

Test Substance

Identity:	447:34-2 dimethylhydantoin (CAS RN 77-71-4; 5,5- Dimethylhydantoin)
Purity:	Not stated

Method

Method/guideline followed:	Ames, B. N., et al. 1975. Mutation Research. 31:347-364 and Yahagi, et al. 1977. Mutation Research. 48:121-130.
Type:	Reverse mutation assay
System of testing:	Bacterial
GLP:	Yes
Year:	1982
Species/Strain:	*Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538
Metabolic activation:	With and without S-9 activation; S-9 mix obtained from the liver of Aroclor *1254*-induced rats.
Concentrations tested:	100, 500, 2500, 5000 and 10,000 µg per plate
Statistical methods:	None
Remarks:	The preincubation assay was performed with and without metabolic activation. The S-9 mix was prepared in the testing laboratory immediately before use. The solvent was deionized, distilled water. The positive control used for all tester strains with metabolic activation was 2-aminoanthracene at concentrations from 1.0 to 4.0 µg/plate. The positive controls used in the assays without metabolic activation were 2-nitrofluorene (for TA98 and TA1538 at 10 and 1.0 µg/plate, respectively), 1,3-propan sultone (for TA100 and TA1535 at 0.4 µl/plate) and 9-aminoanthracene (for TA1538 at 1.0 µg/plate). A preliminary toxicity test was performed with tester strain TA100 at eight concentrations up to 10,000 µg/plate.

Results

Result:	The test substance showed no evidence of mutagenic activity when tested in this bacterial system in the presence and absence of a liver activation system.
Cytotoxic concentration:	No toxicity was seen at concentrations up to and including 10,000 µg/plate
Genotoxic effects:	Negative
Statistical results:	None
Remarks:	

Conclusions When tested at dose levels up to 10,000 µg/plate, 447:34-2 (DMH) was not mutagenic in this bacterial test system. (Author of report)

Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch): 1B

Remarks: Reliable without restriction; comparable to guideline study.

References

Haworth, S. R. 1982. *Salmonella*/mammalian-microsome preincubation mutagenicity assay (Ames test). Study number T1803.502. Microbiological Associates, Bethesda, MD, US.

Other

Last changed: January 22, 2002

Order number for sorting: 39

Remarks:

5.5 GENETIC TOXICITY *IN VITRO*

Test Substance

Identity:	447:34-2 dimethylhydantoin (CAS RN 77-71-4; 5,5-Dimethylhydantoin)
Purity:	Not stated

Method

Method/guideline followed:	Clive, D. and J. F. S. Spector. 1975. Mutation Research. 31:17-29.
Type:	Mammalian cell forward mutation assay
System of testing:	Non-bacterial
GLP:	Yes
Year:	1982
Species/Strain:	L5178Y TK +/- mouse lymphoma cells
Metabolic activation:	With and without S-9 activation; S-9 mix obtained from the liver of Aroclor-induced rats.
Concentrations tested:	10 concentrations from 563 to 10,000 µg per plate
Statistical methods:	None
Remarks:	The cultures treated in the absence of S-9 were cloned over a range of concentrations that produced from 72% to 109% total growth, and the S-9 activated cultures were cloned over a range of concentrations that produced from 93% to 122% total growth. The solvent used in this assay was FOP. Positive controls used were ethylmethanesulfonate and 7,12-dimethylbenz(a)anthracene. A positive response was indicated if there was a positive dose response and one or more of the three highest doses exhibited a mutant frequency which was two-fold greater than the background level.

Results

Result:	The test substance showed no evidence of mutagenic activity when tested in the presence and absence of a liver activation system.
Cytotoxic concentration:	>5000 µg/plate
Genotoxic effects:	Negative
Statistical results:	None
Remarks:	The solvent control plates for the nonactivation assay were lost due to contamination; therefore, the results were evaluated in comparison with historical solvent control data. It was realized that the use of historical solvent control data for evaluating a test article in this system in not optimal, but in light of the low mutation frequencies of the cultures treated at extremely high doses, the lack of significant levels of toxicity at the maximum dose, and the lack of any indication of a dose-related response, it was felt that the results are clearly negative in this test system. In addition, it was evident that the assay was working properly since the positive control for the nonactivation assay,

ethylmethanesulfonate (EMS), induced a very large increase in the mutation frequency of treated cultures.

Conclusions

When tested at dose levels up to 10,000 µg/plate, dimethylhydantoin was not mutagenic in the mouse lymphoma mutagenesis assay with or without metabolic activation. (Author of report)

Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch): 1B

Remarks: Reliable without restriction; comparable to guideline study.

References

Kirby, P. E. 1982. L5178Y TK+/- mouse lymphoma mutagenesis assay. Study number T1803.701001. Microbiological Associates, Bethesda, MD, US.

Other

Last changed: January 22, 2002

Order number for sorting: 40

Remarks:

5.5 GENETIC TOXICITY *IN VITRO*

Test Substance

Identity:	5,5-Dimethyl-2,4-imidazolidinedione (CAS RN 77-71-4; 5,5-Dimethylhydantoin)
Purity:	100%

Method

Method/guideline followed:	Not stated
Type:	Cytogenic assay (Chromosome aberration)
System of testing:	Non-bacterial
GLP:	Yes (Japanese GLPs)
Year:	1995
Species/Strain:	CHL/IU cells (derived from the female Chinese hamster lung)
Metabolic activation:	With and without S-9 activation; S-9 mix obtained from the liver of phenobarbital and 5,6-benzoflavone-induced rats. S-9 mix was obtained from Kikkoman Co. and stored frozen (-80 °C) until used.
Concentrations tested:	313, 625, 1250, 2500 and 5000 µg/ml
Statistical methods:	None
Remarks:	Saline was the solvent used for this assay. Positive controls used for this test were mitomycin C (MMC) and benzo[a]pyrene (BP). Two plates were used for each dose level. Cultured cells were exposed to the following treatments: 1) continuous treatment for 24 hours without S9; 2) continuous treatment for 48 hours without S9; 3) pulse treatment for 6 hours without S9 and an expression time of 18 hours; and 4) pulse treatment for 6 hours with S9 and an expression time of 18 hours.

Results

Result:	In both the continuous and pulse treatment, no significant increase of structural or numerical chromosomal aberrant cells was observed.
Cytotoxic concentration:	No cytotoxicity noted at concentrations up to and including 5000 µg/ml with and without activation.
Genotoxic effects:	Negative
Statistical results:	None
Remarks:	

Conclusions	5,5-Dimethyl-2,4-imidazolidinedione was considered not to be clastogenic under these test conditions on the chromosome aberration test using CHL/IU cells *in vitro*. (Author of report)
Remarks:	The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch):	2A
Remarks:	Reliable with restrictions; acceptable, well-documented publication/study report which meets basic scientific principles.

References

Suzuki, O. 1995. Metaphase chromosome aberration assay in cultured mammalian cells. Test number 7715. Genetic Laboratory, JBC, Inc., Japan.

Other

Last changed:	January 22, 2002
Order number for sorting:	41
Remarks:	

5.5 GENETIC TOXICITY *IN VITRO*

Test Substance

Identity:	447:34-2 dimethylhydantoin (CAS RN 77-71-4; 5,5-Dimethylhydantoin)
Purity:	Not stated

Method

Method/guideline followed:	As described by Williams, G. M. 1977. Cancer Research. 37:1845-1851.
Type:	Unscheduled DNA synthesis
System of testing:	Nonbacterial
GLP:	Yes
Year:	1982
Species/Strain:	Rat hepatocytes
Metabolic activation:	None
Concentrations tested:	1.0, 10, 100, 1,000, 10,000 and 20,000 µg/ml
Statistical methods:	None performed
Remarks:	An initial toxicity assay was performed with eleven dose levels ranging from 2,000 to 0.05 µg/ml. For the UDS assay, three replicate plates were seeded with 2.5 x 10^5 HPC/plate and treated with the test concentrations stated above. The concurrent positive control was 7,12-dimethylbenz(a)anthracene at concentrations of 50 and 25 µg/ml and DMSO, which was used to dissolve the positive control substance, was used as the solvent control. The test substance was diluted with water or WME.

Results

Result:	None of the test substance dose levels caused a significant increase in the mean net nuclear counts and no indication of dose response was observed with this test substance.
Cytotoxic concentration:	The initial toxicity test showed a relative toxicity of 26% at 2,000 µg/ml. The UDS assay resulted in a relative survival index of 30 and 96 at concentration of 20,000 and 10,000 µg/ml, respectively.
Genotoxic effects:	Negative
Statistical results:	None
Remarks:	

Conclusions The results of the assay indicate that under the test conditions, the test substance did not increase the unscheduled DNA synthesis as measured by the grain counts over the nuclei. (Author of report)

Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch):	2A
Remarks:	Reliable with restrictions; acceptable, well-documented publication/study report which meets basic scientific principles.

References

Thilagar, A. 1982. Unscheduled DNA synthesis in primary culture of rat hepatocytes (by autoradiography). Study number T1803.380002. Microbiological Associates, Bethesda, MD, US.

Other

Last changed:	January 22, 2002
Order number for sorting:	42
Remarks:	

5.5 GENETIC TOXICITY *IN VITRO*

Test Substance

Identity:	447:34-2 dimethylhydantoin (CAS RN 77-71-4; 5,5-Dimethylhydantoin)
Purity:	Not stated

Method

Method/guideline followed:	Not stated
Type:	Cytogenic assay (chromosomal aberration)
System of testing:	Nonbacterial
GLP:	Yes
Year:	1982
Species/Strain:	Chinese hamster ovary (CHO) cells
Metabolic activation:	With and without S-9 activation; S-9 mix obtained from the liver of Aroclor 1242-induced rats.
Concentrations tested:	8457, 11250 and 15000 µg/ml with activation 11250, 15000 and 20000 µg/ml without activation
Statistical methods:	None performed
Remarks:	The concurrent positive control substances were triethylenemelamine (without activation) and cyclophosphamide (with S-9 activation). Water was used as the solvent for the test substance. An initial toxicity assay was performed with nine dose levels ranging from 0.99 to 10,000 µg/m with no toxicity observed. In order to test the toxicity of the test substance up to 20,000 µg/ml, a parallel toxicity assay was performed with six concentrations ranging from 4746 to 20,000 µg/ml.

Results

Result:	Under the conditions of the test, the test substance did not cause a significant increase in the frequencies of chromosome aberrations in the Chinese hamster ovary cells, both with and without S-9 metabolic activation. The positive controls, with and without activation, produced significant numbers of chromosome aberrations.
Cytotoxic concentration:	In general, the test substance was more toxic in the activation system then in the nonactivation system. At 20,000 µg/ml the test substance caused 100% toxicity in the activation system compared to 18% toxicity in the non-activated system. The concentration of 15,000 µg/ml was also toxic in the activation system with 56% toxicity but was not toxic (0% toxicity) in the nonactivation system at this concentration.
Genotoxic effects:	Negative
Statistical results:	None
Remarks:	

Conclusions Under the conditions of this test, the test substance did not cause a significant increase in the frequencies of chromosome aberrations over that of the solvent control in both the activated and non-activated systems. (Author of report)

Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch): 2A

Remarks: Reliable with restrictions; acceptable, well-documented publication/study report which meets basic scientific principles.

References

Thilagar, A. 1982. Cytogenicity study – Chinese hamster ovary (CHO) cells *in vitro*. Study number T1803.338. Microbiological Associates, Bethesda, MD, US.

Other

Last changed: January 22, 2002

Order number for sorting: 55

Remarks:

5.6 GENETIC TOXICITY *IN VIVO*

Test Substance

Identity: 5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity: Not stated

Method

Method/Guideline followed: Not stated
Type: Bone marrow cytogenetic assay
GLP: Yes
Year: 1982
Species: Rat
Strain: Sprague-Dawley CD®
Sex: Male and female
Route of administration: Oral gavage
Doses/concentration levels: 200, 660 and 2000 mg/kg
Exposure period: 6, 12, 24 and 48 hours and 7 days
Statistical methods: Kruskal-Wallis nonparametric analysis of variance; nonparametric all pairwise group comparisons; Fisher's exact test; linear trend by linear regression; analysis of covariance
Remarks: A single dose of the test substance was administered via oral gavage to three groups of 15 male and 15 female rats at levels of 200, 660 and 2000 mg/kg. 15 Males and 15 females were administered the vehicle control, distilled water. Three males and three females were administered the positive control, cyclophosphamide (40 mg/kg). At 4, 10, 22 and 46 hours, and 7 days after administration of the test and control substances the appropriate groups of rats received a single intraperitoneal injection of colchicines (2.0 mg/kg body weight) to inhibit mitosis and arrest cells in metaphase. Clinical observations were recorded twice daily or prior to sacrifice. Three males and three females from each group were sacrificed at 6, 12, 24, 48 hours and 7 days after the single administration of the test substance. Slides of bone marrow cells from each rat were prepared and evaluated. At least fifty cells in metaphase were examined from each rat that provided analyzable cells.

Results

Effect on mitotic index:

	0 mg/kg	Positive Control	200 mg/kg	660 mg/kg	2000 mg/kg
6-hr.	4.0	-	3.5	3.7	3.0
12-hr.	3.0	-	3.2	4.5	3.0
24-hr.	2.8	0.6	3.4	2.6	1.6
7-day	2.1	-	1.9	1.4	1.4

Genotoxic effects:	Negative
NOAEL (NOEL):	NOEL = 2000 mg/kg
Statistical results:	Described below
Remarks:	All observations throughout the study were normal and no animals died during the study. No statistically significant variance in mean body weight change was seen for any of the treatment group from the seven-day sacrifice when compared to the control group. Results showed that no statistically significant increases in the frequency of chromosomal aberrations compared to control values were seen for any of the dose levels that were analyzed. Analysis of the data by linear regression also revealed no linear trend. Since no evidence of mitotic delay was seen after analysis of the mitotic indices, the slides from the 48-hour sacrifice were not analyzed for chromosomal aberrations.

Conclusions

Under the conditions of this study, DMH is considered not to be clastogenic at any of the levels tested. (Author of report)

Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch): 1B

Remarks: Reliable without restriction; comparable to guideline study.

References

Farrow, M. G. 1982. *In vivo* bone marrow cytogenetic assay in rats 5,5-dimethylhydantoin (DMH). Project number 224-103. Hazleton Laboratories America, Inc., Vienna, VA, US.

Other

Last changed: January 22, 2002

Order number for sorting: 44

Remarks:

5.8 TOXICITY TO REPRODUCTION

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	99.8%

Method

Method/guideline followed:	US EPA Guidelines for Pesticide Registration, Subdivision F, Series 83-4, November 1984 and OECD Guideline 416
Type:	Two-generation
GLP:	Yes
Year:	1991-1992
Species:	Rat
Strain:	CD®
Route of Administration:	Oral (feed)
Doses/concentration levels:	2000, 6000 and 20,000 ppm
Sex:	Male and female
Control group and treatment:	Yes, concurrent – basal diets
Frequency of treatment:	Continuous - ad libitum throughout the study
Duration of test:	Beginning 10 weeks prior to mating of the F_0 generation, throughout mating, gestation, parturition and lactation of two successive litters (F_1 and F_2).
Premating exposure period for males:	10 Weeks prior to mating
Premating exposure period for females:	10 Weeks prior to mating
Statistical methods:	Quantitative continuous variables were intercompared for the three treatment groups and control group by use of Levene's test for equality of variances, analysis of variance (ANOVA) and t-tests. Nonparametric data were statistically evaluated using the Kruskal-Wallis test, followed by the Mann-Whitney U test when appropriate. Frequency data were compared using Fisher's Exact Test.
Remarks:	Dietary concentrations were not adjusted for percent active ingredient since the percent active ingredient was >99%. Twenty-eight males and 28 females were exposed to 5,5-Dimethylhydantoin (DMH) in the diet for a prebreed period of 10 weeks. Following this prebreed exposure period, the animals were randomly paired within dose groups for a 21-day mating period to produce the F_1 generation. Exposure to the test diets continued through mating, gestation, parturition and lactation. After the F_1 pups were weaned, the F_0 animals were necropsied. At weaning, 28 F_1 weanlings/sex/group were randomly selected as parents of the next generation. Selected F_1 weanlings were exposed to the same dietary concentrations of DMH as their parents for at least 10 weeks. After their prebreed period, the F_1 animals were paired as described above to produce the F_2 offspring. Mating, gestation, lactation and necropsy of the

F_1 parents were performed as described above. The study was terminated following weaning of the F_2 offspring. Endpoints evaluated in both generations of parental animals included clinical signs of toxicity, body weights and body weight changes, food consumption, reproductive parameters, necropsy findings for all animals, and microscopic evaluation of reproductive organs from animals in the high dose and control groups. Endpoints evaluated in both generations of offspring included body weights and body weight changes, viability and survival indices, gross external evaluation for all animals, and necropsy findings for at least 10 weanlings/sex/group.

Results

NOEL:	NOEL for reproductive effects at least 20,000 ppm NOAEL for parental animals and offspring = 20,000 ppm
Actual dose received:	for the 2000, 6000 and 20,000 ppm groups were: F0 males – 136, 408 and 1396 mg/kg/day, respectively, during the entire dosing period; F0 females – 176, 516 and 1775 mg/kg/day, respectively, during prebreed period; F1 males – 127, 379 and 1322 mg/kg/day, respectively, during the entire dosing period; and F1 females – 158, 475 and 1602 mg/kg/day, respectively, during prebreed period. Actual dose received was not calculated during gestation or lactation.
F_0 data:	No treatment-related effects were noted in any parameters that were measured for the F_0 generation male or female rats, including mating and reproductive parameters. However, male rats in the 20,000 ppm group had statistically significant increases in food consumption values from week 1 through termination and body weights in these rats were also increased throughout most of the treatment period (statistically increased from week 12 through termination). Female rats in the 20,000 ppm group had statistically significant increases in food consumption values throughout most of the prebreed period.
F_1 data:	Food consumption appeared to be slightly increased for F_1 males in the 20,000 ppm group throughout the entire adult treatment period that were statistically significant from weeks 0 to 1, 4 to 5 and 13 to 16. Except for the increases in food consumption noted above, no treatment-related effects were noted in any parameters that were measured for the F_1 generation male or female rats, including mating and reproductive parameters.
Offspring toxicity:	With the exception of those effects noted below, no treatment-related differences were observed in any parameters that were measured for the F_1 generation. F_1 pup body weights were reduced

during the last two weeks of lactation (postnatal days 14 and 21) and one week after weaning (postnatal day 28) in the 20,000 ppm dose group; weight gains for pups from the 20,000 ppm dose group were substantially reduced from postnatal days 7 to 14 and slightly reduced from postnatal days 14 to 28. Terminal necropsy revealed no treatment-related abnormalities.
F_2 pup body weights and weight gains were reduced during the last two weeks of lactation in the 20,000 ppm dose group. Overall, body weight effects observed in the F_2 offspring were less than or no more severe than effects observed in the F_1 offspring. No treatment-related effects were noted in the other parameters that were measured.

Statistical results: See above.

Remarks:

Conclusions Continuous exposure to DMH in the diet for two generations at dietary concentrations of 2000, 6000 and 20,000 ppm did not result in parental toxicity or adverse effects on reproduction or reproductive tissues at dietary concentrations as high as 20,000 ppm. Small increases in parental food consumption and body weights and slight transient decreases in offspring body weight were observed at the 20,000 ppm dose level. (Author of report)

Remarks: The author of the report indicated that the NOEL for reproductive effects of at least 20,000 ppm and the NOEL for parental animals and offspring was 6000 ppm. The endpoints used to define the toxicity to parental animals were increases in body weight and food consumption at 20,000 ppm. These differences are not considered to be adverse effects. The endpoint for defining toxicity to the offspring was a transient depression in body weights for the F1 and F2 pups in the 20,000 ppm dose group from postnatal day 14 through 28. This transient reduction in body weight may be a result of increased compound consumption due to self-feeding. Therefore, the NOAEL for both parental animals and offspring is considered to be 20,000 ppm. This conclusion is confirmed in a second two-generation study where no effects were observed at oral gavage doses up to 1000 mg/kg/day. (ACC Brominated Biocides Panel, DMH Task Group).
The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability: 1A

Remarks: Reliable without restriction; guideline study.

References

Neeper-Bradley, T. L. and M. F. Kubena. 1994. Two-generation reproduction study in CD® rats with 5,5-dimethylhydantoin administered in the diet. Project number 91N0094. Bushy Run Research Center, Union Carbide Corporation, Export, PA, US.

Other available reports

Other

Last changed: May 12, 2003
Order number for sorting: 45
Remarks:

5.8 TOXICITY TO REPRODUCTION

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	96.0 to 98.7%

Method

Method/guideline followed:	US EPA FIFRA Section 83-4
Type:	Two generation
GLP:	Yes
Year:	1992
Species:	Rat
Strain:	Crl:CD®BR
Route of Administration:	Oral gavage
Doses/concentration levels:	250, 500 and 1000 mg/kg/day
Sex:	Male and female
Control group and treatment:	Yes, 1% aqueous methylcellulose
Frequency of treatment:	Once daily
Duration of test:	Two generations
Premating exposure period for males:	70 or 71 Days (F_0 or F_1, respectively)
Premating exposure period for females:	70 or 71 Days (F_0 or F_1, respectively)
Statistical methods:	Chi-square test with Yates correction factor; one-way ANOVA with Dunnett's test; Kolmogorov-Smirnov test
Remarks:	Groups of rats (30 males and 30 females), which comprised the F_0 generation, were administered the test substance in 1% aqueous methylcellulose via oral gavage at concentrations of 250, 500 and 1000 mg/kg/day. A concurrent control group of 30 males and 30 females received the vehicle alone on a comparable regimen at 10 ml/kg. F_0 parental rats were approximately six weeks old at study initiation. Rats were paired on a 1:1 basis within each treatment group. A vaginal copulatory plug or the presence of sperm in a vaginal smear confirmed positive evidence of mating. The F_0 parental rats were treated for 71 days prior to the first pairing and throughout all subsequent phases of the study until one day prior to the necropsy of each rat. All rats were observed twice daily for appearance and behavior prior to and during the study. Body weights and food consumption were recorded at appropriate intervals. All females were allowed to deliver and rear their pups to weaning (lactation day 21). One litter was produced in each generation. Offspring from the F_0 rats (F_1 litters) were selected to constitute the F_1 generation. The study design for the F_1 generation was identical to the F_0 generation, 30 rats per sex were selected for each dose group. Beginning day 22 *post partum*, the selected F_1 parental rats were treated for at least 70 days prior to the

first pairing and throughout all subsequent phases of the study until one day prior to the necropsy of each rat. The F_0 and F_1 parental rats and five selected F_1 and F_2 pups per sex from each dose group received complete detailed gross pathological examinations, in which kidney, liver, pituitary, ovaries and testes weights were recorded. Designated tissues were evaluated for histopathological changes in the control and all treatment groups.

Results

NOAEL: For reproductive toxicity = 1000 mg/kg/day
For parental toxicity = 1000 mg/kg/day
For neonatal toxicity = 250 mg/kg/day

Actual dose received: 250, 500 and 1000 mg/kg/day

F_0 and F_1 data: Administration of the test substance did not produce any apparent adverse effects on survival, general physical condition, body weights, food consumption or reproductive parameters (fertility, gestation length and parturition) for the F_0 parental rats at any dose level tested. F_1 live litter size, pup survival, sex ratios and general physical condition were not adversely affected by parental treatment with the test substance at any dose level tested. Decreases in mean neonatal body weights occurred in the 500 and 1000 mg/kg/day groups during lactation day 4 through day 28 of postnatal life. This effect was sustained through the first four weeks of the F_1 male growth phase. Decreased food consumption generally paralleled the body weight effects at these dose levels. An increased mean kidney weight (relative to the final body weight) in both F_0 and F_1 males at the 1000 mg/kg/day dose level was attributed to normal variation based on the small weight increase (6 to 7%), the absence of treatment-related microscopic renal lesions and the absence of a similar effect in the 1000 mg/kg/day females. No adverse effects on survival, general physical condition, fertility, gestation length or parturition were apparent in the F_1 parental rats.

Offspring toxicity: F_2 live litter size and sex ratios were not adversely affected by parental administration of the test substance. Pup viability (1000 mg/kg/day), mean pup body weights (500 and 1000 mg/kg/day) and final body weight (males in the 500 and 1000 mg/kg/day groups) were lower than observed in the concurrent control group.

Statistical results: Described above.

Remarks:

Conclusions Oral gavage administration of DMH for two consecutive generations resulted in a reproductive, parental and neonatal NOAELs for toxicity of 1000, 1000 and 250 mg/kg/day,

respectively. (ACC Brominated Biocides Panel, DMH Task Group)

Remarks: The original final report concluded that the parental NOAEL was 500 mg/kg/day; however, the EPA DER #12 for this study (MRID No. 42462502; HED Doc. No. 010538) concluded that the parental NOAEL should be 1000 mg/kg/day.
The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability: 1A

Remarks: Reliable without restriction; guideline study.

References

Nemec, M. D. 1992. Two-generation reproduction study of dimethylhydantoin administered orally in rats. Study number WIL-12153. WIL Research Laboratories, Inc., Ashland, OH, US.

Other

Last changed: April 28, 2003

Order number for sorting: 46

Remarks:

5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	Not stated

Method

Method/guideline followed:	US EPA TSCA guidelines, 40 CFR Part 798, Subsection 4900, September 1985.
GLP:	Yes
Year:	1986
Species:	Rat
Strain:	Sprague-Dawley
Route of administration:	Oral
Doses/concentration levels:	1000 mg/kg/day
Sex:	Female
Exposure period:	Days 6 - 15 of gestation
Frequency of treatment:	Daily
Control group and treatment:	Yes, sterile water
Duration of test:	Gestation day 20
Statistical methods:	t-test with an F test for homogeneity of variance, weighted t-test, Fisher's exact test or Mann-Whitney U test.
Remarks:	The test substance was administered in sterile water orally, once daily, at a concentration of 1000 mg/kg/day on gestation days 6 through 15. A similar volume of sterile water was given to the vehicle control group. The positive controls received 6-aminonicotinamide in sterile water in doses of 10 mg/kg on day 10 of gestation or 8 mg/kg on day 15 of gestation. Twenty to 26 mated females were in each group. Females were sacrificed on gestation day 20. All live fetuses were examined for external abnormalities. Approximately one-half of each litter was examined for skeletal anomalies and the remaining fetuses were examined for soft tissue anomalies.

Results

Maternal toxicity NOEL:	1000 mg/kg/day
Developmental toxicity NOEL:	1000 mg/kg/day
Actual dose received:	1000 mg/kg/day
Maternal data:	No treatment-related effects were observed on mortality, pregnancy, clinical observations, body weights, food consumption, necropsy observations or implantations.

Fetal data:	No treatment-related effects were noted in fetal body weights. There were no increases in external, visceral or skeletal malformations or variations.
Statistical results:	None stated
Remarks:	No teratogenic or embryotoxic effects were observed with this test substance.

Conclusions

Under the conditions of this test, DMH was neither fetotoxic nor teratogenic at 1000 mg/kg/day orally. (Author of report)

Remarks: Only a single dose used. Study included as supporting evidence for lack of developmental toxicity. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch): 1A

Remarks: Reliable without restriction; guideline study.

References

Hoar, R. M. 1986. Developmental toxicity study in rats on ethyl-methyl-hydantoin and dimethyl-hydantoin limit test - TSCA guidelines. Study number T86M006G. Findley Research, Inc., Fall River, MA, US.

Other

Last changed: January 22, 2002

Order number for sorting: 47

Remarks:

5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	Not stated

Method

Method/guideline followed:	EPA TSCA guidelines 40 CFR Part 798, Subsection 4900
GLP:	Yes
Year:	1986
Species:	Rabbit
Strain:	New Zealand White
Route of administration:	Oral
Doses/concentration levels:	1000 mg/kg/day
Sex:	Female
Exposure period:	Days 6 - 18 of gestation
Frequency of treatment:	Daily
Control group and treatment:	Yes, sterile water
Duration of test:	Gestation day 29
Statistical methods:	t-test with an F test for homogeneity of variance; weighted t-test (each group with a variance not homogeneous with the control group was tested by the modified t-test of Satterthwaite for comparison of means); Fisher's exact test; or Mann-Whitney U test. The litter was considered to be the unit of treatment.
Remarks:	The test substance was administered in sterile water orally, once daily, at a concentration of 1000 mg/kg/day on gestation days 6 through 18. A similar volume of sterile water was given to the vehicle control group. The positive controls received 6-aminonicotinamide (6-AN) in sterile water in doses of 3 mg/kg on either days 9, 10 or 11 of gestation.

Results

Maternal toxicity NOEL:	1000 mg/kg/day
Developmental toxicity NOEL:	1000 mg/kg/day
Actual dose received:	1000 mg/kg/day
Maternal data:	There was a significant increase in the average number of implantation sites in the females receiving DMH and 6-AN.
Fetal data:	No teratogenic or embryotoxic effects were observed with this test substance.
Statistical results:	Described below.

Remarks:	Although the number of spontaneous abortions in this study appeared unusually high, the incidence was not statistically significant. In addition, with one exception, the noted abortions were associated with the inseminated sperm from the same male rabbit.

Conclusions

Under the conditions of this test, DMH was neither fetotoxic nor teratogenic when administered orally at a concentration of 1000 mg/kg/day. (ACC Brominated Biocides Panel, DMH Task Group)

Remarks: Only a single dose used. Study included as supporting evidence for lack of developmental toxicity. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch): 1A

Remarks: Reliable without restriction; guideline study.

References

Hoar, R. M. 1986. Developmental toxicity study in rabbits on ethyl-methyl-hydantoin and dimethyl-hydantoin limit test - TSCA guidelines. Study number T86M007G. Findley Research, Inc., Fall River, MA, US.

Other

Last changed: January 22, 2002

Order number for sorting: 48

Remarks:

5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	99.8%

Method

Method/guideline followed:	US EPA Guidelines for Pesticide Registration, Subdivision F, Series 83-3, November 1984 and OECD Guideline No. 414
GLP:	Yes
Year:	1991
Species:	Rat
Strain:	CD®
Route of administration:	Oral
Doses/concentration levels:	100, 300 and 1000 mg/kg/day
Sex:	Female
Exposure period:	Days 6 - 15 of gestation
Frequency of treatment:	Daily
Control group and treatment:	Yes, 10.0 ml/kg Milli-Q® filtered water
Duration of test:	Gestation day 21
Statistical methods:	Quantitative continuous variables were intercompared for the three treatment groups and control group by use of Levene's test for equality of variances, analysis of variance (ANOVA) and t-tests. Nonparametric data were statistically evaluated using the Kruskal-Wallis test, followed by the Mann-Whitney U test when appropriate. Frequency data were compared using Fisher's Exact Test.
Remarks:	Twenty-five copulation plug-positive females/group were administered 5,5-dimethylhydantoin (DMH) by oral gavage on gestation days 6 through 15. DMH was diluted in Milli-Q® filtered water at dose levels of 100, 300 and 1000 mg/kg/day and at a constant dose volume of 10.0 ml/kg. An additional twenty-five females, assigned to the control group, received water at a dose volume of 10.0 ml/kg/day. Animals were observed daily, twice daily during dosing, and maternal body weights were measured on gestation days 0, 6, 9, 12, 15, 18 and 21. Maternal food consumption was measured at 3-day intervals from gestation days 0 through 21. On gestation day 21, all dams were sacrificed and evaluated for liver and gravid uterine weights, number of corpora lutea, and number and status of implantation sites (including early and late resorptions and live and dead fetuses). All live and dead fetuses were dissected from the uterus, weighed and examined externally for malformations, variations and gender determinations. Approximately one-half of the live fetuses in each litter were examined for visceral and craniofacial malformations and variations. The remaining one-half of the fetuses were stained

with alizarin red S and were examined for skeletal malformations and variations.

Results

Maternal toxicity NOEL:	1000 mg/kg/day
Developmental toxicity NOEL:	1000 mg/kg/day
Actual dose received:	100, 300 and 1000 mg/kg/day
Maternal data:	The pregnancy rate was equivalent among groups and ranged from 92 to 100%. No females died, aborted, delivered early, or were removed from the study prior to scheduled sacrifice. At scheduled sacrifice, all females that bore litters had one or more viable fetuses. Twenty-three to 25 live litters were available for evaluation from each group. There were no treatment-related clinical signs or effects on body weight, body weight gain or food consumption at any dose level. There were no treatment-related findings during necropsy of the dams on gestation day 21. There were no treatment-related effects on terminal body weight, gravid uterine weight, corrected body weight, correct body weight gain, or absolute and relative liver weight. No treatment-related differences were observed in the total umber of implantations, the number of viable and nonviable implants, or in sex ratios.
Fetal data:	There were no effects of treatment on fetal body weights/litter, or on the incidences of external, visceral, and skeletal malformations or variations.
Statistical results:	See above
Remarks:	

Conclusions

Administration of DMH by gavage to pregnant CD® rats during organogenesis produced no clear maternal or developmental toxicity. The no-observed-effect level for both maternal toxicity and developmental toxicity was at least 1000 mg/kg/day. (Author of report)

Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch):	1A
Remarks:	Reliable without restriction; guideline study.

References

Driscoll, C. D. and T. L. Neeper-Bradley. 1992. Developmental toxicity evaluation of 5,5-dimethylhydantoin (DMH) administered by gavage to CD® rats. Project number 91N0048. Bushy Run Research Center, Union Carbide Chemicals and Plastics Company Inc., Export, PA, US.

Other

Last changed:	January 22, 2002
Order number for sorting:	49
Remarks:	

5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	96.0 to 98.7%

Method

Method/guideline followed:	US EPA FIFRA Section 83-3
GLP:	Yes
Year:	1989
Species:	Rabbit
Strain:	New Zealand White
Route of administration:	Oral gavage
Doses/concentration levels:	100, 500 and 1000 mg/kg/day
Sex:	Female
Exposure period:	Days 6 - 18 of gestation
Frequency of treatment:	Daily
Control group and treatment:	Yes, 1.0% aqueous methylcellulose
Duration of test:	Gestation Day 29
Statistical methods:	Chi-square with Yate's correction factor; Fisher's Exact test; Mann-Whitney U-test; ANOVA with Dunnett's test; Kruskal-Wallis test
Remarks:	Based on the results of a range-finding test (see below), three groups of 20 artificially inseminated rabbits were administered the test substance in 1.0% aqueous methylcellulose orally, once daily, at concentrations of 100, 500 and 1000 mg/kg/day on gestation days 6 through 18. Twenty control females were concurrently dosed with 1.0% aqueous methylcellulose on a comparable regimen. A dose volume of 5 ml/kg was used in all dose groups. Rabbits were approximately six months old at study initiation. Throughout gestation, all females were observed twice daily for appearance and behavior. Body weights were recorded on gestation days 0, 6, 12, 18, 24 and 29. Food consumption was recorded daily. All surviving females were sacrificed for Cesarean section on day 29 of gestation. The uteri and ovaries were examined and the numbers of fetuses, early and late resorptions, total implantations and corpora lutea were recorded. Mean gravid uterine weights and net body weight changes were calculated for each group. Fetuses were weighed, sexed and examined for external, skeletal and soft tissue malformations and developmental variations.

Range-finding test
Five groups of seven artificially inseminated New Zealand White rabbits were administered the test substance in 1.0% aqueous methylcellulose orally, once daily, at concentrations of 250, 500, 1000, 2000 and 2500 mg/kg on gestation days 6 through 18. Seven control females were concurrently dosed with 1.0% aqueous methylcellulose on a comparable regimen. A dose volume of 10 ml/kg was used in all dose groups. Rabbits were approximately seven months old at study initiation. Throughout gestation, all females were observed twice daily for appearance and behavior. Body weights were recorded on gestation days 0, 6, 9, 12, 18, 24 and 29. Food consumption was recorded daily. All surviving females were sacrificed for Cesarean section on day 29 of gestation. Fetuses were weighed and examined for external malformations and developmental variations.

Results

Maternal toxicity NOEL: NOAEL = 500 mg/kg/day
Developmental toxicity NOEL: NOAEL = 100 mg/kg/day
Actual dose received: 100, 500 and 1000 mg/kg/day
Maternal data: No treatment-related deaths occurred at any dose level. Clinical signs observed during the study were not suggestive of a treatment-related effect. The predominant effects on maternal body weight and food consumption data occurred during the initial six days of test substance administration. A mean body weight loss and decreased food consumption were observed in the 1000 mg/kg/day groups during this interval. Food consumption remained reduced in the 1000 mg/kg/day group throughout the remainder of the treatment period. No treatment-related macroscopic findings were observed at necropsy in any dose group.
Fetal data: Intrauterine growth and survival were unaffected by treatment at dose levels of 100, 500 and 1000 mg/kg/day. Adactyly and brachydactyly of the #1 digit on both forepaws were noted in four fetuses in the same litter at a dose level of 1000 mg/kg/day; these malformations were considered to be treatment-related based on the results of the range-finding developmental study with this test substance. The percentages of fetuses with 27 presacral vertebrae were numerically increased at dose levels of 500 and 1000 mg/kg/day and represented a possible expression of developmental toxicity.
Statistical results: Described above
Remarks: Range-finding test
Maternal data: No treatment-related deaths or abortions occurred at any dose level. Clinical signs related to test substance administration (decreased defecation and white to brownish crystalline-like material in feces) were observed in the 2500 mg/kg/day group. Body weight losses and reductions in food

consumption were dose-related in the 1000, 2000 and 2500 mg/kg/day groups during gestation days 6 to 9 and 9 to 12. These adverse effects on body weight and food intake continued in the 2500 mg/kg/day group for the remainder of the treatment period. No treatment-related gross necropsy findings were observed at any dose level.
Fetal data: Postimplantation losses were increased and live litter size was decreased at dose levels of 2000 and 2500 mg/kg/day. A severe reduction in mean fetal body weight was observed in the 2500 mg/kg/day group. External fetal malformations, primarily involving defects of the digits (adactyly and brachydactyly), were noted at dose levels of 1000, 2000 and 2500 mg/kg/day in one, seven and ten fetuses, respectively. No external fetal variations were observed in any dose group.

Based on the results of the range-finding test, a dose level of 500 mg/kg/day was considered to be the NOAEL for maternal and developmental toxicity. Dose levels of 100, 500 and 1000 mg/kg/day were selected for the definitive test.

Conclusions

Based on the results of this study, a dose level of 500 mg/kg/day was considered to be the NOAEL for maternal toxicity and a dose level of 100 mg/kg/day was considered to be the NOAEL for fetal developmental toxicity. (Author of report)

Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch): 1A

Remarks: Reliable without restriction; guideline study.

References

Nemec, M. D. 1992. A developmental toxicity study of dimethylhydantoin in rabbits. Study number WIL-12174. WIL Research Laboratories, Inc., Ashland, OH, US.

Nemec, M. D. 1989. A range-finding developmental toxicity study of dimethylhydantoin in rabbits. Study number WIL-12151. WIL Research Laboratories, Inc., Ashland, OH, US.

Other

Last changed: January 22, 2002

Order number for sorting: 50 and 52

Remarks:

5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	Approximately 100%

Method

Method/guideline followed:	Not stated
GLP:	Yes
Year:	1982
Species:	Rat
Strain:	Sprague-Dawley COBS® CD®
Route of administration:	Oral intubation
Doses/concentration levels:	500, 2000 and 4500 mg/kg/day
Sex:	Female
Exposure period:	Days 6 - 19 of gestation
Frequency of treatment:	Daily
Control group and treatment:	Yes, 0.5% aqueous methylcellulose
Duration of test:	Gestation Day 25
Statistical methods:	Chi-square with Yate's correction factor; Fisher's Exact test; Mann-Whitney U-test; ANOVA with Dunnett's test
Remarks:	Based on the results of a range-finding test (see below), three groups of 25 bred female rats were administered the test substance in 0.5% aqueous methylcellulose via oral intubation, once daily, at concentrations of 500, 2000 and 4500 mg/kg/day on gestation days 6 through 19. Twenty-five control females were concurrently dosed with 0.5% aqueous methylcellulose on a comparable regimen at 20 ml/kg/day. Rats were approximately 13 weeks old at the time of initiation of breeding. Throughout gestation all females were observed twice daily for toxicity and weighed at appropriate intervals. On gestation day 20, all females were sacrificed for the scheduled Cesarean section; fetuses were weighed, sexed and examined for external, skeletal and soft tissue anomalies and developmental variations.

<u>Range-finding test</u>

Five groups of five mated female rats were administered the test substance in 0.5% aqueous methylcellulose orally, once daily, at concentrations of 1000, 2500, 5000, 7500 and 10,000 mg/kg/day on gestation days 6 through 19. Five control females were concurrently dosed with 1.0% aqueous methylcellulose on a comparable regimen at 25 ml/kg. Rats were approximately 16 weeks old at the time of initiation of breeding. Throughout gestation, all females were observed twice daily for toxicity and weighed at appropriate intervals. On gestation day 20, all surviving females were sacrificed for the schedule uterine examination.

Results

Maternal toxicity NOEL:	500 mg/kg/day
Developmental toxicity NOAEL:	2000 mg/kg/day for teratogenicity
Actual dose received:	500, 2000 and 4500 mg/kg/day
Maternal data:	All of the females survived to the scheduled day of sacrifice. Signs of toxicity were not apparent in the 500 mg/kg/day dose group. In the 2000 and 4500 mg/kg/day dose groups, maternal and fetal toxicity were expressed by decreases in maternal body weight gain, reduced fetal body weights and increases in various developmental variations (consisting primarily of reduced ossification of various portions of the skeleton or unossified bones). The reduced fetal ossification was associated with the reduced fetal body weight and was considered to be a secondary response resulting from maternal toxicity. Likewise, increased incidences of bent ribs and 14th full ribs in the high dose group were considered to be a response to maternal toxicity and not a teratogenic response. The degree of maternal toxicity observed in the 2000 mg/kg/day dose group was sufficient for evaluating the teratogenic potential of the test substance; there were no major malformations or increased developmental variants expressed in the 500 or 2000 mg/kg/day dose groups that suggested a teratogenic response.
Fetal data:	Described above
Statistical results:	Described above
Remarks:	<u>Range-finding test</u> Maternal data: Signs of toxicity to treatment were observed in the 5,000, 7500 and 10,000 mg/kg/day groups. Ataxia and lethargy were noted in the majority of animals in these groups between gestation days 6 and 10. Additional comments on the general physical condition of the rats in the 7500 and 10,000 mg/kg/day groups included dried orange or red matter around the mouth. One female in the 7500 mg/kg/day group and two in the 10,000 mg/kg/day group died between gestation days 6 and 8. Causes of death could not be determined at necropsy. Decreases in mean body weight gains over various intervals during gestation in the 5,000, 7500 and 10,000 mg/kg/day groups resulted in moderate decreases over the entire gestation and treatment intervals (0 to 20 and 6 to 16, respectively). The effect on body weight gain was not apparently dose-dependent. Uterine examination values were unaffected by treatment. There was no embryolethality observed in the two litters that were available for examination in the 10,000 mg/kg/day group.

Conclusions

Under the conditions of this test, the NOEL for maternal toxicity was 500 mg/kg/day and the NOAEL for developmental toxicity was less than or equal to 2000 mg/kg/day. (Author of report)

Remarks: The endpoint has been adequately characterized. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch): 1B

Remarks: Reliable without restriction; comparable to guideline study.

References

Rodwell, D. E. 1983. A teratology study in rats with 5,5-dimethylhydantoin. Study number WIL-12002. WIL Research Laboratories, Inc., Ashland, OH, US.

Rodwell, D. E. 1982. A range-finding teratology study in rats with 5,5-dimethylhydantoin. Study number WIL-12001. WIL Research Laboratories, Inc., Ashland, OH, US.

Other

Last changed: January 22, 2002

Order number for sorting: 51 and 53

Remarks:

5.10 ADDITIONAL REMARKS

Test Substance

Identity:	5,5-Dimethylhydantoin (CAS RN 77-71-4)
Purity:	Not stated

Method

Method/guideline followed:	Not stated
Type:	Absorption and elimination
GLP:	Yes
Year:	1982-1983
Species/Strain:	Rat/CD Charles River
Sex:	Male and female
Route of administration:	Oral gavage
No. of animals per sex per dose:	5
Vehicle:	Water
Doses/concentration levels:	20 and 100 mg/kg
Route of administration:	Oral
Remarks:	Rats were administered single oral doses of dimethylhydantoin-^{14}C (DMH-^{14}C) at either 100 (high dose) or 20 mg/kg (low dose). The disposition of the ^{14}C was followed for a seven-day period. The dosing syringe for each animal was washed after dosing and the amount of ^{14}C was measured in the wash. Urine and feces were collected and measured for the amount of ^{14}C at the following periods: 0 – 8 hours, 8 – 16 hours, 15 – 24 hours, 24 – 32 hours, 32 – 48 hours, then 24 hour collections on Study Days 2 through 5. All animals were killed on Study Day 6. The following tissues were removed and immediately frozen: heart, liver, kidneys, spleen, abdominal fat, right leg muscle, leg bone, gonads and brain tissue. These tissues were measured for amount of ^{14}C. The interior of the cage was washed with methanol and ^{14}C was measured in the wash liquid. For statistical significance, measurable counting rates of radioactivity needed to be more than twice background.

Results

Remarks:	The average recovery of ^{14}C from the rats was 95%. The compound was absorbed rapidly and was eliminated primarily in the urine with only minor metabolic conversion. The disposition essentially was the same for male and female rats at both the high and low dose levels. Treatment of the rats with the test substance for at least 14 days before administration of the DMH-^{14}C had no effect on disposition. The average amount eliminated in the urine was 91% of the dose. The elimination also was rapid, as 88% was eliminated in the first 24 hours after dosing. The parent DMH-^{14}C was the only major radioactive component found in urine by thin layer chromatographic analysis. One minor metabolite was

detected, which amounted to 2.5% of the urinary ^{14}C. Measurable levels of ^{14}C residues were not found in tissues of rats that received the low dose. With the techniques used, it was claimed that the levels of residue in tissues of the low dose animals were less than 20 ppb. In the case of rats receiving the high dose, low levels of ^{14}C were detected in kidney and bone tissues; however, all measurements were not significant. The male rats had higher levels of residue in the kidney tissues than the females. The levels in bone tissue were similar in both males and females.

Conclusions

Under the conditions of this test, DMH was rapidly absorbed and eliminated (elimination occurring mainly through the urine). Extensive conversion to metabolites did not occur. Kidney and bone tissues from the rats that received a single oral dose of 100 mg/kg DMH-^{14}C contained low but measurable levels of ^{14}C. (Author of report)

Remarks: This study provides additional information on the absorption and elimination of DMH administered orally in the rat. (ACC Brominated Biocides Panel, DMH Task Group)

Data Quality

Reliability (Klimisch): 2A

Remarks: Reliable with restrictions; acceptable, well-documented study report which meets basic scientific principles.

References

Resnis, P. and E. M. Craine. 1983. The absorption and elimination of dimethylhydantoin-^{14}C by rats. Project number WIL-12003. WIL Research Laboratories, Inc., Ashland, OH, US.

Other

Last changed: January 22, 2002

Order number for sorting: 11

Remarks: