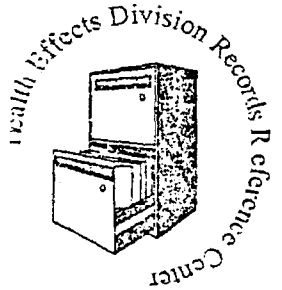
HIARC Briefing Packages

PC Code 000011

Iodomethane

Date of Package

7-30-02



Signature & Date

Shirley Lendarris 7-22-02

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Chemical:	**4-CHLOROPHENOXYANILINE**
PC Code:	**000011**
HED File Code	**21110 HIARC Briefing Pkgs**
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THERE WILL BE A HIARC MEETING FOR IODOMETHANE ON TUESDAY, JULY 30, 2002, ROOM 817 AT 9:00 AM

Reviewer: J. Whalan
BSS: R. Loranger

William Burnam

Elizabeth Doyle

Pamela Hurley

Elizabeth Mendez

David Nixon

Ayaad Assaad

John Liccione

Jess Rowland

Jonathan Chen

Steve Knizner

Brenda Tarplee

Sue Makris

OTHERS

PROPOSED DATA PRESENTATION TO HIARC

(Revised 04/12/02)

Iodomethane

000011

July 30, 2002

Data Evaluation / Report Presentation

John E. Whalan
Toxicologist

Secondary or Peer Review

Pamela Hurley
Toxicologist

1 INTRODUCTION

Chemical Name: Iodomethane

Date Submitted: July 18, 2002?

Arvesta Corporation (formerly TomenAgro) has requested the registration of iodomethane, a methyl bromide alternative, as a soil fumigant for use on strawberries and tomatoes. The toxic mode of action on target pests, laboratory animals, and humans is not known. Because there are no food residues in crops grown in treated soil, this is not a food use, and there are no residential uses. Iodomethane has never been presented to the HIARC or its predecessors, and no regulatory endpoints have ever been selected. Thus, the HIARC is asked to select inhalation endpoints since this is the only likely route of exposure for workers.

Proposed formulations include 98:2, 50:50, and 25:75 formulations of iodomethane and chloropicrin. Formulating with chloropicrin allows much less iodomethane to be used. An advantage of these products is that they can be applied by the same means and equipment as is currently used for methyl bromide. Acute toxicity studies have been performed for the technical and the 98:2 and 50:50 formulations. The registrant is hoping HED can use the data from these formulations to bridge to the 25:75 formulation.

Description:	Deep yellow, translucent liquid
Lot/Batch #:	007403/02
Purity:	99.6% a.i.
Compound Stability:	The test substance was stable for the duration of the study.
CAS #:	74-88-4
Molecular Weight	141.95 g/Mol
Structure:	

$$I\text{-}CH_3$$

The Toxicity Categories for iodomethane are I for eye irritation, II for oral toxicity and skin irritation, III for dermal toxicity, and IV for inhalation toxicity. It is corrosive to the eyes, and is a moderate skin irritant with rapid onset of effects.

In addition to the acute batteries, the other studies submitted include a 13-week inhalation toxicity study in rats, inhalation developmental toxicity studies in rats and rabbits, four mutagenicity studies, an inhalation acute neurotoxicity study in rats, and a comparative oral v inhalation metabolism study in rats. These are all Acceptable/Guideline studies. A 2-generation reproductive toxicity study, which is currently under review, is not required for a non-food use. Although a 21-day dermal toxicity study was performed to satisfy Japanese data requirements, this

study was waived; there is no way to quantify the dermal dose because the test article evaporates so quickly due to its high vapor pressure.

The comparative oral v inhalation metabolism study in rats was not required by HED. Arvesta performed this study because California required chronic and carcinogenicity studies. Rather than doing these studies via the inhalation route, which would be extremely costly and difficult, Arvesta hoped that the comparative metabolism study would allow the results in the oral studies to be extrapolated to the inhalation route. The metabolism study demonstrates that iodomethane is rapidly absorbed by both routes of exposure. In all treatment groups, the initial half-life was 5.1-7.2 hours, and the terminal half-life was 116-136 hours.

2 FQPA - HAZARD CONSIDERATIONS

There are no FQPA considerations because iodomethane is a non-food use and it is not used residentially.

3 HAZARD IDENTIFICATION

1. Acute Reference Dose (aRfD) - Not applicable

2. Acute Reference Dose (aRfD) - Not applicable

3. Chronic Reference Dose (cRfD) - Not applicable

4. Incidental Oral Exposure: Short-Term (1 - 30 days) - Not applicable

5. Incidental Oral Exposure: Intermediate-Term (1 - 6 Months) - Not applicable

6. Dermal Absorption - Not applicable

7. Short-Term Dermal (1 - 30 days) Exposure Not applicable

8. Intermediate-Term Dermal (1 - 6 Months) Exposure - Not applicable

9. Long-Term Dermal (> 6 Months) Exposure - Not applicable

10. Inhalation Exposure: All-Time Intervals

Proposed Study: Inhalation Developmental Toxicity Study in Rabbits §870.3700

MRID No.: 45593811

Executive Summary: In a developmental toxicity study (MRID 45593811), groups of 24 female New Zealand White rabbits were dynamically exposed to iodomethane vapor (Lot/batch # 007403/02; 99.6% a.i.) in whole-body inhalation chambers at analytical

concentrations of 0, 2, 10, or 20 ppm (0, 0.012, 0.058, or 0.12 mg/L/day) six hours per day on gestation days (GDs) 6 through 28. All surviving does were sacrificed on GD 29, and their fetuses were removed by cesarean section and examined.

No mortalities occurred during the study. When compared to concurrent controls, no treatment-related changes were observed in body weights, body weight gains, food consumption, sex ratios, or maternal gross pathology.

At 20 ppm, an increased number of late resorptions/doe were observed (1.6 treated vs. 0.1 controls), which resulted in increased post-implantation loss in these animals (2.0 treated vs. 0.7 controls). In addition, decreased ($p<=0.05$) gravid uterine weights were noted (decreased 31%). This decrease was attributed to decreased numbers of live fetuses/doe (decreased 41%) and decreased fetal weights (decreased 20%). Increased incidences of hair loss and wet, clear matting around the nose were noted in the 20 ppm animals compared to controls. Although these findings are of equivocal toxicological importance, they are evidence of nasal irritation. The post-implantation loss, decreased number of live fetuses, and decreased fetal weights may have been a consequence of subjecting the does to repeated respiratory irritation.

The maternal LOAEL is 20 ppm (0.12 mg/L/day) based on post-implantation loss due to late resorptions, and a decreased number of live fetuses. The maternal NOAEL is 10 ppm (0.058 mg/L/day).

The developmental toxicity LOAEL is 20 ppm (0.12 mg/L/day) based on decreased fetal weights (↓20%). The developmental toxicity NOAEL is 10 ppm (0.058 mg/L/day).

Proposed Concentration/Endpoint for Risk Assessment: The maternal NOAEL is 0.058 mg/L/day based on post-implantation loss due to late resorptions, and a decreased number of live fetuses at the LOAEL of 0.12 mg/L/day.

Comments about Study/Margins of Exposure: It is proposed that this endpoint be used in risk assessments for all durations of human exposure. The following table demonstrates that the length of the inhalation toxicity study has little effect on toxicity:

Study	NOAEL	LOAEL
Acute neurotoxicity - rats	0.16 mg/L	0.54 mg/L
Developmental toxicity - rats	0.12 mg/L/day	0.35 mg/L/day
Developmental toxicity - rabbits	0.058 mg/L/day	0.12 mg/L/day
13-week toxicity - rats	0.12 mg/L/day	0.41 mg/L/day

The NOAELs and LOAELs in this table are similar for all studies, but the maternal NOAEL in the rabbit developmental toxicity study is about half that of the other NOAELs, possibly due to an idiosyncratic effect in rabbits.

4 CLASSIFICATION OF CARCINOGENIC POTENTIAL

1. Combined Chronic Toxicity/Carcinogenicity Study in Rats - This study is not required because iodomethane is a non-food use.

2. Carcinogenicity Study in Mice - This study is not required because iodomethane is a non-food use.

3. Classification of Carcinogenic Potential - Carcinogenic potential is not a concern because iodomethane is a non-food use.

5 MUTAGENICITY

Negative responses were observed in an Ames Assay, an *in vitro* mammalian cell mutation test in Chinese Hamster Ovary Cells, and in an *in vivo* micronucleus assay in mice. The only positive finding was in an *in vitro* chromosomal aberration test in Chinese Hamster Ovary in which there was induction of structural chromosome aberrations (clastogenesis). There was no induction of numerical aberrations in CHO cells, however. The following executive summaries describe the findings in these four studies

Bacterial Reverse Mutation Test (Ames Assay)

In repeat reverse gene mutation preincubation assays in bacteria, histidine-deficient strains (*his*$^-$) TA98, TA100, TA1535 and TA1537 of *Salmonella typhimurium* and trytophan-deficient (*try*$^-$)WP2 (uvrA) of *Escherichia coli* were exposed to iodomethane (99.7% a.i.; Lot No. 007403) in sterile distilled water (SDW) at twelve concentrations ranging from 0.015 to 5000 µg/plate. In a confirmatory assay, cultures were exposed to six concentrations ranging from 15 to 5000 µg/plate. In addition to cultures exposed to the vehicle, SDW, other cultures were treated with strain-specific mutagens. Following exposures, cultures were incubated at 37 ± 2°C for 24 - 72 hours, at which times reversions to prototrophy were determined.

Toxicity was observed at 5000 µg/plate +/-S9 in both assays, but no precipitation. At no concentration, however, were any increases in the number of revertant colonies (*his*$^-$ to *his*$^+$; *try*$^-$ to *try*$^+$) compared to vehicle control values observed. Therefore, **iodomethane is concluded to be non-mutagenic in these bacterial assays.**

***In Vitro* Mammalian Cell Mutation Test in Chinese Hamster Ovary Cells**

In a mammalian cell gene mutation assay (MRID 45593815), cultures of Chinese hamster ovary (CHO-K_1BH_4) cells were exposed for 5 hours to iodomethane (99,7% a.i.; Lot No. 007403) in sterile distilled water (SDW) at concentrations ranging from 100 to 500 (or 600) µg/mL in the presence and absence of metabolic activation. Following exposure, determinations of mutant frequencies (> 40 mutants per 10^6 clonable cells) were made. In addition to cultures exposed to the solvent, SDW, other cultures were treated with the mutagens, ethylmethansulfonate (EMS) and benzo(a)pyrene [B(a)P], to serve as positive controls for the non-activation (-S9) and activation (+S9) test series.

No visible precipitation was observed, but substantial toxicity (≤22%) occurred at ≥505 µg/mL ± S9. Cloning efficiency <50% of the solvent control was observed at doses of ≥125 µg/mL -S9 and ≥150 µg/mL +S9. However, at no test dose in the presence or absence of activation was there any significant increase in mutant colonies. The positive controls responded appropriately with large increases in mutants.

***In Vitro* Chromosomal Aberration in Chinese Hamster Ovary**

In an *in vitro* cytogenetic (chromosome aberration) assay (MRID 45593814), cultures of Chinese hamster ovary (CHO) cells were exposed to iodomethanne (99.7% a.i.; Lot No. 007403) in sterile distilled water (SDW) for 4 hours at concentrations ranging from 25 or 50 to 350 µg/mL in the presence and absence of a mammalian activation system, then transferred to test article-free medium for a 16-hour recovery period, or exposed continuously for 20 hours at concentrations ranging from 25 to 250 µg/mL.

At 20 hours after initiation of exposure, cells were harvested following 2 hours treatment with the metaphase-arresting alkaloid, Colcemid, and both toxicity (mitotic indices) and frequency of aberrant metaphases determined. In addition to cultures exposed to the vehicle, SDW, other cultures were treated with the clastogens, mitomycin C (MMC, 0.1 - 0.2 µg/mL) and cyclophosphamide (CP, 10 - 20 µg/mL), to serve as positive controls for the non-activation and activation test series.

Substantial toxicity (at least 50% cell growth inhibition) was observed at dose levels of 426 µg/mL and above in both activated and non-activated 4-hour exposure groups, as well as in the 20-hour non-activated continuous exposure groups.

Dose-related and significant increases in structural chromosome aberrations were seen at 150 and 250 µg/mL -S9 (4-hour treatment), at 100 and 200 µg/mL +S9 (4-hour treatment) and at 50 to 250 µg/mL -S9 (20-hour treatment). In general, chromatid breaks and exchanges were the most frequently observed aberrations. Therefore, **iodomethane is positive for the induction of structural chromosome aberrations (clastogenesis), but negative for induction of numerical aberrations in CHO cells in this assay.**

***In Vivo* Micronucleus Assay in Mice**

In a cytogenetic (micronucleus) assay (MRID 45593816), groups of mice (5/sex/harvest) were injected once intraperitoneally with iodomethane (99.7% a.i.; Lot No. 007403) in sterile distilled water (SDW) at doses of 25, 50 or 100 mg/kg and bone marrow collected 24 or 48 hours post-dose. In addition to animals treated with the vehicle, SDW, a group of mice (5M/5F) was injected i.p. with cyclophosphamide (CP, 2.5 mg/mL), to serve as positive control.

The highest dose selected for the study (100 mg/kg) was considered the maximum tolerated dose (MTD), based on the evidence of mortality and other clinical signs at ≥200 mg/kg, in the toxicity test. There was no clear evidence of a toxic effect in these animals or a cytotoxic effect in the target tissue. There was also no significant increase in micronucleated-PCE in iodomethane-treated groups relative to the respective controls in either males or females 24 or 48 hours after dose administration.

Therefore, iodomethane is considered to be negative in the mouse micronucleus assay.

6 HAZARD CHARACTERIZATION

To be inserted in the final HIARC document.

7 DATA GAPS / REQUIREMENTS

There are no data gaps. The registrant is submitting a two generation reproductive toxicity study which is not required for non-food use registration.

ACUTE TOXICITY

Acute Toxicity of Iodomethane

Guideline No.	Study Type	MRID #(s)	Results	Toxicity Category
81-1	Acute Oral - rat	45593803	LD_{50} = 79.8 mg/kg ♂ LD_{50} = 131.9 mg/kg ♀	II
81-1	Acute Oral - mouse	45593804	LD_{50} = 155 mg/kg ♂ LD_{50} = 214 mg/kg ♀	II
81-2	Acute Dermal	45593805	LD_{50} >2000 mg/kg	III
81-3	Acute Inhalation	45593806	LC_{50} = 4.0? m/L	IV
81-4	Primary Eye Irritation	45593807	Corrosive	I
81-5	Primary Skin Irritation	45593808	Severe irritant	II
81-6	Dermal Sensitization	45593809	Negative	

Toxicity Profile of Iodomethane Technical

OPPTS No./Study Type	MRID	Results
870.3100 Subchronic Feeding - Rat	–	Not required for non-food fumigant use.
870.3100 Subchronic Feeding - Mice	–	Not required for non-food fumigant use.
870.3100 Subchronic Feeding - Mice	–	Not required for non-food fumigant use.
870.3150 Subchronic Feeding - Dog	–	Not required for non-food fumigant use.
870.3200 21-Day Dermal - Rat	–	The test article quickly evaporates due to its high vapor pressure, so there is no way of quantifying dermal doses. Although a study was performed to satisfy Japanese requirements, this study is not required by HED.
870.3465 13-Week Inhalation - Rat WIL Research Laboratories, Inc. Study No. WIL-418015 January 28, 2002	45593810	**NOAEL = 21 ppm (0.12 mg/L/day)** **LOAEL = 70 ppm (0.41 mg/L/day) based on initial decreases in body weights, body weight gains, and food consumption (males); and nasal degeneration.** Analytical concentrations tested: 0, 5, 21, or 70 ppm (0, 0.029, 0.12, or 0.41 mg/L/day) in a whole-body chamber, 6 h/day, 5 days/week for 4 weeks (interim sacrifice) or 13 weeks. **Acceptable/Guideline**
870.3700 Inhalation Developmental Toxicity - Rat Wil Research Laboratories, Inc. Study No. WIL-418010 January 11, 2002	45593812	**Maternal NOAEL = 20 ppm (0.12 mg/L/day)** **Maternal LOAEL = 60 ppm (0.35 mg/L/day) based on based on decreased body weight gain (↓19%; ↓5-6% absolute body weight).** **Developmental NOAEL = 60 ppm (0.35 mg/L/day)** **Developmental LOAEL was not observed** Analytical concentrations tested: 0, 5, 20, 60 ppm (0, 0.03, 0.12, or 0.35 mg/L/day) in a whole-body inhalation chamber, 6 h/day on GDs 6-19. **Acceptable/Guideline**

OPPTS No./Study Type	MRID	Results
870.3700 Inhalation Developmental Toxicity - Rabbit WIL Research Laboratories, Inc. Study No. WIL-418002 January 28, 2002	45593811	**Maternal NOAEL = 10 ppm (0.058 mg/L/day)** **Maternal LOAEL = 20 ppm (0.12 mg/L/day) based on post-implantation loss due to late resorptions, and a decreased number of live fetuses.** **Developmental NOAEL = 10 ppm (0.058 mg/L/day)** **Developmental LOAEL = 20 ppm (0.12 mg/L/day) based on decreased fetal weights (↓20%).** Analytical concentrations tested: 0, 2, 10, or 20 ppm (0, 0.012, 0.058, or 0.12 mg/L/day) in a whole-body inhalation chamber, 6 h/day, on GDs 6-28. **Acceptable/Guideline**
870.3800 Inhalation 2-Generation Reproductive Toxicity - Rat WIL Research Laboratories, Inc. Study No. WIL-418004 May 24, 2001		Currently under review
870.4100 Chronic Feeding Toxicity - Dog	–	Not required for non-food fumigant use.
870.4200 Carcinogenicity Feeding - Mouse (18 months)	–	Not required for non-food fumigant use.
870.4300 Chronic Feeding Toxicity/Carcinogenicity- Rat	–	Not required for non-food fumigant use.
870.5100 Bacterial Reverse Mutation Test (Ames Assay) BioReliance Laboratories Study AA38UL.504004 March 14, 2001	45593813	Nonmutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537; and in *Escherichi coli.*

OPPTS No./Study Type	MRID	Results
870.5300 *In Vitro* Mammalian Cell Mutation Test in Chinese Hamster Ovary Cells BioReliance Laboratories Study AA38UL.782.BTL August 8, 2001	45593815	Negative
870.5375 *In Vitro* Chromosomal Aberration in Chinese Hamster Ovary BioReliance Laboratories Study AA38UL.331.BTL August 21, 2001	45593814	Positive for the induction of structural chromosome aberrations (clastogenesis), but negative for induction of numerical aberrations in CHO cells in this assay.
870.5395 *In Vivo* Micronucleus Assay in Mice BioReliance Laboratories Study AA38UL.123.BTL October 2, 2001	45593816	Negative
870.6200 Inhalation Acute Neurotoxicity - Rats WIL Research Laboratories, Inc. Study No. WIL-418008 January 7, 2002	45593817	**NOAEL = 27 ppm (0.16 mg/L).** **LOAEL = 93 ppm (0.54 mg/L) based on FOB findings (clonic convulsions, decreased body temperature), and decreased motor activity (↓75-78% in males, 81-84% in females).** FOB findings and decreased motor activity indicated that iodomethane was neurotoxic at 93 (0.54 mg/L) and 401 ppm (2.33 mg/L). Analytical concentrations tested: 0, 27, 93, 401 ppm (0.16, 0.54, 2.33 mg/L) as a single, whole-body, 6-hour exposure. **Acceptable/Guideline**
870.6200 Feeding Subchronic Neurotoxicity - Rats	–	Not required for non-food fumigant use.

OPPTS No./Study Type	MRID	Results
870.7485 Metabolism - Rat WIL Research Laboratories, Inc. Study No. WIL-418007 March 27, 2002	45641401	Sprague-Dawley rats were orally dosed or exposed via inhalation with [^{14}C] CH_3I. Maximum blood concentrations were achieved within 4 hours (oral) and 0-2 hours (inhalation), and were proportional to dose/concentration. Initial $t_{½}$ was 5.1-7.2 hours, and terminal $t_{½}$ was 116-136 hours. Radioactivity recovery was low in the main test, due to inefficient CO_2 trapping. Overall recovery in the supplementary test was increased due to increased recovery of carbon dioxide. In the supplemental test, recovered radioactivity was primarily as CO_2 (39.40-60.81% dose) and in the urine (26.50-33.40% dose) in all treated groups, while feces accounted for <2% dose. Radioactivity remained in the carcasses (11.92-14.39% dose) of all treated animals 168 hours following treatment in the main test. Elimination $t_{½}$ were 17.8-22.3 hours for urine and 29.7-38.0 hours for feces in all treatment groups of the main test. The elimination $t_{½}$ was 5.8-6.8 hours for CO_2 in all treatment groups of the supplementary test. At 0-1 hour post-treatment in orally treated rats and 233 ppm inhalation exposed rats, relatively high levels of radioactivity were observed in the liver and GI tract. Radioactivity was relatively high in the kidney, lung, and nasal turbinates of the 25 ppm inhalation exposed rats and in the kidney, thyroid, and lung of the 233 ppm inhalation exposed rats. At 6 hours post-oral dosing, tissue concentrations increased in the spleen (at 1.5 mg/kg only), kidney, brain, thyroid, lung, nasal turbinates, and fat (at 1.5 mg/kg only). Tissue concentrations decreased in all tissues of the inhalation exposed rats at 6 hours after exposure. At 168 hours post-dose, radioactivity had declined in all tissues and was highest in the kidney, liver, and thyroid. Tissue concentrations increased (not proportionally) with dose. The major metabolites were expired CO_2, and N-(methylthioacetyl) glycine and S-methyl glutathione which were excreted in the urine. Minor metabolites were methylthioacetic acid, methyl mercapturic acid, and S-methyl cysteine.

OPPTS No./Study Type	MRID	Results
870.7600 Dermal Penetration - Rat	–	Not required for non-food fumigant use. The test article quickly evaporates due to its high vapor pressure, so it is impossible to quantify a dermal dose.

METHYL IODIDE

CAS number: 74-88-4

Synonyms: Iodomethane

Molecular formula: CH_3I

Skin

TLV–TWA, 2 ppm (12 mg/m^3)

Summary

A TLV–TWA of 2 ppm (12 mg/m^3) is recommended for worker exposure to methyl iodide, in part, by analogy to the TLV for methyl bromide, which ACGIH considers to be approximately half as toxic. This value is intended to minimize the potential for eye irritation observed in exposed rats. It is also based, in part, on death from reported cancer in mice exposed weekly via injection, to a dose approximating a worker TWA exposure to 40–50 ppm; no such deaths were observed among mice exposed at half this dose. It also should provide a wide margin of protection against central nervous system (CNS) effects in the form of nausea, vomiting, vertigo, slurred speech, visual disturbances, tremor, irritability, coma, and eventual death reported for humans exposed to obviously high concentrations of methyl iodide at their worksites. Skin contact and absorption of methyl iodide is considered a possible contribution to the toxicity associated with the reported human exposures. Although tumorigenic responses were observed in rats and mice injected subcutaneously or intraperitoneally with methyl iodide, a TLV carcinogenicity notation is not assigned pending further review of the data.

Chemical and Physical Properties

Methyl iodide is a colorless liquid that turns yellow, red, or brown when exposed to light and moisture. Methyl iodide has a sweet ethereal odor with poor warning properties. Chemical and physical properties include:[1]

Molecular weight: 141.95
Specific gravity: 2.28 at 20°C
Melting point: –66.5°C
Boiling point: 42.5°C
Vapor pressure: 375 torr at 20°C
Solubility: soluble in about 50 parts of water; miscible with alcohol and ether
Decomposition products: iodide and hydrogen iodide may be released when methyl iodide undergoes thermal decomposition (270°C)

Conversion factors at 25°C and 760 torr:
1 ppm = 5.81 mg/m^3; 1 mg/m^3 = 0.172 ppm

Major Uses

Because of its high refractive index, methyl iodide is used in microscopy. It is also used as imbedding material for examining diatoms, in testing for pyridine, and as a methylating agent.

Animal Studies

Acute

An oral LD_{50} for methyl iodide of 150 to 220 mg/kg body weight has been reported for mice.[2] Hepatotoxicity was observed. Von Oettingen et al.[3] reported that a 15-minute exposure at 3800 ppm was fatal to rats. Bachem[4] found methyl iodide about 6 times as acutely toxic as methyl bromide to mice; the minimal fatal dose with 24 hours exposure being about 75 ppm. Buckell[5] determined the LC_{50} for mice for a 57-minute exposure to be 900 ppm. He considered methyl iodide at least as toxic as methyl bromide and 10 times as acutely toxic as carbon tetrachloride. Deichman and Gerarde[6] reported a rat LC_{50} of 232 ppm for a 4-hour exposure.

Subchronic

Rats exposed by inhalation to methyl iodide for 14 weeks at 30 and 60 ppm showed ocular irritation and depressed body weights without clinical or microscopic pathologic changes. Mortality was produced in rats within 4 weeks at exposures of 143 ppm. No signs of an adverse response were seen at 10 ppm.[7]

Chronic/Carcinogenicity

Because it is an alkylating agent, methyl iodide has been included in carcinogenicity tests. It produced local sarcomas in BD rats when injected subcutaneously with a weekly dosage of 10 mg/kg for an unstated period of time.[8] Intraperitoneal injections reportedly increased the incidence of lung tumors in Strain A mice, a cancer susceptible

strain.[9] The mice were injected weekly for 24 weeks with doses of 0.31 mmoles/kg (44 mg/kg/week). Survival was adversely affected. Half this dose per week allowed survival of all 20 mice so treated. This dose, 22 mg/kg/day, would equate to 20 to 25 ppm for an adult human inhaling the vapors for 8 hours, which lends some support to the recommended TLV–TWA.

Genotoxicity Studies

Methyl iodide was reported mutagenic for *Salmonella typhimurium* bacterial strains TA1535 and TA100 and a direct-acting mutagen for mouse lymphoma L5178Y/TK± cells.[10]

Human Studies

Garland and Camps[11] reported a fatal case of poisoning from methyl iodide in a chemical plant worker. The signs and symptoms included nausea, vomiting, diarrhea and oliguria, vertigo, slurred speech, visual disturbances, ataxia, tremor, irritability, drowsiness, and coma. The urine contained 90 mg of iodide per liter (45 mg per 24 hours), and the brain contained 6 mg of combined iodine.

A similar response from exposure to methyl iodide was reported by Appel et al.[12] in a male chemist; however, no indication of the inhaled concentrations of methyl iodide were given. Severe, prolonged, and possibly permanent central nervous system (CNS) injury was observed. Iodine was qualitatively determined in the urine as strongly positive. The report summarizes reports of several other similar cases, but no details of exposure concentrations are presented. Although there are no direct studies or case reports on dermal absorption of methyl iodide and resultant systemic toxicity, the above reports [11,12] imply that skin contact and absorption may have contributed to the observed toxic responses and that protective measures should be taken to prevent such exposure.

TLV Recommendation

A TLV–TWA of 2 ppm for methyl iodide, approximately half that for methyl bromide (see *TLV Documentation* for Methyl bromide), is recommended to minimize the potential for ocular irritation in animals[7] and CNS symptoms reported from fatal human cases of methyl iodide exposure.[11,12] Although only indirect evidence indicates a potential for dermal absorption,[11,12] a Skin notation is recommended as an additional preventive measure. Because the increase in lung tumors seen in Strain A mice[9] is not statistically significant, ACGIH recommends that methyl iodide carry no carcinogenicity notation. Sufficient data were not available to recommend SEN or carcinogenicity notations or a TLV–STEL. The reader is expected to be familiar with the section on *Excursion Limits* in the "Introduction to the Chemical Substance TLVs" of the current edition of the *Documentation of the TLVs and BEIs* for the guidance and control of excursions above the TLV–TWA, even when the 8-hour TWA is within the recommended limit.

Historical TLVs

1965: *Proposed:* TLV–TWA, 5 ppm; Skin
1967–1980: TLV–TWA, 5 ppm; Skin
1976–1980: TLV–STEL, 10 ppm
1979: *Proposed:* TLV–TWA, 2 ppm; TLV–STEL, 5 ppm; A2, Suspected Human Carcinogen; Skin
1981–1985: TLV–TWA, 2 ppm; TLV–STEL, 5 ppm; Skin; A2 Carcinogen
1984: *Proposed:* Withdraw TLV–STEL
1986–1995: TLV–TWA, 2 ppm; Skin; A2
1995: *Proposed:* Withdraw A2, Suspected Human Carcinogen
1996–present: TLV–TWA, 2 ppm; Skin

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DER #1

Iodomethane: Subchronic Inhalation Toxicity Study in Rats
Sponsor Name: Arvesta Corporation (Formerly Tomen Agro, Inc.). Year of Study - 2002.
MRID Nos. 45593810

DATA EVALUATION RECORD

IODOMETHANE

Study Type: §82-4, Subchronic Inhalation Toxicity Study in Rats

Work Assignment No. 4-02-174C (formerly 4-01-174C) MRID 45593810

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by
Pesticides Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
Rockville, MD 20850-3268

Primary Reviewer
John W. Allran, M.S.

Signature: John W Allran
Date: 5/13/02

Secondary Reviewer
Kelley VanVreede, M.S.

Signature: Kelley VanVreede
Date: 5/13/02

Program Manager
Mary L. Menetrez, Ph.D.

Signature: Mary L. Menetrez
Date: 5/13/02

Quality Assurance
Steve Brecher, Ph.D.

Signature: Steven Brecher
Date: 5/13/02

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: John Whalan **Signature:** John Whalan
Registration Action Branch 2, Health Effects Division (7509C) **Date** 7-17-02
EPA Secondary Reviewer: Alan Levy **Signature:** Alan C. Levy
Registration Action Branch 2, Health Effects Division (7509C) **Date** 7-17-02
EPA Work Assignment Manager: Sanyvette Williams-Foy **Signature:**
Registration Action Branch 2, Health Effects Division (7509C) **Date** 7/18/02

TXR#: 0050463

DATA EVALUATION RECORD

STUDY TYPE: Subchronic Inhalation Toxicity - rat; OPPTS 870.3465 [§82-4]; OECD 413.

PC CODE: 000011 **DP BARCODE:** D280803
SUBMISSION NO.: S609892

TEST MATERIAL (PURITY): Iodomethane (TM-425; 99.7% a.i.)

SYNONYMS: CH_3I; Methyl iodide

CITATION: Kirkpatrick, D.T. (2002) A 13-Week Inhalation Toxicity Study (With a Four-Week Interim Necropsy) of Iodomethane in Albino Rats. WIL Research Laboratories, inc. Ashland, OH. Laboratory Study No.: WIL-418015, January 28, 2002. MRID 45593810. Unpublished.

SPONSOR: Tomen Agro, Inc., 100 First Street, Suite 1700, San Francisco, CA

EXECUTIVE SUMMARY: In a subchronic inhalation toxicity study (MRID 45593810), iodomethane (99.7% a.i.; Lot/batch # 007403/02) was administered via whole-body inhalation to Crl:CD®(SD)IGS BR rats (20/sex/concentration) for 6 hours/day, 5 days/week for 13 weeks at analytical concentrations of 0, 5, 21, or 70 ppm (0, 0.029, 0.12, or 0.41 mg/L/day). Ten rats/sex/concentration were sacrificed after 4 weeks, and the remaining 10 rats/sex/concentration were sacrificed after 13 weeks. There were no effects of treatment on mortality, ophthalmology, urinalysis, hematology, organ weights, or gross pathology.

At 70 ppm, decreased ($p<=0.05$) body weights (decr. 7-13%) and cumulative body weight gains (decr. 26-34%) were observed in the males in the first 6 weeks. In the females at this concentration, cumulative body weight gains were decreased ($p<=0.05$) during the first 6 weeks and at week 12 (decr. 21-33%). Food consumption was decreased ($p<=0.01$) in the males at weeks 1 and 5 (↓12-14%). Following exposure, increased incidence and frequency of wet, yellow material was observed in the urogenital area of the males (4/20 vs 0/20 controls) and females (6/20 vs 0/20 controls). Frequency of this observation was 8% in the males and 20% in the females. Although this finding may have been due to treatment, it was considered to be of equivocal toxicological significance. Cholesterol was increased (incr. 43-67%; $p<=0.01$) in the males and females at weeks 4 and 13, but there were no corroborating macroscopic or

microscopic findings indicative of an effect on the liver.

Irritation of the respiratory system was observed in the 70 ppm males and females at the interim and terminal sacrifices. Microscopic findings indicated minimal to mild degeneration/regeneration of the nasal tissues characterized by subacute inflammation, respiratory epithelial metaplasia, degeneration, goblet cell hypertrophy, and squamous cell hyperplasia. Additionally in the females at this concentration, minimal alveolar macrophages were observed at the terminal sacrifice.

The only findings at 21 ppm were decreased body weights (decr. 10%; $p<=0.05$) and cumulative body weight gains (decr. 23%; $p<=0.01$) in the males at week 6.

The LOAEL for this study is 70 ppm (0.41 mg/L/day) based on initial decreases in body weights, body weight gains, and food consumption (males); and nasal degeneration. The NOAEL is 21 ppm (0.12 mg/L/day).

The submitted study is classified as **acceptable/guideline** and satisfies the guideline requirements for a subchronic inhalation toxicity study in the rat (OPPTS 870.3465; OECD 413).

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Iodomethane

Description:	Deep yellow translucent liquid
Lot/Batch #:	007403/02
Purity:	99.7% a.i.
Compound Stability:	Test substance was >99.6% a.i. throughout the duration of the study.
CAS #:	74-88-4
Molecular Weight	141.95 g/Mol
Structure:	$I\text{-}CH_3$

2. Vehicle: Air

3. Test animals:

Species:	Rat	
Strain:	Crl:CD®(SD)IGS BR	
Age/weight at study initiation:	Approximately 8 weeks/221-282 g, males; 162-213 g, females	
Source:	Charles River Laboratories, Raleigh, NC	
Housing:	Individually, in suspended wire mesh cages	
Diet:	Certified Rodent LabDiet® 5002 (PMI Nutrition International, Inc.), *ad libitum*, except during each 6-hour daily exposure and prior to blood sampling.	
Water:	Reverse-osmosis tap water, *ad libitum*, except during each 6-hour daily exposure.	
Environmental conditions:	**Temperature:**	21.4-22.6°C
	Humidity:	40.4-63.1%
	Air changes:	Not provided
	Photoperiod:	12 hours light/12 hours dark
Acclimation period:	15 days	

B. STUDY DESIGN

1. In life dates - Start: 06/20/01 End: 09/20/01

2. Animal assignment - Animals were randomly assigned, stratified by weight, to the test groups presented in Table 1.

Table 1. Study design [a]

Nominal Conc (ppm)	Analytical Conc. (ppm)	MMAD µm	GSD	Rats/sex [b]
0	0	NR	NR	20
6.6 ± 0.4	5 ± 0.6	NR	NR	20
24 ± 0.7	21 ± 1.0	NR	NR	20
77 ± 3.5	70 ± 2.10	NR	NR	20

a Data were obtained from pages 17, 711, and 725 of the study report. Values presented are the mean ± SD for the overall (13-week) study period.

b Ten rats/sex/group were sacrificed after 4 weeks of exposure; the remaining 10 rats/sex/group were sacrificed after 13 weeks of exposure.

NR Not required for vaporous compounds.

3. **Concentration selection rationale** - It was stated that exposure levels for the current 13-week study (presented in Table 1) were selected based on the results of a previous inhalation range-finding study in rats (WIL-418003); however, no further information was provided.

4. **Generation of the test atmosphere / chamber description** - Rats were dynamically exposed to iodomethane vapor for 6 hour/day, 5 days/week for 13 weeks via whole-body inhalation in 2.0 m^3 stainless-steel and glass Hazelton-style inhalation chambers. Test atmospheres were generated using an ambient temperature bubbler-type vaporization system, in which air is bubbled through the liquid test article. Test article vapors were collected in 250 mL glass gas washing bottles and were dispersed using compressed air, regulated by metering needle valves, through a 25 or 50 mm fritted disc. Dispersed gas was carried via Teflon tubing to a 2" I.D. glass chamber inlet, where the concentration was diluted to the target level by chamber ventilation air flow. Air supply to each chamber was charcoal- and HEPA-filtered, and of a constant temperature and humidity. Air flow in the chamber ranged from 12 to 15 changes per hour; temperature averaged from 21-25°C; relative humidity averaged 48-61%; and chamber ventilation averaged 453-455 SLPM.

Test atmosphere concentration - Test atmospheres were measured approximately every 35 minutes during each daily 6 hour exposure period using gas chromatography. Mean analytical results for the overall study are reported in Table 1 above. The variation between nominal and analytical concentrations was acceptable.

Particle size determination - Mass mean aerodynamic diameter (MMAD) and geometric standard deviation (GSD) were not determined for test atmospheres because the test article was delivered as a vapor..

5. **Statistics** - The following statistical procedures were employed:

Parameter	Statistical Test
Body weights, body weight gains, food consumption, hematology, clinical chemistry, and organ weights	One-way analysis of variance (ANOVA), followed by Dunnett's test if significant ANOVA.
Leukocytes occurring in low numbers (e.g. monocytes, eosinophils, and basophils)	Not subjected to statistical analyses

The levels denoting significance were $p \leq 0.05$ and $p \leq 0.01$ for each statistical comparison. In general, the statistical methods were considered appropriate. However, it was not stated that homogeneity of variances or normal distribution was determined for any of the data. These assumptions should be verified before proceeding with parametric analyses.

C. METHODS

1. Observations:

a. Cageside Observations - Animals were checked for mortality and moribundity twice daily and were observed for clinical signs of toxicity prior to and up to 2 hours following exposure.

b. Clinical Examinations - Detailed physical examinations were conducted weekly, beginning one week prior to initiation of exposure. In addition, examinations were performed prior to sacrifice.

c. Neurological Evaluations - Neurological endpoints were not specifically examined in this study; however, an acute neurotoxicity study in rats (MRID 45593817) was submitted for review concurrently with this study.

2. Body weight - Each rat was weighed weekly throughout the study, beginning one week prior to test substance administration, and again at termination. Group mean body weight gains were reported for each weekly interval during the study. Cumulative body weight gains were also reported for each week throughout the study.

3. Food consumption - Food consumption (g/animal/day) of each rat was recorded weekly throughout the study beginning one week prior to test article exposure.

4. Ophthalmoscopic examination - The eyes of each animal were examined by indirect ophthalmoscopy one week prior to treatment and again during week 4 prior to the interim sacrifice. The eyes of the remaining 10 rats/sex/concentration were examined during week 13 prior to terminal sacrifice.

5. Hematology & clinical chemistry - Blood was collected from the vena cava of each rat at the scheduled sacrifices (weeks 4 and 13). Animals were fasted overnight prior to blood sampling. The CHECKED (X) parameters were examined.

a. Hematology

X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc. (MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)*
X	Platelet count* [a]		Reticulocyte count
	Blood clotting measurements*		
X	(Activated partial thromboplastin time)		
	(Clotting time)		
X	(Prothrombin time)		

* Recommended for subchronic inhalation studies based on Guideline 870.3465

a Platelet estimates and red cell morphology data were included in individual data only if manual slides were examined after automated differential was conducted.

b. Clinical Chemistry

	ELECTROLYTES		OTHER
X	Calcium	X	Albumin*
X	Chloride	X	Creatinine*
	Magnesium	X	Urea nitrogen*
X	Phosphorus	X	Total Cholesterol*
X	Potassium*	X	Globulins
X	Sodium*	X	Glucose*
		X	Total bilirubin
	ENZYMES (more than 2 hepatic enzymes eg., *)	X	Total protein (TP)*
X	Alkaline phosphatase *		Triglycerides
	Cholinesterase (ChE)		Serum protein electrophoresis
	Creatine phosphokinase	X	Albumin/Globulin ratio
	Lactic acid dehydrogenase (LDH)		
X	Gamma Gutamyltransferase (GGT)		
X	Alanine amino-transferase (ALT/also SGPT)*		
X	Aspartate amino-transferase (AST/also SGOT)*		

* Recommended for subchronic inhalation studies based on Guideline 870.3465

6. **Urinalysis** - Urinalysis was not performed and is not required under Guideline 870.3465.

7. **Sacrifice and pathology** - After 4 weeks (interim sacrifice) or 13 weeks (terminal sacrifice), animals were fasted overnight and euthanized by exsanguination under isoflurane anesthesia. All animals were subjected to a gross pathological examination. The CHECKED (X) tissues were collected, preserved in 10% neutral buffered formalin (except for eyes with optic nerve which were fixed in Davidson's solution and testes with epididymides which were fixed in Bouin's solution), embedded in paraffin, and stained with hematoxylin and eosin. Additionally, the (XX) organs were weighed.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
	Tongue	X	Aorta*	XX	Brain*+
X	Salivary glands*	XX	Heart*+	X	Peripheral nerve*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	X	Pituitary*
X	Duodenum*	XX	Spleen*+	X	Eyes with optic nerve*
X	Jejunum*	XX	Thymus*+		GLANDULAR
X	Ileum*			XX	Adrenal gland*+
X	Cecum*		UROGENITAL	X	Lacrimal gland
X	Colon*	XX	Kidneys*+	XX	Parathyroids*
X	Rectum*		Urinary bladder*	XX	Thyroid*
XX	Liver*+	XX	Testes*+		OTHER
	Gall bladder (not rat)*	XX	Epididymides*+	X	Bone (sternum and/or femur)
	Bile duct (rat)*	X	Prostate*	X	Skeletal muscle
X	Pancreas*	X	Seminal vesicles*	X	Skin
	RESPIRATORY	XX	Ovaries with oviducts*+	X	All gross lesions and masses*
X	Trachea*	XX	Uterus with vagina*+[a]	X	Harderian glands
XX	Lungs including bronchi*	X	Mammary gland*		
X	Nose*[b]				
	Pharynx*				
X	Larynx*				

* Recommended for subchronic inhalation studies on rodents based on Guideline 870.3465
\+ Organ weights required
a Weighed only at the terminal (13-week) sacrifice
b Following decalcification, 6 cross-sections of the nasal cavities were prepared for microscopic examination according to the method of Morgan, 1991.

Microscopic examination was performed on all tissues collected from animals in the control and 70 ppm groups. Additionally, tissues from the kidneys, larynx, liver, lungs, nasal tissues, trachea, and any gross lesions were examined in the intermediate concentration groups.

II. RESULTS

A. OBSERVATIONS

1. **Clinical signs of toxicity** - Following exposure, increased incidence and frequency of wet, yellow material was observed in the urogenital area of the 70 ppm males (4/20 vs 0/20 controls) and females (6/20 vs 0/20 controls; Table 2). Although this finding may have been due to treatment, it was considered to be of equivocal toxicological significance. Several other clinical signs were observed in the 70 ppm animals, such as rales and dried secretions around the mouth, nose, and urogenital area; however, these observations were considered unrelated to treatment because they were low in incidence and frequency (i.e. usually occurring in only 1 animal for 1 day).

Table 2. Incidence [# animals (# occurrences out of 65 [b])] of wet yellow material in the urogenital area of rats immediately following exposure to iodomethane via whole-body inhalation for up to 13 weeks.[a]

Concentration (ppm)			
0	5	21	70
Males			
0 (0)	0 (0)	0 (0)	4 (5)
Females			
0 (0)	0 (0)	2 (2)	6 (13)

a Data were obtained from Table 4 on pages 51-52 of the study report; n=20.

b Total possible incidences following exposure = 65, based on exposure for 5 days/week for 13 weeks.

2. **Mortality** - There were no unscheduled deaths during the study.

B. BODY WEIGHT AND WEIGHT GAIN: At 70 ppm, body weights were significantly decreased ($p \leq 0.05$) in the males during weeks 2, 3, 5, and 6 (↓7-13%; Table 3). Cumulative body weight gains (determined weekly) were decreased ($p \leq 0.05$) in the 70 ppm males at weeks 1, 2, 3, 5, and 6 (↓26-34%) and in the 70 ppm females at weeks 1, 2, 3, 6, and 12 (↓21-33%). Additionally, in the 21 ppm males, decreases were noted in body weights (↓10%; $p \leq 0.05$) and cumulative body weight gains (↓23%; $p \leq 0.05$) at week 6. Cumulative body weight gains were also decreased in the 5 ppm males at week 1 (↓21%; $p \leq 0.05$); however, this decrease was incidental and not concentration-dependent. No other significant changes in body weights or cumulative body weight gains were noted in the males or females.

Table 3. Mean (± SD) body weights and overall body weight gains (g) in rats treated with iodomethane in the diet for up to 13 weeks.[a]

Study Week	N	Concentration (ppm)			
		0	5	21	70
Males					
0	20	247 ± 13.6	247 ± 13.1	248 ± 14.3	247 ± 13.5
2	20	315 ± 19.0	306 ± 20.3	306 ± 26.7	292 ± 25.3** (↓7)
6	10	418 ± 19.2	392 ± 25.5	376 ± 38.4* (↓10)	365 ± 40.8** (↓13)
0-6 gain	10	169 ± 21.0	147 ± 22.5	130 ± 32.1** (↓23)	119 ±32.5** (↓30)
Overall (0-13) gain	10	234 ± 34.5	220 ± 35.4	212 ± 50.4	199 ± 38.7 (↓15)
Females					
0	20	182 ± 11.0	182 ± 10.2	182 ± 9.4	182 ± 10.2
4	20	236 ± 17.7	236 ± 12.3	238 ± 18.1	228 ± 16.4 (↓3)
6	10	266 ± 26.0	250 ± 13.1	252 ± 24.2	242 ± 14.5 (↓9)
0-6 gain	10	81 ± 20.9	71 ± 8.0	70 ± 18.6	59 ± 14.0* (↓27)
Overall (0-13) gain	10	101 ± 19.5	105 ± 12.6	102 ± 26.5	84 ± 16.2 (↓17)

a Data were obtained from the study report, Table 6 on pages 55-60 and Table 7A on pages 67-72. Percent difference from controls, calculated by the reviewers, is included in parentheses.
* Significantly different from the control group at $p \leq 0.05$.
** Significantly different from the control group at $p \leq 0.01$.

C. **FOOD CONSUMPTION**: Food consumption was decreased ($p \leq 0.01$) in the 70 ppm males at weeks 1 and 5 (↓12-14%; Table 4). There were no other changes in food consumption in the males or females that could be attributed to treatment.

Table 4. Mean (± SD) food consumption (g/animal/day) in male rats treated with iodomethane via whole-body inhalation for up to 13 weeks.[a]

Study Week	Concentration (ppm)			
	0	5	21	70
1	22 ± 1.9	21 ± 1.6	21 ± 2.2	19 ± 1.6** (↓14)
5	25 ± 2.6	23 ± 2.2	24 ± 2.6	22 ± 2.4** (↓12)

a Data were obtained from Table 8 on pages 73-74 of the study report; n=20. Percent difference from controls, calculated by the reviewers, is included in parentheses.
** Significantly different from the control group at $p \leq 0.01$.

D. OPHTHALMOSCOPIC EXAMINATION: There were no treatment-related ophthalmological findings. Concentration-related increases in bilateral corneal crystals were observed in the females at week 4 (2, 4, 7, and 7; n=20) and week 12 (1, 2, 5, and 5; n=10) in the 0, 5, 21, and 70 ppm groups, respectively. Because bilateral corneal crystals were present at a comparable or higher incidence in control males at weeks 4 (11/20) and 12 (5/10) and at a higher total incidence in the females during pretest (25/92; not itemized by group), these findings were considered unrelated to treatment.

E. BLOOD ANALYSES

1. Hematology - There were no treatment-related hematological findings. In the males at week 4, prothrombin time was decreased at 70 ppm (↓10%; $p \leq 0.01$), and activated partial thromboplastin time was decreased at 21 and 70 ppm (↓11-12%; $p \leq 0.05$). However, these decreases were considered unrelated to treatment because they were minor and transient (not observed at week 13).

2. Clinical chemistry - Cholesterol was increased (↑43-67%; $p \leq 0.01$) in the 70 ppm males and females at weeks 4 and 13 (Table 5). There were no other concentration-dependent differences in clinical chemistry.

Table 5. Selected mean (± SD) cholesterol (mg/dL) in rats treated with iodomethane via whole-body inhalation for up to 13 weeks.[a]

Study week	N	Concentration (ppm)			
		0	5	21	70
Males					
4	20	44 ± 6.3	55 ± 9.5	51 ± 11.9	68 ± 17.6** (↑55)
13	10	48 ± 14.9	50 ± 13.7	55 ± 9.3	75 ± 12.7** (↑56)
Females					
4	20	49 ± 9.8	62 ± 16.4	62 ± 11.3	82 ± 13.0** (↑67)
13	10	70 ± 22	73 ± 17.1	83 ± 14.6	100 ± 13.2** (↑43)

a Data were obtained from Table 12 on pages 99 and 105 of the study report. Percent difference from controls, calculated by the reviewers, is included in parentheses.

** Significantly different from the control group at $p \leq 0.01$.

F. SACRIFICE AND PATHOLOGY

1. **Organ weight** - Relative (to body weight) liver weight was increased ($p \leq 0.01$) at 70 ppm in the males at week 13 (↑15%) and in the females at weeks 4 (↑8%) and 13 (↑22%; Table 6). Considering the lack of adverse histopathologic findings, this was likely an adaptive response. Additionally at week 13, the following differences ($p \leq 0.05$) from controls were noted but were considered to be minor and/or due to the lower terminal body weights in these animals and were thus deemed unrelated to treatment: (i) decreased absolute brain weight in the 70 ppm males and females (↓4-7%); (ii) decreased absolute heart weight in the 21 and 70 ppm males (↓10-12%); (iii) decreased absolute adrenal gland weight in the 70 ppm females (↓17%); and (iv) increased relative heart weight in the 70 ppm females (↑12%). There were no other concentration-dependent differences in organ weights.

Table 6. Selected mean (± SD) liver weights in rats treated with iodomethane via whole-body inhalation for up to 13 weeks.[a]

Parameter	Study Week	Concentration (ppm)			
		0	5	21	70
Males					
Terminal body weights	13	451 ± 34.7	435 ± 41.1	430 ± 58.1	416 ± 45.2
Liver - absolute (g)	13	11.03 ± 1.428	10.96 ± 1.477	11.40 ± 2.303	11.69 ± 1.476
relative (%)		2.436 ± 0.144	2.513 ± 0.160	2.639 ± 0.284	2.809 ± 0.140** (↑15)
Females					
Terminal body weights	4	212 ± 15.2	211 ± 13.5	213 ± 16.0	198 ± 18.1
	13	266 ± 25.5	263 ± 16.8	265 ± 30.8	245 ± 15.9
Liver - absolute (g)	4	6.63 ± 0.599	6.38 ± 0.445	6.97 ± 0.824	6.70 ± 0.639
relative (%)		3.123 ± 0.160	3.032 ± 0.184	3.260 ± 0.217	3.387 ± 0.122** (↑8)
Liver - absolute (g)	13	7.05 ± 0.512	7.22 ± 0.559	7.81 ± 1.320	7.93 ± 0.838
relative (%)		2.659 ± 0.135	2.749 ± 0.179	2.952 ± 0.364* (↑11)	3.235 ± 0.272** (↑22)

a Data were obtained from Tables 18-21 on pages 113-135 of the study report,; n=10. Percent difference from controls, calculated by the reviewers, is included in parentheses.

** Significantly different from the control group at $p \leq 0.01$.

2. **Gross pathology** - There were no treatment-related macroscopic findings. Several gross observations were noted at 70 ppm (1/20 animals vs 0/20 controls), such as enlarged lymph node and pale pancreas in the males and depressed area(s) on the kidneys in the females; however, these findings were considered unrelated to treatment because they were minimal in incidence and were uncorroborated by microscopic findings that would indicate an effect of treatment.

3. **Microscopic pathology** - Irritation of the respiratory system was observed in the 70 ppm males and females at the interim (Table 7a) and terminal (Table 7b) sacrifices. Signs of local inhalation effects included the following findings in the nasal tissues (usually minimal to mild): (i) subacute inflammation; (ii) respiratory epithelial metaplasia; (iii) degeneration; (iv) goblet cell hypertrophy; and (v) squamous cell hyperplasia. Additionally in the 70 ppm females, minimal alveolar macrophages were observed at the terminal sacrifice (5/10 treated vs 2/10 controls). Finally, in the 70 ppm females, minimal liver necrosis was observed at the interim sacrifice (2/10 treated vs 0/10 controls); however, this finding was considered unrelated to treatment because it was not observed at the terminal sacrifice and it was minor in incidence and severity.

Table 7a. Selected microscopic findings (#affected) in nasal tissues in rats treated with iodomethane via whole-body inhalation for 4 weeks (interim sacrifice).[a]

Nasal Level	Microscopic Observation		Concentration (ppm) 0	5	21	70
		Males				
II	Subacute inflammation -	Minimal	0	0	1	1
	Respiratory epithelial metaplasia -	Minimal	0	0	0	2
III	Respiratory epithelial metaplasia -	Minimal	0	0	0	1
IV	Degeneration -	Total	0	0	0	5
		Minimal	0	0	0	4
		Mild	0	0	0	1
	Respiratory epithelial metaplasia -	Minimal	0	0	0	1
V	Degeneration -	Total	0	0	0	10
		Minimal	0	0	0	9
		Mild	0	0	0	1
VI	Degeneration -	Total	0	0	0	5
		Minimal	0	0	0	4
		Mild	0	0	0	1
		Females				
I	Subacute inflammation -	Minimal	0	0	0	3
II	Degeneration -	Minimal	0	0	0	3
	Respiratory epithelial metaplasia -	Minimal	0	0	1	5
	Goblet cell hypertrophy -	Minimal	0	0	0	1
III	Subacute inflammation -	Minimal	0	1	0	2
	Degeneration -	Minimal	0	0	1	4
IV	Degeneration -	Minimal	1	0	0	6
V	Degeneration -	Minimal	0	0	0	7
VI	Degeneration -	Minimal	0	0	0	1

a Data were obtained from Table 22 on pages 147-149 and 160-162 of the study report; n=10.

Table 7b. Selected microscopic findings (#affected) in nasal tissues in rats treated with iodomethane via whole-body inhalation for 13 weeks (terminal sacrifice).[a]

Nasal Level	Microscopic Observation		Concentration (ppm)			
			0	5	21	70
Males						
I	Squamous cell hyperplasia -	Minimal	0	0	0	1
II	Degeneration -	Minimal	0	0	0	3
	Respiratory epithelial metaplasia -	Minimal	0	0	0	2
III	Degeneration -	Total	0	0	0	8
		Minimal	0	0	0	4
		Mild	0	0	0	4
IV	Degeneration -	Total	0	0	0	10
		Minimal	0	0	0	4
		Mild	0	0	0	5
		Moderate	0	0	0	1
V	Degeneration -	Total	0	0	0	7
		Minimal	0	0	0	3
		Mild	0	0	0	2
		Moderate	0	0	0	2
VI	Degeneration -	Total	0	0	0	4
		Minimal	0	0	0	2
		Mild	0	0	0	2
Females						
II	Degeneration -	Minimal	0	0	0	3
	Respiratory epithelial metaplasia -	Mild	0	0	0	1
III	Degeneration -	Total	0	0	0	7
		Minimal	0	0	0	6
		Mild	0	0	0	1
IV	Degeneration -	Total	0	0	1	9
		Minimal	0	0	1	5
		Mild	0	0	0	4
V	Degeneration -	Total	0	0	1	7
		Minimal	0	0	1	5
		Mild	0	0	0	2
VI	Degeneration -	Total	0	0	0	3
		Minimal	0	0	0	1
		Mild	0	0	0	2

a Data were obtained from Table 23 on pages 176-178 and 191-193 of the study report; n=10.

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS: It was concluded that the LOAEL was 70 ppm based on decreased body weight gains, decreased food consumption (males only), increased cholesterol, increased relative liver weights, and increased incidences of urogenital staining and degeneration/regeneration of the olfactory epithelium in males and females. The NOAEL was 21 ppm.

B. REVIEWER COMMENTS: Following exposure, wet, yellow material was observed in the urogenital area of the 70 ppm males (4/20 vs 0/20 controls) and females (6/20 vs 0/20 controls). Frequency of this observation at 70 ppm was 8% in the males and 20% in the females. Although this finding may have been due to treatment, it was considered to be of equivocal toxicological significance.

At 70 ppm, decreased ($p \leq 0.05$) body weights (↓7-13%) and cumulative body weight gains (↓26-34%) were observed in the males in the first 6 weeks. In the females at this concentration, cumulative body weight gains were decreased ($p \leq 0.05$) during the first 6 weeks and at week 12 (↓21-33%). Additionally in the 21 ppm males, decreases were noted in body weights (↓10%; $p \leq 0.05$) and cumulative body weight gains (↓23%; $p \leq 0.01$) at week 6. The effect of treatment on body weights and body weight gains was only observed during the first 6 weeks, and recovery was observed after week 6. Decreased ($p \leq 0.01$) food consumption occurred in the males at weeks 1 and 5 (↓12-14%).

Cholesterol was increased (↑43-67%; $p \leq 0.01$) in the males and females at weeks 4 and 13. Because there were no corroborating macroscopic or microscopic findings indicative of an effect on the liver, these increases are considered equivocal.

Irritation of the respiratory system was observed in the 70 ppm males and females at the interim and terminal sacrifices. Microscopic findings indicated minimal to mild degeneration/regeneration of the nasal tissues characterized by subacute inflammation, respiratory epithelial metaplasia, degeneration, goblet cell hypertrophy, and squamous cell hyperplasia. Additionally, in the females at this concentration, minimal alveolar macrophages were observed at the terminal sacrifice.

The LOAEL for this study is 70 ppm (0.41 mg/L/day) based on initial decreases in body weights, body weight gains, and food consumption (males); and nasal degeneration. The NOAEL is 21 ppm (0.12 mg/L/day).

The submitted study is classified as **acceptable/guideline** and satisfies the guideline requirements for a subchronic inhalation toxicity study in the rat (OPPTS 870.3465; OECD 413).

C. STUDY DEFICIENCIES: The following deficiency was noted but does not affect the conclusions of this DER:

- No concentration selection rationale was provided.

DATA FOR ENTRY INTO ISIS

90-Day Inhalation Study - rats (870.3465)

PC code	MRID #	Study type	Species	Duration	Route	Dosing method	Conc. range mg/L/day	Concs. tested mg/L/day	NOAEL mg/L/day	LOAEL mg/L/day	Target organ(s)	Comments
000011	45593810	subchronic	rat	90 days	inhalation	whole body	0.029-0.41	0, 0.029, 0.12, 0.41	0.12	0.41	BW, BWG, FC, nasal cavity	Concs. in mg/L/day

DER #2

Iodomethane: Inhalation Developmental Toxicity Study in Rats
Sponsor Name: Arvesta Corporation (Formerly Tomen Agro, Inc.). Year of Study - 2002.
MRID Nos. 45593812

DATA EVALUATION RECORD

IODOMETHANE

Study Type: §83-3a; Developmental Toxicity Study in Rats

Work Assignment No. 4-02-174E (formerly 4-01-174E) (MRID 45593812)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Pesticides Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
Rockville, MD 20850-3268

Primary Reviewer:
Kelley Van Vreede, M.S.

Signature: Kelley Van Vreede
Date: 5/10/02

Secondary Reviewer:
John W. Allran, M.S.

Signature: John W Allran
Date: 5/10/02

Project Manager:
Mary L. Menetrez, Ph.D.

Signature: Mary L Menetrez
Date: 5/10/02

Quality Assurance:
Steven Brecher, Ph.D.

Signature: Steven Brecher
Date: 5/13/02

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: John Whalan **Signature:** John Whalan
Registration Action Branch 2, Health Effects Division (7509C) **Date** 7-17-02
EPA Secondary Reviewer: Alan Levy **Signature:** Alan C. Levy
Registration Action Branch 2, Health Effects Division (7509C) **Date** 7-17-02
Work Assignment Manager: Sanyvette Williams-Foy **Signature:**
Registration Action Branch 2, Health Effects Division (7509C) **Date** 7/18/02

TXR#: 0050463

DATA EVALUATION RECORD

STUDY TYPE: Prenatal Developmental Toxicity Study - Rat; OPPTS 870.3700a [§83-3a]; OECD 414.

PC CODE: 000011 **DP BARCODE:** D280803
SUBMISSION NO.: S609892

TEST MATERIAL (PURITY): Iodomethane (99.6% a.i.)

SYNONYMS: Methyl iodide

CITATION: Nemec, M. D. (2002) An Inhalation Prenatal Developmental Toxicity Study of Iodomethane in Rats.. WIL Research Laboratories, Inc., Ashland, OH. Laboratory Study No.: WIL-418010, January 11, 2002. MRID 45593812. Unpublished.

SPONSOR: Arvesta Corporation, 100 First Street, Suite 1700, San Francisco, CA

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 45593812), groups of 24 female Crl:CD®(SD)IGS BR rats were dynamically exposed to iodomethane vapor (Lot/batch # 007403; 99.6% a.i.) in whole-body inhalation chambers at analytical concentrations of 0, 5, 20, or 60 ppm (0, 0.03, 0.12, or 0.35 mg/L/day) six hours per day on gestation days (GDs) 6 through 19. All surviving dams were sacrificed on GD 20 and their fetuses were removed by cesarean section and examined.

No mortalities occurred during the study. When compared to concurrent controls, no treatment-related changes were observed in clinical signs, the number of live and dead fetuses, resorptions, sex ratios, post-implantation losses, or maternal gross pathology.

In the 60 ppm dams, decreased ($p<=0.01$) body weight gains were noted throughout most of treatment (GDs 6-20; decreased 19%). In addition, adjusted (for gravid uterine weights) body weight gains were decreased ($p<=0.01$) in these animals (decreased 28%). The only statistically significant differences ($p<=0.05$) in body weights were slight (decreased 5-6%), and occurred on GDs 7 and 20. Mean maternal food consumption was decreased ($p<=0.05$) at the beginning

(GDs 6-9) and end (GDs 17-20) of treatment (decreased 7-48%). Food consumption was decreased for the overall treatment interval (GDs 6-20) by 8% relative to concurrent controls.

The maternal LOAEL is 60 ppm (0.35 mg/L/day) based on decreased body weight gain (↓19%; ↓5-6% absolute body weight). The maternal NOAEL is 20 ppm (0.12 mg/L/day).

No treatment-related developmental findings were noted at any concentration tested.

The developmental toxicity LOAEL was not observed. The developmental toxicity NOAEL is 60 ppm (0.35 mg/L/day) .

This study is classified **acceptable/guideline** (OPPTS 870.3700a; OECD 414) and satisfies the requirements for a developmental study in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Flagging, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test material: Iodomethane

Description:	Deep yellow, translucent liquid
Lot/Batch #:	007403
Purity:	99.6% a.i.
Compound Stability:	The test substance was stable in the test atmosphere throughout the study.
CAS #:	74-88-4
Molecular Weight	141.95 g/Mol
Structure:	$I\text{-}CH_3$

2. Vehicle and/or positive control: None

3. Test animals:

Species:	Rat	
Strain:	Crl: CD® (SD) IGS BR	
Age/weight at study initiation:	Approximately 84 days old on GD 0; 250-253 g (group mean weight range on GD 0)	
Source:	Charles River Laboratories, Raleigh, NC	
Housing:	Individually, in suspended wire mesh cages	
Diet:	Certified Rodent LabDiet® 5002 (PMI Nutrition International, Inc.), *ad libitum*, except during exposure periods	
Water:	Reverse osmosis-treated tap water, *ad libitum*, except during exposure periods	
Environmental conditions:	**Temperature:**	18-25°C
	Humidity:	37-59%
	Air changes:	Approximately 12-15/hr.
	Photoperiod:	12 hours light/12 hours dark
Acclimation period:	14 days	

B. PROCEDURES AND STUDY DESIGN

1. In life dates - Start: 05/01/01 End: 05/25/01

2. Mating: Females were mated (1:1) with males from the same supplier and strain. The day on which sperm in a vaginal smear or copulation plug was observed was designated as gestation day (GD) 0.

3. Animal assignment: Animals were assigned (stratified by body weight) to dose groups as indicated in Table 1.

Table 1. Animal assignment [a]

Concentration (ppm)	0	5	20	60
# Females	24	24	24	24

a Obtained from the study report, page 16.

4. **Concentration selection rationale:** It was stated that the concentration levels were selected based on the results of a range finding inhalation study (WIL-418003). Excessive toxicity in the dams was noted at 100/150 ppm (mortality, moribundity, clinical signs, decreased body weight gains, and decreased food consumption). Decreased body weights, body weight gains, and food consumption were observed in the 75 ppm dams. Decreased implantation sites were noted at 75 and 100/150 ppm. The maternal and developmental NOAEL was 25 ppm. Information regarding the duration of exposure was not provided.

5. **Exposure:** Each group of dams was dynamically exposed to iodomethane vapor in one of four glass, whole-body inhalation chambers, for six hours per day on GDs 6 through 19. The vapor was generated using an ambient temperature bubbler-type vaporization system in which air was bubbled through the liquid test article. The generation flow rate ranged from 6 to 50 mL/min. The ventilation flow rate was 450 LPM. Food and water were withheld during exposure.

6. **Exposure characterization:** The nominal chamber concentrations were 0, 7.6, 26, and 70 ppm, and the mean analytical concentrations were 0, 5, 20, and 60 ppm (0.03, 0.12, and 0.35 mg/L/day). Exposure concentrations within each test chamber were measured via gas chromatography approximately every 35 minutes (at least 10 times) during each daily exposure period.

C. OBSERVATIONS

1. **Maternal observations and evaluations:** All dams were observed twice daily for mortality and moribundity. Detailed clinical observations were recorded daily. Body weights for all dams were recorded on GD 0 and daily from GDs 6 to 20. Mean body weight gains were calculated for daily intervals and GDs 6-9, 9-12, 12-16, 16-20, 6-20, and 0-20. Food consumption was measured on GD 0 and daily from GDs 6 to 20. All surviving dams were sacrificed on GD 20 and subjected to gross necropsy. The uterus was removed from each dam and weighed. All fetuses were removed by cesarean section and examined. The number and location of implantations sites, resorptions (early and late), and live and dead fetuses were recorded.

2. **Fetal evaluations:** Each fetus delivered by cesarean section was weighed, sexed, and examined for external and visceral abnormalities. The heads from approximately one-half of the fetuses in each litter were placed in Bouin's fixative for subsequent examination by the Wilson technique. The heads from the remaining fetuses were examined by a mid-coronal slice. All fetal carcasses were eviscerated, fixed in absolute ethanol, macerated in KOH, stained using a modification of the Dawson and Inouye method, and subjected to skeletal examination.

D. DATA ANALYSIS

1. Statistical analyses: Data were subjected to the following statistical procedures listed below. Statistical significance was denoted at α=0.05 and 0.01.

Parameter	Statistical procedure
Corpora lutea Total implantations Viable fetuses Fetal weights Maternal body weight Maternal body weight gains Maternal net body weight Maternal net body weight gains Gravid uterine weight Maternal food consumption	ANOVA (parametric) Dunnett's test (parametric) as necessary
Litter proportions of intrauterine data (considering the litter, rather than the fetus, as the experimental unit), mean litter proportions of malformations and variations	Krukal Wallis test (non-parametric) Mann-Whitney U-test (non-parametric) as necessary

2. Indices: The following index was calculated from cesarean section records of animals in the study:

$$\textit{Postimplantation loss (\%)} = \frac{\textit{\# dead fetuses, resorptions (early and late) per group}}{\textit{\# implantation sites per litter}} \times 100$$

3. Historical control data: Historical control data for cesarean section parameters and fetal abnormalities were presented. Eighteen developmental studies were performed between 4/98 and 6/99.

II. RESULTS

A. MATERNAL TOXICITY

1. Mortality and clinical observations: No mortalities occurred during the study. Increased incidences of abdominal hair loss were noted in the 60 ppm animals compared to controls. This finding was of equivocal toxicological importance.

2. Body weight: Body weight gain data are summarized in Table 2. Decreased ($p \leq 0.01$) body weight gains were noted in the 60 ppm dams throughout most of treatment (GDs 6-20; ↓19%). In addition, adjusted (for gravid uterine weights) body weight gains were decreased ($p \leq 0.01$) in

these animals (↓28%). The only statistically significant differences ($p \leq 0.05$) in body weights were slight (↓5-6%), and occurred on GDs 7 and 20.

Table 2. Mean (±SD) maternal body weight gain (g). [a]

Interval	Concentration in ppm (# of Dams)			
	0 (n=24)	5 (n=23)	20 (n=23)	60 (n=22)
Pretreatment:				
Days 0-6	35±8.6	39±8.4	37±7.7	34±6.6
Treatment:				
Days 6-7	2±3.5	2±4.1	3±3.8	-11±7.9** (↓650)
Days 7-8	2±8.3	3±3.7	3±2.8	7±4.9* (↑250)
Days 6-9	7±5.0	9±5.3	9±5.2	0±6.0** (↓100)
Days 16-20	60±8.4	58±8.8	56±10.9	49±9.0** (↓18)
Days 6-20	111±13.6	109±14.0	104±18.8	90±15.3** (↓19)
Adjusted BW Gain	58.0±12.11	59.7±13.27	57.3±10.94	41.6±13.85** (↓28)

a Data obtained from Tables 5 and 6, pages 44 through 47.
* Significantly different from controls at $p \leq 0.05$.
** Significantly different from controls at $p \leq 0.01$.

3. **Food consumption:** Food consumption data are summarized in Table 3. Mean maternal food consumption was decreased ($p \leq 0.05$) in the 60 ppm dams at the beginning (GDs 6-9) and end (GDs 17-20) of treatment (↓7-48%). Food consumption was decreased for the overall treatment interval (GDs 6-20) by 8% relative to concurrent controls.

Table 3. Mean (±SD) maternal food consumption (g/rat/day). [a]

Interval	Concentration in ppm (# of Dams)			
	0 (n=24)	5 (n=23)	20 (n=23)	60 (n=22)
Pretreatment:				
Days 0-6	23±3.1	23±2.2	23±2.1	23±2.1
Treatment:				
Days 6-7	25±3.7	23±3.0	23±2.4	13±4.6** (↓48)
Days 17-18	27±2.9	27±3.0	27±2.5	25±3.4* (↓7)
Days 6-20	25±2.2	25±1.5	24±2.2	23±2.1** (↓8)

a Data obtained from Table 7, pages 48 through 50.
* Significantly different from controls at $p \leq 0.05$.
** Significantly different from controls at $p \leq 0.01$.

4. **Gross pathology:** No treatment-related gross pathological findings were observed in any group.

5. Cesarean section data: Cesarean section data are presented in Table 4. No treatment-related findings were noted in the number of live and dead fetuses, resorptions, sex ratios, fetal weights, or post-implantation losses.

Table 4. Cesarean section observations [a]

Observation	Concentration (ppm)			
	0	5	20	60
# Animals Assigned (Mated)	24	24	24	24
# Animals Pregnant	24	23	23	22
Pregnancy Rate (%)	100	95.8	95.8	91.7
# Nonpregnant	0	1	1	2
Maternal Wastage				
# Died	0	0	0	0
# Died Pregnant	0	0	0	0
# Died Nonpregnant	0	0	0	0
# Aborted	0	0	0	0
# Premature Delivery	0	0	0	0
Total # Corpora Lutea	401	396	385	368
Corpora Lutea/Dam	16.7±2.12	17.2±2.26	16.7±1.54	16.7±1.70
Total # Implantations	384	376	354	338
(Implantations/Dam)	16.0±1.84	16.3±1.87	15.4±2.74	15.4±1.47
Total # Litters	24	23	23	22
Total # Live Fetuses	367	354	337	326
(Live Fetuses/Dam)	15.3±2.03	15.4±1.53	14.7±3.11	14.8±1.79
Total # Dead Fetuses	0	0	0	0
(Dead Fetuses/Dam)	0.0±0.00	0.0±0.00	0.0±0.00	0.0±0.00
Total # Resorptions [b]	17	22	17	12
Early	17	22	16	12
Late	0	0	1	0
Resorptions/Dam [b]	0.71	0.96	0.74	0.54
Early	0.7±0.75	1.0±1.36	0.7±0.97	0.5±0.67
Late	0.0±0.00	0.0±0.00	0.0±0.21	0.0±0.00
Litters with Total Resorptions	0	0	0	0
Mean Fetal Weight (g)	3.7±0.25	3.7±0.23	3.7±0.22	3.6±0.31
Males	NR	NR	NR	NR
Females	NR	NR	NR	NR
Sex Ratio (male, %)	0.50	0.45	0.53	0.49
Preimplantation Loss (%)	0.7±0.81	0.9±1.39	1.3±2.21	1.4±1.29
Postimplantation Loss (%)	0.7±0.75	1.0±1.36	0.7±1.05	0.5±0.67

a Data obtained from Table 1, page 38 and Table 9, page 54 in the study report.
b Calculated by the reviewers from data presented in this table.
NR Not reported

B. DEVELOPMENTAL TOXICITY

1. **External examination:** Selected external observations are presented in Table 5a. One 60 ppm fetus was observed to have cleft palate, a malformation. This finding was within range of historical controls and was considered to be incidental. No external variations were observed.

2. **Visceral examination:** Selected visceral observations are presented in Table 5b. A major blood vessel variation was noted in the control and 20 ppm groups. Although beyond the range of historical controls, the finding was not concentration-dependent and was considered unrelated to treatment. No visceral malformations were observed.

3. **Skeletal examination:** Selected skeletal observations are presented in Table 5c. No skeletal malformations were observed. Incidences of slight to moderate malaligned sternebra(e), a variation, were concentration-dependently increased in the 20 and 60 ppm groups relative to concurrent controls. Although the fetal incidence at 60 ppm (0.9%) slightly exceeded the historical control range (0.0-0.8%), this variation was considered not to be toxicologically important.

Table 5a. External examinations [a]

Observations [b]	Concentration (ppm)				
	0	5	20	60	Historical Controls [c]
#Fetuses (litters) examined	367 (24)	354 (23)	337 (23)	326 (22)	6028 (403)
Malformations					
Cleft palate	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.3 (4.5)	0.0-0.3

a Data obtained from Table 11, pages 58 in the study report.
b Fetal incidence % (litter incidence %), calculated by the reviewers
c Historical control data were obtained from Appendix D, pages 246 through 249 of the study report, and were reported as percent per litter.

Table 5b. Visceral examinations [a]

Observations [b]	Concentration (ppm)				
	0	5	20	60	Historical Controls [c]
#Fetuses (litters) examined	367 (24)	354 (23)	337 (23)	326 (22)	6027 (403)
Variations					
Major blood vessel variation	0.27 (4.2)	0.0 (0.0)	0.3 (4.3)	0.0 (0.0)	0.0-0.2

a Data obtained from Table 13, page 63 in the study report.
b Fetal incidence % (litter incidence %), calculated by the reviewers
c Historical control data were obtained from Appendix D, pages 246 through 249 of the study report, and were reported as percent per litter.

Table 5c. Skeletal examinations [a]

Observations [b]	Concentration (ppm)				
	0	5	20	60	Historical Controls [c]
#Fetuses (litters) examined	367 (24)	354 (23)	337 (23)	326 (22)	6027 (403)
Variations					
Cervical centrum #1 ossified	18.8 (79.2)	16.2 (69.6)	19.3 (73.9)	16.1 (63.6)	7.3-27.6
Sternebra(e) malaligned (slight/moderate)	0.0 (0.0)	0.0 (0.0)	0.3 (4.3)	0.9 (9.1)	0.0-0.8

a Data obtained from Table 13, page 63 in the study report.
b Fetal incidence % (litter incidence %), calculated by the reviewers
c Historical control data were obtained from Appendix D, pages 246 through 249 of the study report, and were reported as percent per litter.

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS: It was concluded that whole-body inhalation exposure of iodomethane vapor caused reduced maternal body weight gains, body weights, net body weights, net body weight gains, and food consumption at 60 ppm. No developmental toxicity was observed at any concentration tested. The maternal LOAEL was 60 ppm. The maternal NOAEL was 20 ppm. The developmental LOAEL was not observed. The developmental NOAEL was 60 ppm.

B. REVIEWER COMMENTS:

1. Maternal toxicity: Decreased ($p \leq 0.01$) body weight gains were noted in the 60 ppm dams throughout most of treatment (GDs 6-20; ↓19%). In addition, adjusted (for gravid uterine weights) body weight gains were decreased ($p \leq 0.01$) in these animals (↓28%). The only statistically significant differences ($p \leq 0.05$) in body weights were slight (↓5-6%), and occurred on GDs 7 and 20. Mean maternal food consumption was decreased ($p \leq 0.05$) in the 60 ppm dams at the beginning (GDs 6-9) and end (GDs 17-20) of treatment (↓7-48%). The 8% decrease in food consumption at 60 ppm relative to controls for the overall treatment interval (GDs 6-20) is not considered adverse. Increased incidences of abdominal hair loss in the 60 ppm animals compared to controls was not an adverse finding.

The maternal LOAEL is 60 ppm (0.35 mg/L/day) based on decreased body weight gain (↓19%; ↓5-6% absolute body weight). The maternal NOAEL is 20 ppm (0.12 mg/L/day).

2. Developmental toxicity:
a. Deaths/Resorptions: No treatment-related differences in the number of fetal deaths or resorptions were noted.

b. Altered Growth: Fetal weights were comparable to controls.

c. Developmental Variations/Anomalies: Incidences of slight to moderate malaligned sternebra(e), a variation, were concentration-dependently increased in the 20 and 60 ppm groups relative to concurrent controls. Although the fetal incidence at 60 ppm (0.9%) slightly exceeded the historical control range (0.0-0.8%), this variation was considered not to be toxicologically important.

d. Malformations: No treatment-related external, visceral, or skeletal malformations were noted.

The developmental toxicity LOAEL was not observed. The developmental toxicity NOAEL is 60 ppm (0.35 mg/L/day).

This study is classified **acceptable/guideline** (OPPTS 870.3700a; OECD 414) and satisfies the requirements for a developmental study in the rat.

C. **STUDY DEFICIENCIES:** No study deficiencies were noted.

DATA FOR ENTRY INTO ISIS

Developmental Study - rat (870.3700a)

PC code	MRID #	Study type	Species	Duration	Route	Dosing method	Conc. range mg/L/day	Conc. tested mg/L/day	NOAEL mg/L/day	LOAEL mg/L/day	Target organ(s)	Comments
000011	45593812	developmental	rat	GD 6-19	inhalation	whole body	0.03-0.35	0, 0.03, 0.12, 0.35	0.12	0.35	decreased BWG decreased FC	maternal concentrations
000011	45593812	developmental	rat	GD 6-19	inhalation	whole body	0.03-0.35	0, 0.03, 0.12, 0.35	0.35	Not observed		developmental concentrations

12

DER #3

Iodomethane: Inhalation Developmental Toxicity Study in Rabbits
Sponsor Name: Arvesta Corporation (Formerly Tomen Agro, Inc.). Year of Study - 2002.
MRID Nos. 45593811

DATA EVALUATION RECORD

IODOMETHANE

Study Type: §83-3b; Developmental Toxicity Study in Rabbits

Work Assignment No. 4-02-174A (formerly 4-01-174A) (MRID 45593811)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Pesticides Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
Rockville, MD 20850-3268

Primary Reviewer:
Kelley Van Vreede, M.S.

Signature: Kelley Van Vreede
Date: 5/10/02

Secondary Reviewer:
John W. Allran, M.S.

Signature: John W Allran
Date: 5/14/02

Project Manager:
Mary L. Menetrez, Ph.D.

Signature: Mary L Menetrez
Date: 5/10/02

Quality Assurance:
Steven Brecher, Ph.D.

Signature: Steven Brecher
Date: 5/13/02

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: John Whalan **Signature:** John Whalan
Registration Action Branch 2, Health Effects Division (7509C) **Date** 7-17-02
EPA Secondary Reviewer: Alan Levy **Signature:** Alan C. Levy
Registration Action Branch 2, Health Effects Division (7509C) **Date** 7-17-02
Work Assignment Manager: Sanyvette Williams-Foy **Signature:**
Registration Action Branch 2, Health Effects Division (7509C) **Date** 7/18/02
Template version 11/01

TXR#: 0050463

DATA EVALUATION RECORD

STUDY TYPE: Prenatal Developmental Toxicity Study - Rabbit; OPPTS 870.3700b [§83-3b]; OECD 414.

PC CODE: 000011 **DP BARCODE:** D280803
SUBMISSION NO.: S609892

TEST MATERIAL (PURITY): Iodomethane (99.6% a.i.)

SYNONYMS: Methyl iodide

CITATION: Nemec, M. D. (2002) An Inhalation Prenatal Developmental Toxicity Study of Iodomethane in Rabbits. WIL Research Laboratories, Inc., Ashland, OH. Laboratory Study No.: WIL-418002, January 28, 2002. MRID 45593811. Unpublished.

SPONSOR: Tomen Agro, Inc., 100 First Street, Suite 1700, San Francisco, CA

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 45593811), groups of 24 female New Zealand White rabbits were dynamically exposed to iodomethane vapor (Lot/batch # 007403/02; 99.6% a.i.) in whole-body inhalation chambers at analytical concentrations of 0, 2, 10, or 20 ppm (0, 0.012, 0.058, or 0.12 mg/L/day) six hours per day on gestation days (GDs) 6 through 28. All surviving does were sacrificed on GD 29, and their fetuses were removed by cesarean section and examined.

No mortalities occurred during the study. When compared to concurrent controls, no treatment-related changes were observed in body weights, body weight gains, food consumption, sex ratios, or maternal gross pathology.

At 20 ppm, an increased number of late resorptions/doe were observed (1.6 treated vs. 0.1 controls), which resulted in increased post-implantation loss in these animals (2.0 treated vs. 0.7 controls). In addition, decreased ($p<=0.05$) gravid uterine weights were noted (decreased 31%). This decrease was attributed to decreased numbers of live fetuses/doe (decreased 41%) and decreased fetal weights (decreased 20%). Increased incidences of hair loss and wet, clear matting around the nose were noted in the 20 ppm animals compared to controls. Although these

findings are of equivocal toxicological importance, they are evidence of nasal irritation. The post-implantation loss, decreased number of live fetuses, and decreased fetal weights may have been a consequence of subjecting the does to repeated respiratory irritation.

The maternal LOAEL is 20 ppm (0.12 mg/L/day) based on post-implantation loss due to late resorptions, and a decreased number of live fetuses. The maternal NOAEL is 10 ppm (0.058 mg/L/day).

The developmental toxicity LOAEL is 20 ppm (0.12 mg/L/day) based on decreased fetal weights (↓20%). The developmental toxicity NOAEL is 10 ppm (0.058 mg/L/day).

This study is classified **acceptable/guideline** (OPPTS 870.3700a; OECD 414) and satisfies the requirements for a developmental study in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Flagging, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test material: Iodomethane

Description:	Deep yellow, translucent liquid
Lot/Batch #:	007403/02
Purity:	99.6% a.i.
Compound Stability:	The test substance was stable for the duration of the study.
CAS #:	74-88-4
Molecular Weight	141.95 g/Mol
Structure:	$I\text{-}CH_3$

2. Vehicle and/or positive control: None

3. Test animals:

Species:	Rabbit	
Strain:	New Zealand White	
Age/weight at study initiation:	6-7 months old; 3514-3586 g (group mean weight range on GD 0)	
Source:	Covance Research Products, Inc., Denver, PA	
Housing:	Individually, in suspended, stainless steel, wire-bottom cages	
Diet:	Certified Rabbit LabDiet® 5322 (PMI Nutrition International, Inc.), *ad libitum*, except during exposure periods	
Water:	Reverse osmosis-treated tap water, *ad libitum*, except during exposure periods	
Environmental conditions:	**Temperature:**	18.9-22.1°C
	Humidity:	44.1-70.9%
	Air changes:	10/hr.
	Photoperiod:	12 hours light/12 hours dark
Acclimation period:	20-27 days	

B. PROCEDURES AND STUDY DESIGN

1. In life dates - Start: 05/14/01 End: 07/11/01

2. Mating: Virgin females were artificially inseminated; diluted semen from one of eight males was used to inseminate 2 or 4 females in each group. Immediately following the insemination procedure, each doe was administered an intravenous injection of human chorionic gonadotropin (100 USP Units) to induce ovulation. The day of insemination was designated as gestation day (GD) 0.

3. Animal assignment: Animals were assigned (stratified by body weight) to dose groups as indicated in Table 1.

Table 1. Animal assignment [a]

Concentration (ppm)	0	2	10	20
# Females	24	24	24	24

a Obtained from the study report, page 18.

4. **Concentration selection rationale:** No rationale was provided for the selection of chamber concentrations.

5. **Exposure:** Each group of does was dynamically exposed to iodomethane vapor in one of four glass, whole-body inhalation chambers, for six hours per day on GDs 6 through 28. The vapor was generated using an ambient temperature bubbler-type vaporization system in which air was bubbled through the liquid test article. The generation flow rate ranged from 3.5 to 8.0 mL/min. The ventilation flow rate was 350 LPM. Food and water were withheld during exposure.

6. **Exposure characterization:** The nominal chamber concentrations were 0, 4.7, 16, and 28 ppm, and the mean analytical concentrations were 0, 2, 10, and 20 ppm (0, 0.012, 0.058, and 0.12 mg/L/day). Exposure concentrations within each test chamber were measured via gas chromatography approximately every 35 minutes (at least 10 times) during each daily exposure period.

C. OBSERVATIONS

1. **Maternal observations and evaluations:** All does were observed twice daily for mortality and moribundity. Detailed clinical observations were recorded daily. Body weights for all does were recorded on GD 0 and daily from GDs 6 to 29. Mean body weight gains were calculated for daily intervals and GDs 6-9, 9-15, 15-21, 21-29, 6-29, and 0-29. Food consumption was measured daily. All surviving does were sacrificed on GD 29 and subjected to gross necropsy. The uterus was removed from each doe and weighed. All fetuses were removed by cesarean section and examined. The number and location of implantations sites, resorptions (early and late), and live and dead fetuses were recorded.

2. **Fetal evaluations:** Each fetus delivered by cesarean section was weighed, sexed, and examined for external and visceral abnormalities. All fetal carcasses were eviscerated, fixed in absolute ethanol, macerated in KOH, stained with Alizarin Red S using a modification of the Dawson method, and subjected to skeletal examination.

D. DATA ANALYSIS

1. **Statistical analyses:** Data were subjected to the following statistical procedures listed below. Significance was denoted at α=0.05 and 0.01.

Parameter	Statistical procedure
Corpora lutea Total implantations Viable fetuses Fetal weights Maternal body weight Maternal body weight gains Maternal net body weight Maternal net body weight gains Gravid uterine weight Maternal food consumption	ANOVA (parametric) Dunnett's test (parametric) as necessary
Litter proportions of intrauterine data (considering the litter, rather than the fetus, as the experimental unit), mean litter proportions of malformations and variations	Krukal Wallis test (non-parametric) Mann-Whitney test (non-parametric) as necessary

2. **Indices:** The following index was calculated from cesarean section records of animals in the study:

$$Postimplantation\ loss = \frac{\#\ dead\ fetuses,\ resorptions\ (early\ and\ late)\ per\ group}{\#\ gravid\ females\ per\ group}$$

3. **Historical control data:** Historical control data for cesarean section parameters and fetal abnormalities were presented. Forty-two studies were conducted between 1992 and 1999. No further information was provided.

II. RESULTS

A. MATERNAL TOXICITY

1. **Mortality and clinical observations:** No mortalities occurred during the study. Increased incidences of hair loss and wet, clear matting around the nose were noted in the 20 ppm animals compared to controls. These findings were of equivocal toxicological importance.

2. **Body weight:** Body weight gain data are summarized in Table 2. Decreased ($p \leq 0.05$) body weight gains were noted in the 20 ppm does during GDs 6-29 (↓47%). This decrease correlated with decreased ($p \leq 0.05$) gravid uterine weight in these animals (↓31%). Because the adjusted (for gravid uterine weight) body weight gains were similar between the 20 ppm does and

controls; it can be deduced that maternal body weight gains were unaffected by treatment at 20 ppm. Body weight gains and gravid uterine weights were comparable between treated animals and controls at 2 and 10 ppm. No differences in body weights were observed in any treated group.

Table 2. Mean (±SD) maternal body weight gain (g). [a]

Interval	Concentration in ppm (# of Does)			
	0 (n=23)	2 (n=20)	10 (n=20)	20 (n=21)
Pretreatment: Days 0-6	252±65.8	267±130.6	242±91.9	276±87.0
Treatment: Days 6-29	262±133.7	305±152.6	219±177.9	138±210.6* (↓47)
Gravid uterine weight	390.6±142.67	353.0±148.00	319.8±131.12	269±113.28* (↓31)
Adjusted BW Gain	123.7±210.59	219.1±284.10	141.5±236.62	145.1±264.00

a Data obtained from Tables 6 and 7, pages 54 through 58.
* Significantly different from controls at $p \leq 0.05$.

3. **Food consumption:** No treatment-related differences in food consumption were observed at any concentration. Sporadic increases ($p \leq 0.05$) in absolute and relative food consumption values were noted in the 2 ppm group; however, these increases were not dose-dependent and were considered not to be adverse.

4. **Gross pathology:** No treatment-related gross pathological findings were observed in any group.

5. **Cesarean section data:** Cesarean section data are presented in Table 3. Decreased ($p \leq 0.01$) live fetuses/doe were noted at 20 ppm (↓41%). This decrease was attributed to an increased number of late resorptions in these animals. In addition, decreased ($p \leq 0.01$) mean fetal weights were observed at 20 ppm. No other treatment-related cesarean section findings were noted.

Table 3. Cesarean section observations [a]

Observation	Concentration (ppm)			
	0	2	10	20
# Animals Assigned (Mated)	24	24	24	24
# Animals Pregnant	23	20	20	21
Pregnancy Rate (%)	95.8	83.3	83.3	87.5
# Nonpregnant	1	4	4	3
Maternal Wastage				
# Died	0	0	0	0
# Died Pregnant	0	0	0	0
# Died Nonpregnant	0	0	0	0
# Aborted	0	0	0	0
# Premature Delivery	0	0	0	0
Total # Corpora Lutea	236	175	185	208
Corpora Lutea/Doe	10.3±2.78	8.8±2.97	9.3±1.89	9.9±2.98
Total # Implantations	157	122	117	118
(Implantations/Doe)	6.8±2.17	6.1±2.90	5.9±2.72	5.6±2.89
Total # Litters	22	19	20	20
Total # Live Fetuses	140	109	91	76
(Live Fetuses/Doe)	6.1±2.61	5.5±2.63	4.6±2.63	3.6±2.22** (141)
Total # Dead Fetuses	0	0	1	1
(Dead Fetuses/Doe)	0.0	0.0	0.1±0.22	0.0±0.22
Total # Resorptions [b]	17	13	25	41
Early	14	7	8	8
Late	3	6	17	33
Resorptions/Doe [b]	0.74	0.65	1.25	1.95
Early	0.6±1.31	0.4±0.49	0.4±0.60	0.4±0.59
Late	0.1±0.46	0.3±1.13	0.9±1.60	1.6±2.11
Litters with Total Resorptions	1	1	0	1
Mean Fetal Weight (g)	47.0±5.18	45.8±7.05	43.3±7.05	37.8±6.98** (120)
Males	NR	NR	NR	NR
Females	NR	NR	NR	NR
Sex Ratio (male, %)	55	43	53	51
Preimplantation Loss	3.4±2.84	2.6±2.68	3.4±2.80	4.3±3.59
Postimplantation Loss	0.7±1.32	0.7±1.35	1.3±1.95	2.0±2.07

a Data obtained from Table 1, page 45 and Table 10, page 67 in the study report.
b Calculated by the reviewers from data presented in this table.
NR Not reported

B. DEVELOPMENTAL TOXICITY

1. **External examination:** Selected external observations are presented in Table 4a. One 20 ppm fetus was observed to have carpal and/or tarsal flexure, a malformation. This finding was

within range of historical controls and was considered to be incidental. No other dose-related, external malformations were noted. No external variations were observed.

2. Visceral examination: Selected visceral observations are presented in Table 4b. No visceral malformations were observed. No treatment-related visceral variations were noted.

3. Skeletal examination: Selected skeletal observations are presented in Table 4c. No treatment-related skeletal variations were observed. An increased fetal incidence of unossified sternebra(e) (#5 and/or 6) was noted at 20 ppm (15.7% treated vs. 3.6% controls). This incidence exceeded the historical control range (0-9.3%); however, no corroborating evidence of retarded ossification was observed in these animals. In addition, no treatment-related skeletal malformations were noted.

Table 4a. External examinations [a]

Observations [b]	Concentration (ppm)				
	0	2	10	20	Historical Controls [c]
#Fetuses (litters) examined	140 (22)	109 (19)	91 (20)	76 (20)	4708 (715)
Malformations					
Carpal/tarsal flexure	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	1.3 (5.0)	0.0-1.8
Small nose	0.7 (4.5)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	NR
Subcutaneous hemorrhage	0.0 (0.0)	0.0 (0.0)	1.1 (5.0)	0.0 (0.0)	NR
Bent tail	0.0 (0.0)	0.0 (0.0)	1.1 (5.0)	0.0 (0.0)	NR

a Data obtained from Table 12, pages 71 in the study report.
b Fetal incidence % (litter incidence %), calculated by the reviewers
c Historical control data were obtained from Appendix E, pages 306 through 309 of the study report, and were reported as percent per.

Table 4b. Visceral examinations [a]

Observations [b]	Concentration (ppm)				
	0	2	10	20	Historical Controls [c]
#Fetuses (litters) examined	140 (22)	109 (19)	91 (20)	76 (20)	4708 (715)
Variations					
Major blood vessel variation	2.9 (13.6)	2.8 (15.8)	13.2 (45.0)	9.2 (30.0)	0.0-12.0
Accessory spleen	15.7 (54.5)	18.3 (57.9)	4.4 (20.0)	6.6 (25.0)	6.2-24.6

a Data obtained from Table 14, page 76 in the study report.
b Fetal incidence % (litter incidence %), calculated by the reviewers
c Historical control data were obtained from Appendix E, pages 306 through 309 of the study report, and were reported as percent per litter.

Table 4c. Skeletal examinations [a]

Observations [b]	Concentration (ppm)				
	0	2	10	20	Historical Controls [c]
#Fetuses (litters) examined	140 (22)	109 (19)	91 (20)	76 (20)	4708 (715)
Malformations					
Vertebral anomaly with/without associated rib anomaly	0.0 (0.0)	0.9 (5.3)	1.1 (5.0)	0.0 (0.0)	0.0-7.3
Sternebra(e) malaligned (severe)	0.0 (0.0)	0.9 (5.3)	0.0 (0.0)	0.0 (0.0)	0.0-1.2
Sternebrae fused	0.0 (0.0)	0.9 (5.3)	0.0 (0.0)	0.0 (0.0)	0.0-1.9
Variations					
13th full ribs	37.9 (81.8)	40.4 (89.5)	59.3 (65.0)	35.5 (45.0)	19.4-59.1
Sternebra(e) #5 and/or #6 unossified	3.6 (18.2)	0.0 (0.0)	7.7 (15.0)	15.7 (25.0)	0.0-9.3

a Data obtained from Table 12, page 71 in the study report.
b Fetal incidence % (litter incidence %), calculated by the reviewers
c Historical control data were obtained from Appendix E, pages 306 through 309 of the study report, and were reported as percent per litter.

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS: It was concluded that whole-body inhalation exposure of iodomethane caused reduced maternal body weight gains at 20 ppm. Developmental toxicity was exemplified by increases in postimplantation losses (primarily late resorptions), reduced mean numbers of viable fetuses, and/or reduced mean fetal body weights. The maternal LOAEL was 20 ppm. The maternal NOAEL was 10 ppm. The developmental LOAEL was 10 ppm. The developmental NOAEL was 2 ppm.

B. REVIEWER COMMENTS

1. **Maternal toxicity:** An increased number of late resorptions/doe was observed at 20 ppm (1.6 treated vs. 0.1 controls), which resulted in increased post-implantation loss in these animals (2.0 treated vs. 0.7 controls). In addition, decreased ($p \leq 0.05$) gravid uterine weights were observed in the 20 ppm does (↓31%). This decrease was attributed to decreased numbers of live fetuses/doe (↓41%) and decreased fetal weights (↓20%). Increased incidences of hair loss and wet, clear matting around the nose were noted in the 20 ppm animals compared to controls. Although these findings are of equivocal toxicological importance, they are evidence of nasal irritation. The post-implantation loss may have been a consequence of subjecting the does to repeated respiratory irritation. These comments are based on a consultation with Dr. Stephen Dapson.

The maternal LOAEL is 20 ppm (0.12 mg/L/day) based on post-implantation loss due to late resorptions, and a decreased number of live fetuses. The maternal NOAEL is 10 ppm (0.058 mg/L/day).

2. Developmental toxicity:

a. Deaths/Resorptions: Decreased ($p \leq 0.01$) live fetuses/doe were noted at 20 ppm (↓41%). This decrease was attributed to an increased number of late resorptions in these animals.
b. Altered Growth: Decreased ($p \leq 0.01$) mean fetal weights were observed at 20 ppm (↓20%), possibly as a consequence of subjecting the does to repeated respiratory irritation.
c. Developmental Variations/Anomalies: No treatment-related external, visceral, or skeletal variations were noted.
d. Malformations: No treatment-related external, visceral, or skeletal malformations were noted.

The developmental toxicity LOAEL is 20 ppm (0.12 mg/L/day) based on decreased fetal weights (↓20%). The developmental toxicity NOAEL is 10 ppm (0.058 mg/L/day).

This study is classified **acceptable/guideline** (OPPTS 870.3700a; OECD 414) and satisfies the requirements for a developmental study in the rabbit.

C. **STUDY DEFICIENCIES:** No rationale was provided for the selection of chamber concentrations.

DATA FOR ENTRY INTO ISIS

Developmental Study - rabbit (870.3700a)

PC code	MRID #	Study type	Species	Duration	Route	Dosing method	Conc. range mg/L/day	Conc. tested mg/L/day	NOAEL mg/L/day	LOAEL mg/L/day	Target organ(s)	Comments
000011	45593811	developmental	rabbit	GD 6-28	inhalation	whole body	0.012-0.12	0, 0.012, 0.058, 0.12	0.058	0.12	incr. late resorptions incr. post-implantation loss decreased live fetuses	maternal concentrations
000011	45593811	developmental	rabbit	GD 6-28	inhalation	whole body	0.012-0.12	0, 0.012, 0.058, 0.12	0.058	0.12	decreased fetal weights	developmental concentrations

DER #4

Iodomethane: Inhalation Acute Neurotoxicity Screening Battery in Rats
Sponsor Name: Arvesta Corporation (Formerly Tomen Agro, Inc.). Year of Study - 2002.
MRID Nos. 45593817

DATA EVALUATION RECORD

IODOMETHANE

Study Type: §81-8, Acute Neurotoxicity Screening Battery in Rats

Work Assignment No. 4-02-174D (Formerly 4-01-174D) (MRID 45593817)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Pesticides Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
Rockville, MD 20850-3268

Primary Reviewer:
Kelley Van Vreede, M.S.

Signature: Kelley Van Vreede
Date: 5/15/02

Secondary Reviewer:
David A. McEwen, B.S.

Signature: David A. McEwen
Date: 5/15/02

Project Manager:
Mary L. Menetrez, Ph.D.

Signature: Mary L. Menetrez
Date: 5/15/02

Quality Assurance:
Steve Brecher, Ph.D.

Signature: Steven Brecher
Date: 5/15/02

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: John Whalan **Signature:** John Whalan
Registration Action Branch 2, Health Effects Division (7509C) **Date** 7-17-02
EPA Secondary Reviewer: Alan Levy **Signature:** Alan C. Levy
Registration Action Branch 2, Health Effects Division (7509C) **Date** 7-17-02
Work Assignment Manager: Sanyvette Williams **Signature:**
Registration Action Branch 2, Health Effects Division (7509C) **Date** 7/19/02

TXR#: 0050463

DATA EVALUATION RECORD

STUDY TYPE: Acute Neurotoxicity, OPPTS 870.6200a [§81-8]; [gavage; rat]; (OECD 424).

PC CODE: 000011 **DP BARCODE:** D280803
SUBMISSION NO.: S609892

TEST MATERIAL (PURITY): Iodomethane (100% purity, assumed by Sponsor)

SYNONYMS: Methyl iodide

CITATION: Schaefer, G.J. (2002) An Acute Neurotoxicity Study of Iodomethane in Rats. WIL Research Laboratories, Inc., Ashland, OH. Laboratory Study No.: WIL-418008, January 7, 2002. MRID 45593817. Unpublished.

SPONSOR: Arvesta Corporation, 100 First Street, Suite 1700, San Francisco, CA.

EXECUTIVE SUMMARY: In an acute neurotoxicity study (MRID 45593817), iodomethane (100% purity, Batch/Lot # 007403 Drum 2) was dynamically administered as a vapor in a single, six-hour, whole body inhalation exposure to 12 Crl:CD® (SD)IGS BR rats/sex/group at analytical concentrations of 0, 27, 93, or 401 ppm. The time of peak effect was estimated to be three hours post-exposure. Neurobehavioral assessment (functional observational battery and motor activity testing) was performed on all animals on days 0 (before and after exposure), 7, and 14. At study termination, all rats were euthanized and perfused *in situ*. Six animals/sex in the control and 401 ppm groups were subjected to histopathological evaluation of brain and peripheral nervous system tissues. Four studies were submitted to generate positive control data and validate the procedures of the performing lab in performing the FOB and in assessing motor activity, FOB, and neuropathology. All studies were performed by WIL Research Laboratories (Ashland, OH); and were conducted between December 1990 and May 1999. No further information was provided.

At 93 and 401 ppm, body weight gains were decreased ($p \leq 0.05$) in the males during days 0-7 (↓21-55%). Compared to controls, body weights on day 7 were decreased 4% in males and females at 93 ppm, and 10% in males and 2% in females at 401 ppm. Findings noted during the FOB were limited to day 0. In the **homecage**, clonic convulsions (repetitive movements of the

mouth and jaw) were noted in the 93 and 401 ppm males and in the 401 ppm females. During the **handling** observations, slightly drooping eyelids were observed in the 93 ppm females and the 401 ppm males and females. In the **open field**, clonic convulsions were observed in a single 93 ppm female. Decreased body temperature was noted in the 93 and 401 ppm males and females. Furthermore, decreased ($p \leq 0.05$) total and ambulatory motor activity were noted in the 93 (↓75-78%) and 401 (↓87-97%) males and 93 (↓81-84%) and 401 (↓85-95%) ppm females on day 0.

Additionally, in the 401 ppm exposure group, one female was found dead on day 6. This animal experienced clonic convulsions, yellow material around the urogenital area, dried red material around the nose, mouth, and eye, shallow respiration, and decreased defecation prior to death. The most commonly observed clinical signs in the surviving animals were decreased defecation and dried red material around the nose, mouth and/or eyes in both sexes. Dried yellow material around the urogenital area was observed in the females. A single incidence of drooping eyelids (right and/or left) was observed in a female. Although the occurrence of this finding was extremely low, it appeared to correlate with observations noted during the FOB. Body weights were decreased ($p \leq 0.05$) in the males on study days 7 (↓10%) and 14 (↓8%). FOB findings noted on day 0 included the following: (i) **homecage** - more animals were sitting with head held low and fewer animals were observed to have their eyes wide open when compared to controls; (ii) **handling** - increased incidences of gasping and salivation; (iii) **open field** - hunched body, clonic convulsions, and slight, but definite, impairment of gait score. In addition, decreased ($p \leq 0.05$) rotorod performance was observed in both sexes on day 0 (↓43-51%).

The only finding noted at 27 ppm was decreased ($p \leq 0.05$) total and ambulatory motor activity in the females on day 0 (↓27-32%). This finding was not corroborated by additional evidence of neurotoxicity and was only noted in one sex. Therefore, decreased motor activity at 27 ppm was considered to be equivocal.

The LOAEL for this study is 93 ppm (0.54 mg/L) based on FOB findings (clonic convulsions, decreased body temperature), and decreased motor activity (↓75-78% in males, 81-84% in females). The NOAEL for this study is 27 ppm (0.16 mg/L).

FOB findings and decreased motor activity indicated that iodomethane was neurotoxic at 93 (0.54 mg/L) and 401 ppm (2.33 mg/L).

The study is classified as **acceptable/guideline**, and satisfies the guideline requirement for an acute neurotoxicity study in rats (870.6200a).

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: Iodomethane

Description:	Deep yellow, translucent liquid
Lot/Batch #:	*007403 Drum 2*
Purity:	Assumed to be 100% by the Sponsor
Compound Stability:	The test substance was stable for the duration of the study.
CAS # of TGAI:	74-88-4
Molecular Weight	141.95 g/Mol
Structure:	$I\text{-}CH_3$

2. Vehicle: Air

3. Test animals

Species:	Rat
Strain:	Crl:CD® (SD)IGS BR
Age/mean weight at study initiation:	44-47 days old; males: 111-146 g females: 90-121 g
Source:	Charles River Laboratories, Inc. (Raleigh, NC)
Housing:	Individually, in suspended stainless steel, wire-mesh cages
Diet:	Purina Certified Rodent LabDiet #5002 (Purina Mills, Inc.), *ad libitum* except during exposures
Water:	Tap water, *ad libitum*, except during exposures
Environmental conditions:	**Temperature:** 22.3-22.7°C **Humidity:** 42.0-60.1% **Air changes:** Not reported **Photoperiod:** 12 hrs dark/12 hrs light
Acclimation period:	At least 13 days

B. STUDY DESIGN:

1. In life dates - Start: 5/7/01 End: 5/25/01

2. Animal assignment and treatment: Animals were randomly assigned (stratified by body weight) to the test groups noted in Table 1. The test substance was administered via a single, six-hour, whole body inhalation exposure; animals were observed for two weeks following exposure. No rationale was provided was selection of the exposure concentrations.

Table 1. Study Design

Experimental Parameter	Concentration Group (ppm)			
	Control	27	93	401
Total number of animals/sex/group	12/sex	12/sex	12/sex	12/sex
Behavioral testing (FOB, Motor Activity)	12/sex	12/sex	12/sex	12/sex
Neuropathology	6/sex	0	0	6/sex
Blood cholinesterase determination	NA	NA	NA	NA
Brain cholinesterase determination	NA	NA	NA	NA

3. Generation of the test atmosphere/chamber description: Rats were dynamically exposed to iodomethane vapor in four 2.0 m^3 stainless steel and glass, whole body chambers. Ventilation airflow was maintained at approximately 450 L/min and the chamber temperature was 22-23°C with a relative humidity of 42-46%. The time to equilibrium (t_{99}) was approximately 20 minutes.

Test article vapor was generated using an ambient temperature bubbler-type vaporization system, in which air was bubbled through the liquid test article. Chamber conditions (airflow, temperature, relative humidity, etc) were recorded approximately every 35 minutes during the 6-hour exposure period. The target concentrations were 0, 25, 100, and 400 ppm. The mean nominal concentrations were 0, 44, 140, and 423 ppm. The analytical concentrations were determined by gas chromatography to be 0, 27, 93, and 401 ppm (0.16, 0.54, and 2.33 mg/L).

4. Statistics: Data were subjected to the following statistical procedures listed below. All analyses were two tailed (except as noted) for significance levels of α=0.05 and α=0.01.

Parameter	Statistical procedure
Body weights Body weight gains Continuous FOB data Motor activity Brain weights/measurements	One-way ANOVA, followed by Dunnett's test as necessary.
Descriptive FOB data	Fisher's Exact Test

C. METHODS / OBSERVATIONS

1. Mortality and clinical observations: All animals were observed twice daily for mortality and moribundity. Detailed clinical observations were recorded daily.

2. Body weight: All animals were weighed pre-test and on study days 0, 7, and 14.

3. Food consumption/efficiency: Food consumption and efficiency were not determined.

4. Cholinesterase determination: Cholinesterase activity was not measured.

5. Neurobehavioral assessment

a. Functional Observational Battery (FOB): All animals were subjected to FOB evaluations prior to treatment, 3 hours post-exposure (estimated time of peak effect), and on days 7 and 14. The technicians were blind with respect to the treatment status of the animals. FOB scoring criteria are reported in Appendix A. The FOB assessment included the following parameters:

The CHECKED (X) parameters were examined.

	HOME CAGE OBSERVATIONS		HANDLING OBSERVATIONS		OPEN FIELD OBSERVATIONS
X	Posture*	X	Reactivity*	X	Mobility
X	Biting	X	Lacrimation* / chromodacryorrhea	X	Rearing+
X	Convulsions*	X	Salivation*	X	Arousal/ gereral activity level*
X	Tremors*	X	Piloerection*	X	Convulsions*
	Abnormal Movements*	X	Fur appearance	X	Tremors*
X	Palpebral closure*	X	Palpebral closure*		Abnormal movements*
X	Feces consistency	X	Respiratory rate+	X	Urination / defecation*
		X	Red/crusty deposits*	X	Grooming
	SENSORY OBSERVATIONS	X	Mucous membranes /eye /skin color	X	Gait abnormalities / posture*
X	Approach response+	X	Eye prominence*	X	Gait score*
X	Touch response+	X	Muscle tone*	X	Bizarre / stereotypic behavior*
X	Startle response*			X	Backing
X	Pain response*			X	Time to first step
X	Pupil response*				
X	Eyeblink response		PHYSIOLOGICAL OBSERVATIONS		NEUROMUSCULAR OBSERVATIONS
X	Forelimb extension	X	Body weight*	X	Hindlimb extensor strength
X	Hindlimb extension	X	Body temperature+	X	Forelimb grip strength*
X	Air righting reflex+	X	Catalepsy	X	Hindlimb grip strength*
X	Olfactory orientation			X	Landing foot splay*
			OTHER OBSERVATIONS	X	Rotarod performance

*Required parameters; +Recommended parameters

b. Locomotor activity: Locomotor activity was measured in all animals following the FOB prior to exposure and on days 0 (within 3 hours post-exposure), 7, and 14. Activity was recorded by an automated motor activity monitoring device (Photobeam Activity System, San Diego Instruments) for 60 minutes (divided into five minute intervals). Data for ambulatory and total motor activity were tabulated.

6. **Sacrifice and pathology:** Upon study termination, all surviving rats were anesthetized by sodium pentobarbital injection and sacrificed by *in situ* perfusion fixation. Brain weights and dimensions were recorded. The following tissues from the 6 animals/sex in the control and 401 ppm groups were embedded in paraffin or plastic, sectioned, stained with hematoxylin-eosin, and examined microscopically.

	CENTRAL NERVOUS SYSTEM		PERIPHERAL NERVOUS SYSTEM
	BRAIN		**SCIATIC NERVE**
	Forebrain	X	Mid-thigh
X	Cerebrum	X	Sciatic Notch
	Midbrain		
X	Cerebellum		**OTHER**
X	Pons		Sural Nerve
X	Medulla oblongata	X	Tibial Nerve
	SPINAL CORD	X	Peroneal Nerve
X	Cervical swelling, C3-C7	X	Lumbar dorsal root ganglia, T13-L4
X	Lumbar swelling ,T13-L4	X	Lumbar dorsal root fibers, T13-L4
	Thoracic swelling	X	Lumbar ventral root fibers, T13-L4
	OTHER	X	Cervical dorsal root ganglia, C3-C7
X	Tegmenta	X	Cervical dorsal root fibers, C3-C7
X	Central grey matter	X	Cervical ventral root fibers, C3-C7
X	Cerebral peduncles	X	Optic nerves
X	Basal ganglia	X	Eyes
X	Tectum	X	Gastrocnemius muscle
X	Trigeminal ganglia/nerves		
X	Hippocampus		
X	Olfactory bulb		
X	Thalamus/hypothalamus		

7. **Positive Controls:** Four studies were submitted to generate positive control data and validate the procedures of the laboratory performing the FOB and in assessing motor activity, FOB, and neuropathology. All studies were performed by WIL Research Laboratories (Ashland, OH); and were conducted between December 1990 and May 1999. No further information was provided.

Motor activity was evaluated using a single i.p. injection of d-amphetamine sulfate or chlorpromazine hydrochloride. D-amphetamine was administered to 12 Sprague-Dawley rats/sex/group at dose levels of 0, 2, or 4 mg/kg. A concentration-related increase in motor activity was observed in these animals. Chlorpromazine was administered to 12 Sprague-Dawley rats/sex/group at dose levels of 0, 5, or 10 mg/kg. A concentration-dependent decrease in motor activity was observed in these animals.

FOB and motor activity procedures were validated using a single i.p. injection of carbaryl. Carbaryl was administered to 12 rats/sex/group (strain not reported) at dose levels of 0, 2, 10, or

50 mg/kg. The following findings were noted during the FOB in the 10 and 50 mg/kg animals, primarily 30 minutes post-dosing: (i) altered posture, palpebral closure, and convulsions (tremors) during the home cage observations; (ii) altered ease of removal (from the home cage) and handling, salivation, fur appearance, and eye prominence during the handling observations; (iii) increased time to first step, alterations in mobility, gait, gait score, arousal, convulsions, and the number of rearing episodes during the open-field observations; (iv) alterations in the approach, touch, startle, tail pinch and pupil responses, olfactory orientation and air righting reflex during the sensory observations; (v) alterations in hindlimb extensor strength, grip-strength and rotarod performance during the neuromuscular observations; and (vi) alterations in catalepsy time and body temperature during the physiological observations. In addition, decreased total and ambulatory motor activity was observed in the 10 and 50 mg/kg animals, 30 minutes post-dosing.

FOB procedures were validated and pathology positive control data were generated using acrylamide and trimethyltin chloride. Acrylamide was administered to 12 rats/sex/group (strain not reported) at dose levels of 0, 5, 10, or 20 mg/kg/day, 5 days/week, for four consecutive weeks. The following FOB alterations were noted in the 10 and 20 mg/kg animals on days 14, 21, and 28: (i) alterations in muscle tone during handling; (ii) alterations in startle and tail pinch responses and air righting reflex during the sensory observations; (iii) alterations in hindlimb extensor strength, fore- and hindlimb grip strength, decreased rotarod performance and increased hindlimb foot-splay; and (iv) decreased body weights and body temperature. Animals in the 20 mg/kg group exhibited histopathological lesions indicative of neurotoxicity. Trimethyltin chloride was administered at 7.5 mg/kg to 5 rats/sex as a single intraperitoneal injection. Forty percent of male rats exhibited neuronal loss in the dentate gyrus. Twenty percent of male rats exhibited chromatolysis in the gasserian ganglion neurons.

Inter-observer reliability of personnel was evaluated using a single gavage dose of 3'-3'-iminodipropionitrile (IDPN). IDPN was administered to 5 rats/sex/group at dose levels of 0 or 2000 mg/kg. The results of this study indicated that the personnel performing the FOB observed control animals similarly and detected the major behavioral signs associated with IDPN toxicity.

II. RESULTS

A. OBSERVATIONS

1. Mortality and clinical signs: Selected clinical signs are presented in Table 2. The most commonly observed clinical signs were decreased defecation and dried red material around the nose, mouth and/or eyes in both sexes. These findings were generally observed at 401 ppm. Additionally at 401 ppm, dried yellow material around the urogenital area was observed in the females. A single incidence of drooping eyelids (right and/or left) was observed in a 401 ppm female. Although the occurrence of this finding was extremely low, it appeared to correlate with observations noted during the FOB.

Table 2. Selected clinical signs in rats treated once via inhalation with iodomethane (total incidences/# affected animals) [a].

Observation	Concentration (ppm)			
	Control	27	93	401
Males				
Dried red material around nose	0/0	0/0	5/2	4/3
Dried red material around mouth	0/0	0/0	0/0	6/5
Decreased defecation	0/0	0/0	1/1	9/9
Females				
Dried red material around right eye	0/0	0/0	0/0	2/2
Dried red material around left eye	0/0	0/0	0/0	4/3
Dried red material around nose	0/0	0/0	0/0	7/4
Dried red material around mouth	0/0	0/0	0/0	7/7
Decreased defecation	0/0	0/0	2/2	20/12
Dried yellow material urogenital area	0/0	0/0	0/0	10/3
Right eyelid drooping	0/0	0/0	0/0	1/1
Left eyelid drooping	0/0	0/0	0/0	1/1

a Data were extracted from the study report Table 1, pages 45 through 48.
n = 12

2. **Mortality:** One 401 ppm female was found dead on day 6. This animal experienced clonic convulsions, yellow material around the urogenital area, dried red material around the nose, mouth, and eye, shallow respiration, and decreased defecation prior to death. The only findings revealed at necropsy were red and yellow matting on the skin. This mortality was considered to be treatment-related.

B. **BODY WEIGHT AND BODY WEIGHT GAIN:** Body weights were decreased ($p \leq 0.05$) in the 401 ppm males on study days 7 (↓10%) and 14 (↓8%; Table 3). Body weight gains were decreased ($p \leq 0.05$) in the 93 and 401 ppm males during days 0-7 (↓21-55%). No treatment-related differences in body weights or body weight gains were observed in the females.

Table 3. Body weight and overall body weight gain (g) in rats treated once via inhalation with iodomethane [a].

Observation	Concentration (ppm)			
	Control	27	93	401
Body weight-Males (g)				
Pretest	167±14.1	167±16.0	166±16.7	166±13.1
Day 0	224±15.1	226±18.6	224±19.4	223±14.7
Day 7	271±17.0	272±25.7	261±21.9 (↓4)	244±15.8** (↓10)
Day 14	314±21.2	316±31.4	307±26.3	290±15.6* (↓8)
Body weight-Females (g)				
Pretest	134±13.6	136±7.9	135±11.0	135±8.5
Day 0	162±12.2	165±10.0	164±11.4	165±8.2
Day 7	183±15.2	183±12.2	176±11.4 (↓4)	179±11.9 (↓2)
Day 14	199±15.2	201±11.0	195±12.4	194±11.8
Body weight gain-Males (g)				
Days 0-7	47±6.8	46±11.3	37±4.3** (↓21)	21±4.4** (↓55)
Days 7-14	43±6.1	44±10.3	46±8.5	45±3.8
Body weight gain-Females (g)				
Days 0-7	21±5.8	18±7.3	12±5.5** (↓43)	15±9.0
Days 7-14	17±4.8	18±6.0	19±5.2	15±5.3

a Data were extracted from the study report Tables 2 and 3, pages 49-52. Percent difference from controls is presented parenthetically.
n = 11-12
* *Significantly different from controls at* $p \leq 0.05$.
** Significantly different from controls at $p \leq 0.01$.

C. **FOOD CONSUMPTION/EFFICIENCY:** Food consumption and efficiency were not reported.

D. **Cholinesterase activities:** Cholinesterase activity was not measured.

E. **Neurobehavioral results**

1. **FOB Findings:** Selected FOB homecage observations are presented in Table 4a. On day 0, clonic convulsions (repetitive movements of the mouth and jaw) were noted in the 93 and 401 ppm males (1/12 and 3/12 treated, respectively vs. 0/12 controls, not statistically significant [NS]) and 401 ppm females (4/12 treated vs. 0/12 controls, NS). Additionally on day 0, sitting with head held low was observed at 401 ppm (males: 4/12 treated vs. 0/12 controls, NS; females:

8/12 treated vs. 0/12 controls, p≤0.05). Furthermore, fewer 401 ppm animals were observed to have their eyes wide open when compared to controls on day 0 (males: 8/12 treated vs. 12/12 controls, NS; females: 5/12 treated vs. 12/12 controls, p≤0.05). No other treatment-related homecage observations were noted.

Table 4a. Functional observation battery results, homecage observations [a].

Observation	Concentration (ppm)			
	Control	27	93	401
Males				
Clonic convulsions, repetitive movements of mouth and jaw				
-Pretest	0	0	0	0
-Day 0	0	0	1	3
-Day 7	0	0	0	0
-Day 14	0	0	0	0
Sitting, head held low				
-Pretest	0	0	0	0
-Day 0	0	0	0	4
-Day 7	0	0	0	0
-Day 14	0	0	0	0
Palpebral closure, eyelids wide open				
-Pretest	12	12	12	12
-Day 0	12	12	12	8
-Day 7	12	12	12	11
-Day 14	11	12	11	12
Females				
Clonic convulsions, repetitive movements of mouth and jaw				
-Pretest	0	0	0	0
-Day 0	0	0	0	4
-Day 7	0	0	0	0
-Day 14	0	0	0	0
Sitting, head held low				
-Pretest	0	0	0	0
-Day 0	0	0	0	8*
-Day 7	0	0	0	0
-Day 14	0	0	0	0
Palpebral closure, eyelids wide open				
-Pretest	12	12	12	12
-Day 0	12	12	10	5*
-Day 7	12	12	11	11
-Day 14	12	12	11	11

a Data were extracted from Tables 4 through 11 on pages 53 through 68 of the study report. Values represent number of affected animals

n = 11-12

* Significantly different from controls at p≤0.05

Selected FOB handling observations are presented in Table 4b. Slightly drooping eyelids were observed in the 93 ppm females (1/12, NS) and in the 401 ppm males (1/12, NS) and females (4/12, NS) on day 0. Additionally on day 0, gasping was observed in the 401 ppm animals (males: 3/12, NS; females: 4/12, NS). Furthermore, an increased incidence of salivation in the 401 ppm animals was observed on day 0 (males: 5/12, $p \leq 0.05$; females: 5/12, $p \leq 0.05$). No other treatment-related findings were noted during handling.

Table 4b. Functional observation battery results, handling observations [a].

Observation	Concentration (ppm)			
	Control	27	93	401
Males				
Eyelids slightly drooping				
-Pretest	0	0	0	0
-Day 0	0	0	0	1
-Day 7	0	0	0	0
-Day 14	0	0	0	0
Gasping				
-Pretest	0	0	0	0
-Day 0	0	0	0	3
-Day 7	0	0	0	0
-Day 14	0	0	0	0
Salivation, slight				
-Pretest	0	0	0	0
-Day 0	0	0	0	5*
-Day 7	0	0	0	0
-Day 14	0	0	0	0
Females				
Eyelids slightly drooping				
-Pretest	0	0	0	0
-Day 0	0	0	1	4
-Day 7	0	0	0	0
-Day 14	0	0	0	0
Gasping				
-Pretest	0	0	0	0
-Day 0	0	0	0	4
-Day 7	0	0	0	0
-Day 14	0	0	0	0
Salivation, slight				
-Pretest	0	0	0	0
-Day 0	0	0	0	5*
-Day 7	0	0	0	0
-Day 14	0	0	0	0

a Data were extracted from Tables 12 through 19 on pages 69 through 116 of the study report. Values represent number of affected animals
n=11-12
* Significantly different from controls at $p \leq 0.05$

Selected FOB open field observations are presented in Table 4c. The following observations were noted on day 0 in the 401 ppm animals (only the female incidences were statistically significant, $p \leq 0.05$; vs. 0/12 controls): (i) hunched body (males: 4/12; females 11/12); (ii) clonic convulsions, repetitive movements of the mouth and jaw (males: 3/12; females: 7/12); and (iii) slight, but definite, impairment of gait score (males: 1/12; females: 7/12). In addition, clonic convulsions, repetitive movements of the mouth and jaw were observed in a single 93 ppm female on day 0. No other treatment-related open field observations were noted.

Table 4c. Functional observation battery results, open field observations[a].

Observation	Concentration (ppm)			
	Control	27	93	401
Males				
Gait, hunched body				
-Pretest	0	0	0	0
-Day 0	0	0	0	4
-Day 7	0	0	0	0
-Day 14	0	0	0	0
Clonic convulsions, repetitive movements of mouth and jaw				
-Pretest	0	0	0	0
-Day 0	0	0	0	3
-Day 7	0	0	0	0
-Day 14	0	0	0	0
Gait score, slight impairment but definite				
-Pretest	0	0	0	0
-Day 0	0	0	0	1
-Day 7	0	0	0	0
-Day 14	0	0	0	0
Females				
Gait, hunched body				
-Pretest	0	0	0	0
-Day 0	0	0	0	11*
-Day 7	0	0	0	0
-Day 14	0	0	0	0
Clonic convulsions, repetitive movements of mouth and jaw				
-Pretest	0	0	0	0
-Day 0	0	0	1	7*
-Day 7	0	0	0	0
-Day 14	0	0	0	0
Gait score, slight impairment but definite				
-Pretest	0	0	0	0
-Day 0	0	0	0	7*
-Day 7	0	0	0	0
-Day 14	0	0	0	0

a Data were extracted from Tables 20 through 27 on pages 117 through 148 of the study report. Values represent number of affected animals

n = 11-12

* Significantly different from controls at $p \leq 0.05$

Selected FOB neuromuscular observations are presented in Table 4d. Decreased ($p \leq 0.05$) rotorod performance was observed in the 401 ppm males and females on day 0 (↓43-51%). No other treatment-related neuromuscular findings were noted. Increased ($p \leq 0.05$) rotorod performance was observed in the 27 and 401 ppm males on day 14 (↑46-55%); however, this finding was not concentration-dependent and was considered not to be adverse.

Table 4d. Functional observation battery results, neuromuscular observations (mean±SD)[a].

Observation	Concentration (ppm)			
	Control	27	93	401
Males				
Rotorod performance (sec.)				
-Pretest	55.0±48.78	85.8±50.53	71.0±46.73	69.4±46.77
-Day 0	96.4±41.35	94.1±42.49	107.7±30.69	47.5±32.93** (↓51)
-Day 7	94.2±42.61	119.9±0.23	80.2±43.75	108.2±20.33
-Day 14	77.3±42.74	120.0±0.00** (↑55)	100.5±36.73	112.6±17.38* (↑46)
Females				
Rotorod performance (sec.)				
-Pretest	66.4±52.25	73.1±52.04	55.1±50.82	65.7±51.79
-Day 0	102.9±39.90	101.9±42.31	96.1±37.53	58.5±42.87* (↓43)
-Day 7	92.1±48.11	108.9±28.82	101.8±36.44	98.5±38.05
-Day 14	102.6±38.54	112.5±26.01	100.3±38.75	94.4±44.52

a Data were extracted from Tables 36 through 43 on pages 181 through 196 of the study report. Percent difference from controls is presented parenthetically.
n = 11-12
* Significantly different from controls at $p \leq 0.05$.
** Significantly different from controls at $p \leq 0.01$.

Selected FOB physiological observations are presented in Table 4e. Decreased ($p \leq 0.01$) body temperature was noted in the 93 and 401 ppm males (34.2-37.2°C treated vs. 38.3°C controls) and females (34.0-37.1°C treated vs. 38.4°C controls) on day 0. In addition, decreased ($p \leq 0.05$) body weights were observed in the 401 ppm males on days 7 and 14 (↓9-11%). No other treatment-related physiological observations were noted.

Table 4e. Functional observation battery results, physiological observations (mean±SD) [a].

Observation	Concentration (ppm)			
	Control	27	93	401
Males				
Body temperature (°C)				
-Pretest	37.8±0.19	38.0±0.19	37.9±0.23	37.8±0.28
-Day 0	38.3±0.23	38.3±0.28	37.2±0.74**	34.2±1.07**
-Day 7	38.0±0.27	38.2±0.28*	38.0±0.17	37.9±0.18
-Day 14	37.5±0.90	37.5±1.08	37.8±0.77	37.6±1.13
Body weight (g)				
-Pretest	160.1±13.80	159.6±15.59	159.4±16.41	159.8±12.48
-Day 0	208.9±14.75	211.8±17.72	206.7±17.98	204.5±14.58
-Day 7	264.7±16.62	265.4±25.10	253.4±21.39	236.0±15.08** (↓11)
-Day 14	307.8±20.73	309.3±30.75	298.7±25.61	281.2±14.12* (↓9)
Females				
Body temperature (°C)				
-Pretest	38.0±0.31	37.9±0.22	37.9±0.18	37.8±0.19
-Day 0	38.4±0.33	38.3±0.32	37.1±0.67**	34.0±0.95**
-Day 7	38.3±0.48	38.2±0.21	38.1±0.34	38.1±0.43
-Day 14	37.7±0.76	37.9±0.69	37.8±0.66	38.1±0.44
Body weight (g)				
-Pretest	128.6±13.17	131.4±7.91	129.4±11.14	130.8±8.62
-Day 0	153.6±11.43	156.3±8.56	151.5±10.08	151.4±7.28
-Day 7	180.4±14.56	181.7±11.81	173.3±10.39	174.2±12.22
-Day 14	197.4±15.10	199.8±10.94	191.3±11.09	191.5±10.55

a Data were extracted from Tables 44 through 47 on pages 197 through 204 of the study report. Percent difference from controls is presented parenthetically.
n = 11-12
* Significantly different from controls at $p \leq 0.05$
* Significantly different from controls at $p \leq 0.01$

2. Motor activity: Mean motor activity data are presented in Table 5. Decreased ($p \leq 0.05$) total and ambulatory motor activity were noted in the 93 (↓75-78%) and 401 (↓87-97%) ppm males and 27 (↓27-32%), 93 (↓81-84%), and 401 (↓85-95%) ppm females on day 0. No other differences in mean motor activity were noted. Subsession data indicated that habituation was normal (Appendix B).

Table 5. Total motor activity in rats treated once via inhalation with iodomethane [a].

Observation		Concentration (ppm)			
		Control	27	93	401
Males					
Pre-test	Total	969±513.2	809±438.4	777±396.2	1015±522.5
	Ambulatory	324±219.6	247±151.4	249±139.6	313±197.4
Day 0	Total	800±322.6	637±287.9	201±77.8** (↓75)	102±64.6** (↓87)
	Ambulatory	260±115.5	194±101.5	58±32.0** (↓78)	8±8.3** (↓97)
Day 7	Total	1217±344.4	1049±381.7	1446±481.8	1244±450.2
	Ambulatory	418±129.7	348±155.9	509±195.9	428±220.9
Day 14	Total	1468±434.6	1232±462.6	1255±372.5	1412±355.4
	Ambulatory	514±145.5	384±161.7	430±154.4	491±127.7
Females					
Pre-test	Total	1038±867.2	831±265.3	1033±344.6	855±348.8
	Ambulatory	335±302.3	253±111.9	347±145.3	283±148.2
Day 0	Total	1059±282.3	776±446.0* (↓27)	204±45.4** (↓81)	156±165.3** (↓85)
	Ambulatory	363±98.9	248±159.4* (↓32)	57±23.0** (↓84)	18±19.4** (↓95)
Day 7	Total	1287±454.9	1231±369.7	1252±321.8	1140±457.4
	Ambulatory	459±163.4	432±179.8	457±156.3	424±204.1
Day 14	Total	1556±469.4	1347±366.5	1213±562.2	1094±310.9
	Ambulatory	600±217.0	490±169.6	446±257.0	394±140.2

a Data were extracted from the study report Table 48, pages 205 through 206. Percent difference from controls is presented parenthetically.
n = 11-12
* Significantly different from controls at $p \leq 0.05$.
** Significantly different from controls at $p \leq 0.01$.

F. SACRIFICE AND PATHOLOGY:

1. **Brain weight:** Brain weights were comparable between treated and control groups.

2. **Neuropathology:** Minimal axonal degeneration was noted in the control and 401 ppm animals of both sexes. Incidences of axonal degeneration were consistently higher than controls at 401 ppm (1-4/6 treated vs. 0-2/6 controls); however, this type of degeneration is common in rats. Therefore, these findings were considered to be of equivocal toxicological importance.

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS: It was concluded that acute, inhalation exposure to iodomethane resulted in systemic and neurological toxicity at 93 and 401 ppm. Red/yellow material on various body surfaces, decreased defecation, decreased body weight gains, FOB findings indicative of neurotoxicity, and decreased motor activity were observed at these exposure concentrations. Additionally, mortality, drooping eyelids, and decreased body weights (males) were observed at 401 ppm. The LOAEL was 93 ppm. The NOAEL was 27 ppm.

B. REVIEWER COMMENTS: One 401 ppm female was found dead on day 6. This animal experienced clonic convulsions, yellow material around the urogenital area, dried red material around the nose, mouth, and eye, shallow respiration, and decreased defecation prior to death. The most commonly observed clinical signs in the surviving animals were decreased defecation and dried red material around the nose, mouth and/or eyes in both sexes. These findings were generally observed at 401 ppm. Additionally at 401 ppm, dried yellow material around the urogenital area was observed in the females. A single incidence of drooping eyelids (right and/or left) was observed in a 401 ppm female. Although the occurrence of this finding was extremely low, it appeared to correlate with observations noted during the FOB. Body weights were decreased ($p \leq 0.05$) in the 401 ppm males on study days 7 (↓10%) and 14 (↓8%). Body weight gains were decreased ($p \leq 0.05$) in the 93 and 401 ppm males during days 0-7 (↓21-55%). Compared to controls, body weights on day 7 were decreased 4% in males and females at 93 ppm, and 10% in males and 2% in females at 401 ppm.

On day 0, in the **homecage**, clonic convulsions (repetitive movements of the mouth and jaw) were noted in the 93 and 401 ppm males (1/12 and 3/12 treated, respectively vs. 0/12 controls, not statistically significant [NS]) and 401 ppm females (4/12 treated vs. 0/12 controls, NS). Additionally on day 0, sitting with head held low was observed at 401 ppm (males: 4/12 treated vs. 0/12 controls, NS; females: 8/12 treated vs. 0/12 controls, $p \leq 0.05$). Furthermore, fewer 401 ppm animals were observed to have their eyes wide open when compared to controls on day 0 (males: 8/12 treated vs. 12/12 controls, NS; females: 5/12 treated vs. 12/12 controls, $p \leq 0.05$). No other treatment-related homecage observations were noted. During the **handling** observations, slightly drooping eyelids were observed in the 93 ppm females (1/12 treated vs. 0/12 controls, NS) and in the 401 ppm males (1/12 treated vs. 0/12 controls, NS) and females (4/12 treated vs. 0/12 controls, NS) on day 0. Additionally on day 0, gasping was observed in the 401 ppm animals (males: 3/12 vs. 0/12 controls, NS; females 4/12 vs. 0/12 controls, NS). Furthermore, an increased incidence of salivation in the 401 ppm animals was observed on day 0 (males: 5/12 treated vs. 0/12 controls, $p \leq 0.05$; females: 5/12 treated vs. 0/12 controls, $p \leq 0.05$).

The following **open field** observations were noted on day 0 in the 401 ppm animals (only the female incidences were statistically significant, $p \leq 0.05$): (i) hunched body (males: 4/12 treated vs. 0/12 controls; females 11/12 treated vs. 0/12 controls); (ii) clonic convulsions, repetitive movements of the mouth and jaw (males: 3/12 treated vs. 0/12 controls; females: 7/12 treated vs. 0/12 controls); and (iii) slight, but definite, impairment of gait score (males: 1/12 treated vs. 0/12 controls; females: 7/12 treated vs. 0/12 controls). In addition, clonic convulsions, repetitive movements of the mouth and jaw were observed in a single 93 ppm female on day 0.

Decreased ($p \leq 0.05$) rotorod performance was observed in the 401 ppm males and females on day 0 (↓43-51%). Decreased ($p \leq 0.01$) body temperature was noted in the 93 and 401 ppm males and females on day 0. In addition, decreased ($p \leq 0.05$) body weights were observed in the 401 ppm males on days 7 and 14 (↓9-11%). Furthermore, decreased ($p \leq 0.05$) total and ambulatory motor activity were noted in the 93 (↓75-78%) and 401 (↓87-97%) males and 27 (↓27-32%), 93 (↓81-84%), and 401 (↓85-95%) ppm females on day 0.

The LOAEL for this study is 93 ppm (0.54 mg/L) based on FOB findings (clonic convulsions, decreased body temperature), and decreased motor activity (↓75-78% in males, 81-84% in females). The NOAEL for this study is 27 ppm (0.16 mg/L).

FOB findings and decreased motor activity indicated that iodomethane was neurotoxic at 93 (0.54 mg/L) and 401 ppm (2.33 mg/L).

The study is classified as **acceptable/guideline**, and satisfies the guideline requirement for an acute neurotoxicity study in rats (870.6200a).

C. **STUDY DEFICIENCIES:** No study deficiencies were noted.

DATA FOR ENTRY INTO ISIS

Acute Neurotoxicity Study - rats (870.6200a)

PC code	MRID #	Study type	Species	Duration	Route	Dosing method	Conc range mg/L	Concs tested mg/L	NOAEL mg/L	LOAEL mg/L	Target organ(s)	Comments
000011	45593817	acute neurotox	rats	15 days	inhal ation	whole body	0.16-2.33	0, 0.16, 0.54, 2.33	0.16	0.54	FOB, motor activity	Conc in mg/L

APPENDIX A

Scoring Criteria for the Functional Observational Battery

Definition:

The Functional Observational Battery (FOB) is a procedure used to detect gross functional deficits in test animals.

Description:

The FOB consists of a series of tests. The tests are categorized into home-cage, handling, open-field, sensory, neuromuscular, and physiological observations and are as follows:

1. Home-Cage Observations
   a. Posture
   b. Convulsions
   c. Tremors
   d. Biting
   e. Palpebral (eyelid) closure
   f. Feces Consistency

2. Handling Observations

   a. Ease of removal from cage
   b. Ease of handling animal in hand
   c. Lacrimation
   d. Chromodacryorrhea
   e. Salivation
   f. Piloerection
   g. Fur appearance
   h. Palpebral closure
   i. Respiratory rate
   j. Respiratory character
   k. Red deposits
   l. Crusty deposits
   m. Mucous membranes/eye/skin color
   n. Eye prominence
   o. Muscle tone

3. Open-Field Observations

a. Time to first step (seconds)
b. Rearing
c. Mobility
d. Backing
e. Grooming
f. Gait
g. Convulsions
h. Tremors
i. Gait Score
j. Arousal
k. Bizarre/Stereotypic behavior
l. Urination
m. Defecation

4. Sensory Observations

a. Approach response
b. Touch response
c. Startle response
d. Tail pinch
e. Olfactory orientation
f. Pupil response
g. Eyeblink response
h. Forelimb extension
i. Hindlimb extension
j. Air righting reflex

5. Neuromuscular Observations

a. Hindlimb extensor strength
b. Grip strength-hind and forelimb
c. Rotarod performance
d. Hindlimb foot splay

6. Physiological Observations

a. Catalepsy
b. Body Temperature
c. Body Weight

Procedure

The FOB was perfomed on those study days specified in the study protocol. Test animals were removed from their cages one at a time on the designated day of testing, and, unless specified in the study protocol, were taken through the FOB in the following order: FOB 1 (inclusive of categories la-1f and 2a), FOB2 (inclusive of categories 2b-2o, 3a-3m and 4a-4j) and FOB3 (inclusive of categories 5a-5d and 6a-6c).

Testing was performed by trained technicians, who did not know the group assignment of the animals. A description of the scoring criteria for each test is provided below:

1. HOME-CAGE OBSERVATIONS

Observations of the animal in its home cage and while opening the cage were performed and scored as follows:

a. Posture

Sitting or standing normally	1
Asleep, lying on side or curled up	2
Alert, oriented toward observer	3
Sitting, head held low	4
Flattened, limbs may be extended	5
Lying on side, limbs in air	6
Immobile	7
Rearing	8

b. Convulsions

I. Clonic

Absent	1
Repetitive movement of mouth and jaws	2
Clonic tremors of the limbs (contraction followed by relaxation)	3
Whole body tremors	4
Clonic convulsions	5
Wet Dog Shakes	6

II. Tonic

Absent	1
Tonic: contraction of extensors such that limbs are rigid and extended	2
Opisthotonus: head, body and limbs rigidly arched backwards	3
Emprosthotonus: head, body and limbs extended forward	4
'Popcorn seizure': animal repeatedly jumps or bounces in air	5
Asphyxial: bouts of severe clonic-tonic convulsions	6

c. Tremors

None	1
Slight (1.5 mm)	2
Moderately coarse (3 mm), slight impairment of locomotion	3
Markedly coarse (4.5 mm), moderate/marked impairment of locomotion	4
Extremely coarse (6 mm), locomotion impossible	5

d. Biting

None	1
Biting of cage	2
Biting of self	3

e. Palpebral (eyelid) closure

Eyelids wide open	1
Eyelids slightly drooping	2
Drooping eyelids (half closed)	3
Eyelids completely shut	4

f. Feces Consistency

Pellets	1
Pellets, partially formed	2
Unformed, diarrhea	3
Pellets absent	4

2. HANDLING OBSERVATIONS

Animals were removed singly from their cages and observed and scored as follows:

a. Ease of removal from cage

Very easy: animal sits quietly, allows investigator to pick it up	1
Easy: with or without vocalization, without resistance or slight resistance to being picked up	2
Moderately difficult: animal rears, often following investigators hand	3
Freezes: with or without vocalization	4
Difficult: runs around cage, is hard to grab, with or without vocalization	5
Very difficult: tail and throat rattles with or without vocalization, may attack hand	6

b. Ease of handling animal in hand

Low: no resistance, animal is easy to handle	1
Moderately low: slight resistance to being handled, with or without vocalization	2
Moderately high: rat may freeze, or be tense or rigid in hand, with or without vocalization	3
High: squirming, twisting, attempting to bite with or without vocalization	4

c. Lacrimation

None	1
Slight	2
Severe	3

d. Chromodacryorrhea

Absent	1
Present	2

e. Salivation

None	1
Slight	2
Severe	3

f. Piloerection

None	1
Slight	2
Severe	3

g. Fur Appearance

Normal: clean and groomed	1
Slightly soiled	2
Very soiled, crusty	3

h. Palpebral closure

Eyelids wide open	1
Eyelids slightly drooping	2
Drooping eyelids (half closed)	3
Eyelids completely shut	4

i. Respiratory Rate

Normal: by observation (80-110/min.)	1
Decreased: below 80/min.	2
Increased: above 110/min.	3

j. Respiratory Character

Normal	1
Rales: abnormal sound accompanying breathing	2
Retching	3
Dyspneic: short of breath	4
Gasping	5

k. Red Deposits - eyes, nose, mouth

Present	1
Absent	2

l. Crusty Deposits - eyes, nose, mouth

Present	1
Absent	2

m. Mucous membranes/eye/skin color

Pink	1
Pale	2
Darkened	3
Darkened, brown	4
Bright, deep red flush	5

n. Eye Prominence

Normal	1
Exophthalmus	2
Enophthalmus	3

o. Muscle Tone

The musculature of the limbs was palpated between the thumb and forefinger.

Muscle is firm but not hard (normal)	1
Muscle is soft and flabby,	2
Muscle is tense and hard	3

3. OPEN-FIELD OBSERVATIONS

Animals were placed singly in the open-field arena (24" x 24"x 6"; constructed from Plexiglas® and painted black) and evaluated over a 2-minute observation period as follows:

a. Time to first step (seconds)

The time taken for the animal to take its first step in the open-field arena was recorded in seconds.

b. Rearing

The number of times the animal reared back onto its hind legs and stood up with both front paws raised off the surface was recorded over a 2-minute observation period in the open-field arena.

c. Mobility (scored within 30 seconds of placing animal in the open-field arena)

Normal	1
Slightly Impaired	2

Moderately Impaired	3
Totally Impaired, Locomotion impossible	4

d. Backing

The number of times the animal took three or more backward steps over a 2-minute observation period in the open-field arena was recorded.

e. Grooming

The number of times the animal groomed itself over a 2-minute observation period in the open-field arena was recorded. Grooming includes washing the face and head with the forepaws, scratching the head or body with a hind paw, and biting the fur.

f. Gait

Normal, head horizontal, abdomen just above surface, slight up and down movement with each step	1
Walks on tiptoes	2
Body drags, abdomen makes contact with surface, body sway	3
Hindlimbs splayed or dragging, unable to support weight	4
Hunched body, bottom up, nose held down, arched back	5
Ataxia, excessive sway, rocks or lurches as animal proceeds forward	6

g. Convulsions

I. Clonic

Absent	1
Repetitive movement of mouth and jaws	2
Clonic tremors of the limbs (contraction followed by relaxation)	3
Whole body tremors	4
Clonic convulsions	5
Wet Dog Shakes	6

II. Tonic

Absent	1
Tonic: contraction of extensors such that limbs are rigid and extended	2
Opisthotonus: head, body and limbs rigidly arched	

backwards	3
Emprosthotonus: head, body and limbs arched forward	4
'Popcorn seizure': animal repeatedly jumps or bounces in air	5
Asphyxial: bouts of severe clonic-tonic convulsions	6

h. Tremors

None	1
Slight (1.5rnm)	2
Moderately coarse (3 rnm), slight impairment of locomotion	3
Markedly coarse (4.5 rnm), moderate/marked impairment of locomotion	4
Extremely coarse (6 rnm), locomotion impossible	5

i. Gait Score: Ability to locomote despite abnormalities in gait

Normal	1
Slight impairment, but definite	2
Considerable impairment, without falling	3
Marked impairment, falls every 4 to 6 steps	4
Severe impairment, cannot walk without falling	5

j. Arousal

Very low: Stupor, coma, little or no responsiveness	1
Low: Somewhat stuporous	2
Normal: Alert, exploratory movements	3
Somewhat high: Slight excitement, tense, excited sudden darting or freezing	4
Very high: Hyperalert, excited, sudden bouts of running or body movements	5

k. Bizarre/Stereotypic Behavior

None	1
Head Flick: head shaking or backward flip of head	2
Head Search: stereotyped, repetitive turning of head from side to side as though searching the environment	3
Hallucinatory: animal appears to be responding to objects not present	4
Compulsive licking or biting	5
Prancing: restless shifting from one forelimb to other, with slight turning of the body from side to side	6
Upright walking: on hindlimbs only	7
Aimless wandering: progressive, slow, plodding movements about environment, with no apparent purpose	8
Circling: tendency to move in circles around and along objects, or in an open environment	9
Waltzing: rapid turning in circles	10
Retropulsion: where animal walks backwards	11
Spatial disorientation: walking or stumbling into objects	12
Side to side rocking	13
Straub tail: increased tail elevation	14
Vertical Jumping	15
Pacing without purpose	16
Head bobbing	17
Writhing: lying down, wavelike movement of abdomen, alternating limb movements	18

l. Urination

The number of pools of urine in the open-field arena was counted.

m. Defecation

The number of fecal boli in the open-field arena was counted.

4. SENSORY OBSERVATIONS

Sensory tests were performed in the open-field arena as follows:

a. Approach Response

The animal was approached head-on with a blunt object held approximately 3 cm from its face for a 4-second period.

No reaction	1
Slow approach, sniffing or turning away	2
More energetic than (2) may include vocalization	3
Freezes, actual muscle contraction	4
Bizarre reaction: jumps, bites or attacks	5

b. Touch Response

The rump of the animal was approached from the side and touched with a blunt object.

No reaction	1
Animal may slowly turn, walk away	2
More energetic response than (2), may include vocalization	3
Freezes, actual muscle contraction	4
Bizarre reaction: jumps, bites or attacks	5

c. Startle Response

A clicker held approximately 5 cm above the head of the animal was used to make a sudden sound.

No reaction	1
Slight reaction, ear flick or some evidence that snap was heard	2
More energetic response than (2), may include vocalization	3
Freezes, actual muscle contraction	4
Bizarre reactions: jumps, attacks, bites	5

d. Tail Pinch

Metal tweezers were used to squeeze tail approximately 2-3 cm from tip.

No reaction	1
Animal may turn or walk away	2
More energetic than (2), may include vocalization	3
Freezes, actual muscle contraction	4
Bizarre reaction: jumps, attacks or bites	5

e. Olfactory Orientation

Approaching the animal from behind, a cotton swab that had been dipped into a jar of commercially available homogenized baby food was brought to within approximately 4-5 cm of the side of the animal's head.

No reaction present	1
Reaction present, animal approaches swab making sniffing movements with nose, may lick swab	2

f. Pupil Response

The beam from a pen light was brought to within approximately 5 mm of the surface of the eye. Changes in pupil size were recorded.

No pupil response	1
Pupil response present	2

g. Eyeblink Response

The comer of the eye was touched gently with a blunt object.

No eyeblink response	1
Eyeblink response present	2

h. Forelimb Extension

The animal was held by the tail and lowered towards a table top. The presence or absence of normal forelimb extension was recorded.

No forelimb extension	1
Forelimb extension present	2

i. Hindlimb Extension

The animal was placed on a table top and lifted by the tail. The presence of normal

hindlimb extension was recorded.

No hindlimb extension	1
Hindlimb extension present	2

j. Air Righting Reflex

The animal was held in a supine position and dropped from a height of approximately 30 cm. The ease of landing was scored as follows:

Normal	1
Slightly uncoordinated	2
Lands on side	3
Lands on back	4

5. NEUROMUSCULAR OBSERVATIONS

a. Hindlimb Extensor Strength

The animal was picked up and slight pressure was applied to its hindlimbs. The normal response is for the animal to extend its hindlimbs against the pressure.

Hindlimb resistance absent	1
Reduced hindlimb resistance, animal shows some weakness	2
Hindlimb resistance present	3

b. Grip Strength - hind and forelimb

Forelimb and hindlimb grip strength were measured using a device similar to the one described by Meyer et al (Neurobehav. Toxicol. 1:233-239, 1979). The animal was allowed to grip aT-shaped grip bar with its forepaws and was pulled back gently along a platform until its grip was broken. As the backward locomotion continued, the animal's hindpaws reached a T-shaped rearlimb grip bar, which it was allowed to grasp and then forced to release by continued pulling. Chatillon push-pull strain gauges (J .A. King, Greensboro, North Carolina) were used to record the maximum strain required to break forelimb and hindlimb grip. The average of three valid measurements was taken as the animal's score for each grip strength measure.

c. Rotarod Performance

During the pretest period, the animals were trained to walk on a rotarod (a 7.0-cm-diameter rod rotating at 12 rpm; AccuScan Instruments, Inc., Columbus,Ohio) for a period of two minutes. The duration of time each animal remained on the rotarod (up to a maximum time of 120 seconds) during testing was recorded.

d. Hindlimb Foot Splay

The heel pads of the hindfeet of the animal were painted with a non-toxic water-based paint. Animals are dropped from a horizontal position approximately 30 cm above a table onto the Hindlimb Foot Splay Test sheet. The distance (to the nearest millimeter) between the inner edge of the ink blots made by each foot was measured. The test was repeated two more times; and the average score (to the nearest millimeter) of the latter two trials was calculated.

6. PHYSIOLOGICAL OBSERVATIONS

a. Catalepsy

The animal was placed on four Plexiglas® platforms (35 mm high and 40 mm in diameter) that were a distance of 100 mm from each other between the fore and hind feet and 60 mm between right and left feet (when measured from the center of the platforms). The time each animal remained on the four platforms was recorded. The duration of immobility was measured (up to a maximum time of 60 seconds).

b. Body Temperature

A thermometer was inserted into the rectum of the animal, and the body temperature was recorded after an equilibration period of approximately 30 seconds.

c. Body Weight

The weight of the animal was recorded.

The Functional Observational Battery is normally recorded on-line via the "IFOB" program in NT-module. In the event that the Data Management System is unavailable for on-line data collection, data are hand-recorded on the Functional Observational Battery Individual Data Sheets (Tl-228, as revised). When appropriate, the hand-recorded data are late entered into the Data Management System.

APPENDIX B

(Pc 000011)

IODOMETHANE HIARC 7-30-2002 ~~7-22-2002~~

Page _____ is not included in this copy.

Pages 100 through 115 are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

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_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

X_____ FIFRA registration data.

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_____ The document is not responsive to the request.

_____ Internal deliberative information.

_____ Attorney-Client work product.

_____ Claimed Confidential by submitter upon submission to the Agency.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

DER #5

Iodomethane: Oral v Inhalation Metabolism Study in Rats
Sponsor Name: Arvesta Corporation (Formerly Tomen Agro, Inc.). Year of Study - 2002.
MRID Nos. 45641401

DATA EVALUATION RECORD

IODOMETHANE

Study Type: §85-1a; Metabolism Study in Rats

Work Assignment No. 4-02-187 (MRID 45641401)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Pesticide Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
Rockville, MD 20850-3268

Primary Reviewer:
Ronnie J. Bever Jr., Ph.D.

Signature: Ronnie J. Bever Jr.
Date: 6/7/02

Secondary Reviewer:
Kelley VanVreede, M.S.

Signature: Kelley VanVreede
Date: 6/10/02

Program Manager:
Mary L. Menetrez, Ph.D.

Signature: Mary L Menetrez
Date: 6/10/02

Quality Assurance:
Steven Brecher, Ph.D.

Signature: Steven Brecher
Date: 6/7/02

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: John Whalan **Signature:** John Whalan
Registration Action Branch 2, Health Effects Division (7509C) **Date** 7-17-02
EPA Secondary Reviewer: Edwin Budd, M.S. **Signature:** Edwin R. Budd
Registration Action Branch 2, Health Effects Division (7509C) **Date** 7/17/02
Work Assignment Manager: Sanyvette Williams-Foy, DVM **Signature:**
Registration Action Branch 2, Health Effects Division (7509C) **Date** 7/18/02

Template version 11/01

TXR#: 0050463

DATA EVALUATION RECORD

STUDY TYPE: Metabolism - Rat; OPPTS 870.7485 (§85-1); OECD 417.

PC CODE: 000011 **DP BARCODE:** D282075
SUBMISSION NO.: S613240

TEST MATERIAL (RADIOCHEMICAL PURITY): Iodomethane (>97%)

SYNONYM: Methyl iodide

CITATION: Sved, D.W. (2002) A Comparative Oral (Gavage) and Inhalation Metabolism and Toxicokinetic Study with Iodomethane in Male Rats. WIL Research Laboratories, Ashland, OH. Laboratory Project Id. No.: WIL-418007, March 27, 2002. MRID 45641401. Unpublished.

SPONSOR: Arvesta Corporation, 100 First Street, Suite 1700, San Francisco, CA

EXECUTIVE SUMMARY: In a rat metabolism study (MRID 45641401), [^{14}C] CH_3I (iodomethane; Lot/Batch # 2962258 and 2962351; >97% radiochemical purity) in deionized water was administered to 12 male Sprague-Dawley rats/dose as a single gavage dose at 1.5 or 24 mg/kg or at an inhalation exposure concentration of 25 or 233 ppm for 5.5 hours. In addition, [^{14}C] CH_3I was administered to 3 male rats/dose as a single gavage dose at 1.0 or 35 mg/kg and 6 male rats/dose at an inhalation exposure concentration of 21 or 209 ppm for 5.5 hours.

Toxicokinetic measurements in the blood demonstrated rapid absorption by both routes of exposure. The highest concentrations in blood occurred within 4 hours following oral administration (1.03 and 16.1 µg/g at the low and high doses, respectively) and within 0-2 hours following inhalation exposure (8.54 and 61.9 µg/g at the low and high doses, respectively). Concentrations in the blood were proportional to dose/concentration. In all treatment groups, the initial half-life was 5.1-7.2 hours, and the terminal half-life was 116-136 hours.

The overall recovery of radioactivity in the main test was 65.4-82.6% in the orally treated rats and 54.4-56.3% in the rats treated via inhalation exposure due to inefficient trapping of carbon dioxide. In the supplementary test, a revised protocol led to an increased overall recovery of radioactivity (91.4-123.5% dose) due to increased recovery of carbon dioxide.

In the supplemental test, recovered radioactivity was found primarily as carbon dioxide (39.40-60.81% dose) and in the urine (26.50-33.40% dose) in all treated groups, while feces accounted for <2% dose. Radioactivity remained in the carcasses (11.92-14.39% dose) of all treated animals 168 hours following treatment in the main test. The elimination half-lives were 17.8-22.3 hours for the urine and 29.7-38.0 hours for the feces in all treatment groups of the main test. The elimination half-life was 5.8-6.8 hours for carbon dioxide in all treatment groups of the supplementary test.

At 0-1 hour post-treatment in the orally treated rats and the 233 ppm inhalation exposed rats, relatively high levels of radioactivity were observed in the liver and GI tract. Radioactivity was relatively high in the kidney, lung, and nasal turbinates of the 25 ppm inhalation exposed rats and in the kidney, thyroid, and lung of the 233 ppm inhalation exposed rats. At 6 hours post-oral dosing, tissue concentrations increased in the spleen (at 1.5 mg/kg only), kidney, brain, thyroid, lung, nasal turbinates, and fat (at 1.5 mg/kg only). Tissue concentrations decreased in other tissues and in all tissues of the inhalation exposed rats at 6 hours after exposure. At 168 hours post-dose, radioactivity had declined in all tissues (to <0.407 µg/g at 1.5 mg/kg, <18.8 µg/g at 24 mg/kg, <3.71 µg/g at 25 ppm, and <24.2 µg/g at 233 ppm) and was highest in the kidney, liver, and thyroid. Tissue concentrations increased (not proportionally) with dose.

In addition to the major metabolite, carbon dioxide (39.40-60.81% dose), two major metabolites were found in the urine. At 1.5 mg/kg, N-(methylthioacetyl) glycine (4.23% dose) and S-methyl glutathione (8.49% dose) were isolated and quantified; these metabolites were present in the other dose groups at 10.12-15.67%. Minor metabolites were also found (methylthioacetic acid, methyl mercapturic acid, and S-methyl cysteine), but not quantified.

This study is classified as **Acceptable/Guideline**, and satisfies the guideline requirement for a Tier 1 metabolism and pharmacokinetics study in rats (OPPTS 870.7485; OECD 417).

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test compound:

Radiolabeled test material:	[^{14}C] CH_3I
Radiochemical purity:	>97%
Specific Activity:	40-60 mCi/mmole
Lot/Batch #:	2962258 and 2962351
Structure:	*CH_3I
Source:	Purchased from Perkin Elmer Life Sciences (Boston, MA)

Non-radiolabeled test material:	Iodomethane technical
Description:	Not reported
Lot/Batch #:	007403/02
Purity:	99.7% a.i.
Contaminants:	Not reported
CAS # of TGAI:	74-88-4
Molecular Weight	141.95 g/Mol
Structure:	CH_3I
Source:	Midwest Research Institute (Kansas City, MO); provided by sponsor

2. Vehicle and/or positive control: Deionized water

3. Test animals:

Species:	Rat	
Strain:	Sprague-Dawley Crl:CD®(SD)IGS BR	
Sex:	All males	
Age and weight at dosing:	~8 weeks; males: 246-353 g	
Source:	Charles River Laboratory (Portage, MI and Raleigh, NC)	
Housing:	Individually, in glass metabolism cages or suspended wire mesh cages	
Diet:	Purina Certified Rodent LabDiet® #5002 (Purina Mills, Inc., Richmond, IN), *ad libitum*, except during inhalation exposures	
Water:	Tap water, *ad libitum*, except during inhalation exposures	
Environmental conditions:	**Temperature:**	67-76°F
	Humidity:	22-44%
	Air changes:	≥10/hour
	Photoperiod:	12-hour light/12-hour dark
Acclimation period:	Approximately 1 week	

4. Preparation of dosing solutions: Oral dosing solutions were prepared by isotopically diluting [^{14}C] CH_3I using deionized water as the carrier. Target concentrations were 0.5 and 5 mg/mL; however, actual administered concentrations were 20.3-30.1% and 47.7-70.2% of the target in the low and high dose groups, respectively. In the main and supplemental groups, mean radioconcentrations were 10.2-10.8 µCi/g and 4.7-5.3 µCi/g with respective specific activities of 1.18-4.44 µCi/mg and 50.8-65.4 µCi/mg. Radiochemical purity was >97%. The formulations were uniform with respect to radioconcentrations as indicated by the low (<10%) coefficients of variation for each analysis. Formulations were used on the day of preparation.

Inhalation exposure dosing solutions were prepared by isotopically diluting [^{14}C] CH_3I in a gas-tight syringe. Target concentrations were 25 and 250 ppm, and 83.4-98.4% of the target was administered in the inhalation low and high exposure groups. In the main and supplemental groups, measured mean test concentrations were 21-25 and 209-233 ppm, Specific activities were 3.79 µCi/mg in the main low concentration group, 0.64 µCi/mg in the main high concentration group, 1.10 µCi/mg in the supplemental low concentration group, and 0.078 µCi/mg in the supplemental high concentration group. Radiochemical purity was >99%. Formulations were used on the day of preparation.

B. STUDY DESIGN AND METHODS:

1. Group arrangements: Animals were assigned randomly to the test groups noted in Table 1.. The Sponsor reported that the low dose/concentration was nontoxic, but high enough so that identification of metabolites was possible; the high dose/concentration was slightly below levels that would cause mortality. The overall recovery of radioactivity in the main test was low due to inefficient trapping of carbon dioxide, so a supplemental test was performed using an optimized carbon dioxide trapping procedure.

Table 1: Dosing groups for iodomethane [a]

Dose Group	Actual average dose/conc.	# male rats	Comments
Main Test			
Single oral low dose	1.5 mg/kg	12	Urine, feces, cage wash, expired air elements, blood samples, and select tissues were periodically collected. Three subgroups of 4 rats/treatment group were sacrificed at 0-1, 6, and 168 hours post-treatment. Sample radioactivity was quantified.
Single oral high dose	24 mg/kg	12	
Low conc. 5.5 h inhalation	25 ppm	12	
High conc. 5.5 h inhalation	233 ppm	12	
Supplemental Test			
Single oral low dose	1.0 mg/kg	3	Urine, feces, cage wash, expired air elements, blood samples, and select tissues were collected immediately following inhalation exposure and at 48 hours after treatment by oral and inhalation routes. Two subgroups of 3 rats/treatment group were used in the inhalation test. Sample radioactivity was quantified.
Single oral high dose	35 mg/kg	3	
Low conc. 5.5 h inhalation	21 ppm	6	
High conc. 5.5 h inhalation	209 ppm	6	

a Data were obtained from this study report from the text on pages 34-35 and Table 1 on page 65.

2. Dosing and sample collection: A single gavage dose of the prepared dosing formulation was administered to Sprague-Dawley rats at a volume of 10 mL/kg. Actual administered radioactive

dose (Table 1) was determined gravimetrically. All inhalation exposures took place in a 186 L polycarbonate dynamic whole-body inhalation chamber for 5.5 hours. Air flow through the chamber was approximately 40-45 L/min. Vapors of the test substance were generated in a gas-washing bottle. The vapor-laden generator air stream was delivered to the exposure chamber inlet where it was diluted to the target concentration with air. The concentrations of iodomethane in the exposure chamber was assayed every 30 minutes during the 5.5 hour exposure.

a. Pharmacokinetic studies:

Main test: In a subgroup of 4 rats/dose, urine, feces, and air were collected separately using glass metabolism cages. Urine was collected on dry ice at 0-6, 6-12, and 12-24 hours post-dose, and then daily through 168 hours post-dose. Feces were collected on dry ice daily through 168 hours post-dose. Expired air components were trapped using a combination of 2% tripropylamine in dimethylsulfoxide (to trap organic vapors) and 0.2 N NaOH (to trap CO_2), except Carbo-Sorb E was used for the first 4 hours (approximately) in the oral dose groups. The use of Carbo-Sorb E (to trap CO_2) was discontinued because the volume of Carbo-Sorb E had decreased by 4 hours and the reagent had thickened. Trapped air components were collected on the same schedule as urine except that oral dose groups had a 0-4 and 4-12 hour post-dose collection time. The cage was rinsed with deionized water following each urine collection, and this rinse was retained as a separate sample. A final cage wash with ethanol was collected at sacrifice. Blood was collected at 12, 24, 48, and 168 hours. In a second subgroup of 4 rats/dose, blood was collected at 1 hour post-oral dose or immediately following the inhalation exposure period. In a third subgroup, blood was collected at 2, 4, and 6 hours. The final blood sample from each animal was collected from the inferior vena cava, and the other blood samples were collected from the tail vein. The spleen, kidneys, liver, brain, thyroid, lungs, nasal turbinates, fat, gastrointestinal tract, and gastrointestinal tract contents (separated from tissue) were collected from all animals and immediately placed on dry ice. Animals were sacrificed at 0-1, 6, and 168 hours post-dose (4 rats/dose/time interval). The carcasses of inhalation exposed animals sacrificed at 0-1 and 168 hours were also collected and weighed. Tissues were weighed and were stored at -20°C when not in use.

Tissue samples, GI contents, and carcass were homogenized separately. Fat samples were dissolved in liquid scintillation cocktail. Fecal samples were homogenized in deionized water (2:1). Other samples were analyzed without prior processing.

Supplemental test: Urine was collected daily, and feces were collected as a single sample. The cage was rinsed with deionized water following the final urine collection, and this rinse was retained as a separate sample. A final cage wash with ethanol was collected at sacrifice. Expired carbon dioxide was collected using Carbo-Sorb E at 0-1, 1-2, 2-4, 4-6, and 6-8 hour post-treatment, then over 4-hour intervals through 48 hours post-treatment.

Both main and supplemental tests: Urine, cage rinse, cage wash, NaOH, and TPA/DMSO samples were analyzed directly for total ^{14}C using liquid scintillation counting (LSC). All other samples were combusted prior to LSC.

b. Metabolite characterization studies: Urine samples containing at least 5% of the administered dose were pooled by collection interval and dose group, filtered (0.45 µm, 98.1-102% recovery), and analyzed using GC-MS, radio-HPLC, and LC-MS/MS to identify excreted metabolites. Only urine was analyzed for a metabolite profile.

3. Statistics: Only descriptive statistics (mean ± S.D., percent coefficient of variation) and linear regression were performed. All calculations were performed using Microsoft Excel. Equations provided for the calculation of toxicokinetic parameters included: $AUC_{0\text{-}168} = \sum (0.5 * (y_1 + y_2) * \Delta t)$; $K_{el} = -\ln_{10} * b$; and $t_{½} = -\ln_{0.5}/k_{el}$.

II. RESULTS

A. PHARMACOKINETIC STUDIES

1. Absorption/Elimination: Toxicokinetic measurements in the blood demonstrated rapid absorption (Tables 2a and 2b). The highest concentrations in blood occurred within 4 hours following oral administration (1.03 and 16.1 µg/g at the low and high doses, respectively) and within 2 hours following inhalation exposure (8.54 and 61.9 µg/g at the low and high concentrations, respectively). Blood concentrations were proportional to dose/concentration. A 24 mg/kg oral dose provided similar concentrations in the blood as a 25 ppm inhalation exposure. Elimination was bi-exponential (line fit: $0.954 > r^2 > 0.997$). In all treatment groups, the initial half-life was 5.1-7.2 hours, and the terminal half-life was 116-136 hours.

Table 2a. Concentration of radioactivity (µg equivalents/g) in rat blood following dosing with [^{14}C] CH_3I. [a]

Time (hour)	Concentration of radioactivity (µg equivalents/g)			
	Oral Administration		Inhalation Exposure	
	1.5 mg/kg	24 mg/kg	25 ppm	233 ppm
1 [b]	0.861±0.082	11.7±1.10	8.54±0.846	61.2±4.09
2	0.927±0.072	12.4±0.672	8.54±0.451	61.9±6.14
4	1.03±0.087	16.1±1.19	7.87±0.440	60.0±7.05
6	0.963±0.132	15.8±0.924	6.76±0.289	54.2±7.79
12	0.663±0.029	11.1±0.759	5.41±0.520	44.3±7.10
24	0.418±0.024	7.03±0.322	4.15±0.582	32.2±5.15
48	0.322±0.029	5.33±0.126	3.47±0.392	24.1±3.92
168	0.175±0.016	2.91±0.243	1.95±0.125	12.9±1.70

a Data are the average of 4 rats/dose group and were obtained from Table 6 on page 74 of this study.
b 0 hours following inhalation exposure.

Table 2b. Kinetic parameters following dosing with [^{14}C] CH_3I. [a]

Parameter	Oral Administration		Inhalation Exposure	
	1.5 mg/kg	24 mg/kg	25 ppm	233 ppm
C_{max} (µg/g)	1.03	16.1	8.54	61.9
T_{max} (h)	4	4	2	2
$AUC_{0\text{-}168}$ (µg-hr/g)	55.4	911	559	4012
Initial phase $t_{½}$ (h)	6.0	6.8	5.1	7.2
Terminal phase $t_{½}$ (h)	121	120	136	116

a Data are the average of 4 rats/dose group and were obtained from Table 6 on page 74 of this study.

The overall recovery of radioactivity at 168 hours post-dose was only 65.4-82.6% in the orally treated animals and 54.4-56.3% in the animals treated via inhalation exposure in the main test due to inefficient trapping of carbon dioxide (Table 3a). However, after optimizing the carbon dioxide trapping procedure, overall recovery of radioactivity at 48 hours post-dose improved to 91.4-123.5% in the supplementary test (Table 3b).

In the supplemental study, carbon dioxide was the major route of elimination (39.40-60.81% dose) in all oral and inhalation treatment groups. In both the main and supplemental studies, recovered radioactivity was found in the urine (26.50-35.27% in all treatment groups, regardless of dose/concentration level or route of exposure), while feces accounted for <2.7% dose in all groups. In all treated rats, radioactivity remained in the carcass at 48 hours post dose (20.85-26.91% dose; supplemental test) and at 168 hours post-dose (11.92-14.39% dose; main test). Overall rates of elimination were similar in all treatment groups, regardless of dose/concentration level or route of exposure. The elimination half-lives were 17.8-22.3 hours for the urine and 29.7-38.0 hours for the feces in all treatment groups of the main test. The elimination half life was 5.8-6.8 hours for carbon dioxide in all treated groups of the supplementary test.

Table 3a. Total recovery of radioactivity at 168 hours post-dose (main test) from rats following dosing with [^{14}C] CH_3I. [a]

Matrix	Recovery of radioactivity (% dose)			
	Oral Administration		Inhalation Exposure	
	1.5 mg/kg	24 mg/kg	25 ppm	233 ppm
Urine and cage rinse	29.02±3.47	35.27±5.61	34.68±11.12	33.63±6.85
Carbon dioxide	34.99±16.83	12.77±11.29	2.98±0.75	2.75±1.21
Organic vapor	0.13±0.06	0.22±0.15	0.12±0.03	0.14±0.03
Feces	2.66±0.52	2.47±0.26	1.58±0.57	1.40±0.22
Cage Wash	0.06±0.02	0.05±0.03	0.06±0.02	0.18±0.16
Tissues	1.70±0.10	1.71±0.15	1.57±0.04	1.70±0.25
Carcass	13.12±1.34	11.92±0.42	14.39±0.64	13.85±1.95
Blood	0.24±0.10	0.32±0.05	0.35±0.08	0.28±0.06
GI tract and contents	0.65±0.05	0.69±0.02	0.60±0.07	0.52±0.03
Total	82.6±14.9	65.4±6.48	56.3±10.7	54.4±9.82

a Data are the mean of 4 rats/dose group and were obtained Tables 2a and 4a on pages 66 and 70 of this study.

Table 3b. Total recovery of radioactivity at 48 hours post-dose in the supplemental test from rats following dosing with [^{14}C] CH_3I. [a]

Matrix	Recovery of radioactivity (% dose)			
	Oral Administration		Inhalation Exposure	
	1.0 mg/kg	35 mg/kg	21 ppm	209 ppm
Urine and cage rinse	30.04±3.81	33.40±2.94	28.73±4.83	26.50±6.44
Carbon dioxide	51.71±28.30	60.81±38.32	46.95±14.86	39.40±14.56
Feces	1.74±0.43	1.73±0.57	1.32±0.39	0.74±0.43
Cage Wash	0.53±0.24	0.62±0.27	1.10±0.29	0.96±0.20
Carcass	20.85±1.88	26.91±0.99	26.72±1.48	23.83±3.81
Total	104.9±26.1	123.5±39.9	104.8±14.5	91.4±18.3

a Data are the mean of 3 rats/dose group and were obtained Tables 2b and 4b on pages 67 and 71 of this study.

3. **Tissue distribution**: At 0-1 hour post-dose (Table 4a) in the orally treated animals and the 233 ppm inhalation exposed rats, relatively high levels of radioactivity were observed in the liver (12.1 µg/g at 1.5 mg/kg and 187-204 µg/g at 24 mg/kg and 233 ppm) and GI tract (11.7 µg/g at 1.5 mg/kg, 78.8 µg/g at 24 mg/kg, and 192 µg/g at 233 ppm). Radioactivity was relatively high in the kidney (50.5 µg/g), lung (75.2 µg/g), and nasal turbinates (51.7 µg/g) of the 25 ppm inhalation exposed rats and in the kidney (319 µg/g), thyroid (198 µg/g), and lung (189 µg/g) of the 233 ppm inhalation exposed rats. At 6 hours post-oral dosing, tissue concentrations

increased in the spleen (at 1.5 mg/kg only), kidney, brain, thyroid, lung, nasal turbinates, and fat (at 1.5 mg/kg only), and concentrations decreased in other tissues and in all tissues of the inhalation exposure animals. At 168 hours post-dose (Table 4b), radioactivity was decreased in all tissues and was highest in the kidney and liver (0.377-0.406 µg/g at 1.5 mg/kg, 7.27-7.34 µg/g at 24 mg/kg, 3.15-3.70 µg/g at 25 ppm, and 23.9-24.1 at 233 ppm), and thyroid (18.7-21.7 µg/g at 24 mg/kg and 233 ppm). Tissue concentrations increased (not proportionally) with dose.

Table 4a. Concentration of radioactivity (µg/g) in blood, tissues, and organs of rats sacrificed at 0-1 hours post-dose following dosing with [^{14}C] CH_3I. [a]

	Oral Administration		Inhalation Exposure	
Tissue	1.5 mg/kg	24 mg/kg	25 ppm	233 ppm
Blood	0.861±0.082	11.7±1.10	8.54±0.846	61.2±4.09
Spleen	1.24±0.327	29.0±9.90	43.4±4.82	152±3.06
Kidney	1.28±0.184	17.3±0.960	50.5±1.94	319±40.7
Liver	12.1±1.08	204±36.9	24.5±2.33	187±31.4
Brain	0.471±0.078	5.97±0.566	21.9±2.23	121±5.08
Thyroid	0.807±0.292	17.9±2.66	106±24.2	198±49.6
Lung	0.752±0.132	11.1±0.996	75.2±4.25	189±10.7
Nasal turbinates	0.549±0.119	9.90±5.24	51.7±9.39	138±6.53
Fat	0.107±0.020	3.53±3.94	3.20±0.241	23.1±2.00
GI tract	11.7±9.04	78.8±13.1	24.3±2.67	192±34.1
GI tract contents	1.12±0.770	37.6±15.0	4.32±2.08	24.4±7.46

a Data are the average of 4 rats and were obtained from Tables 6-9 on pages 74-77 of this study. Tissues were collected at 1 hour post dose from the orally administered rats and 0 hours following inhalation exposure.

Table 4b. Concentration of radioactivity (µg/g) in blood, tissues, and organs of rats sacrificed at 168 hours post-dose following dosing with [^{14}C] CH_3I. [a]

	Oral Administration		Inhalation Exposure	
Tissue	1.5 mg/kg	24 mg/kg	25 ppm	233 ppm
Blood	0.175±0.016	2.91±0.243	1.95±0.125	12.9±1.70
Spleen	0.319±0.027	5.50±0.613	2.49±0.178	16.3±2.19
Kidney	0.406±0.029	7.34±0.665	3.70±0.337	24.1±2.79
Liver	0.377±0.023	7.27±0.601	3.15±0.250	23.9±3.57
Brain	0.154±0.023	2.62±0.257	1.30±0.195	9.12±1.45
Thyroid	0.367±0.078	18.7±27.9	2.57±0.407	21.7±5.24
Lung	0.258±0.019	4.28±0.189	2.40±0.134	16.5±2.15
Nasal turbinates	0.342±0.063	5.85±0.255	3.01±0.352	18.6±3.93
Fat	0.103±0.049	1.26±0.234	0.524±0.072	4.29±1.36
GI tract	0.207±0.005	3.76±0.477	1.79±0.280	10.6±1.20
GI tract contents	0.026±0.007	0.493±0.120	0.194±0.042	1.15±0.227

a Data are the average of 4 rats and were obtained from Tables 6-9 on pages 74-77 of this study.

B. METABOLITE CHARACTERIZATION STUDIES: The major metabolite was carbon dioxide (39.40-60.81% dose). Overall recovered radioactivity in the urine was 26.50-35.27% of the administered dose in all treatment groups, regardless of the dose/concentration level or route of exposure. Two major metabolites were found in the urine (Table 5). At 1.5 mg/kg, N-(methylthioacetyl) glycine (4.23% dose) and S-methyl glutathione (8.49% dose) were isolated and quantified; these metabolites were present in the other dose groups at 10.12-15.67%. Minor metabolites were also found in the urine (methylthioacetic acid, methyl mercapturic acid, and S-methyl cysteine), but were not quantified. There were no significant differences in the metabolism of iodomethane following oral administration or inhalation exposure.

Table 5. Concentration (% dose) of major metabolites in the urine of male rats dosed with [^{14}C] CH_3I. [a]

	Oral Administration		Inhalation Exposure	
Metabolite	1.5 mg/kg [b]	24 mg/kg [c]	25 ppm [d]	233 ppm [e]
N-(methylthioacetyl) glycine	4.23	12.65	15.67	14.17
S-methyl glutathione	8.49	10.92	13.54	10.12

a Data are generally the average of 4 rats and were obtained from Table 16 on page 84 of this study.
b 6-12 h sample
c 6-24 h sample
d 0-24 h sample
e 0-24 h sample

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS: The route of administration of [^{14}C] CH_3I (oral vs inhalation) produced similar results (kinetics, tissue distribution, elimination, and metabolism), except as can be explained by increased load on the portal of entry and first pass metabolism. Iodomethane is absorbed by the oral and inhalation routes and distributed among all tissues tested. Blood concentrations are proportional to dose/concentration and the kinetics are bi-exponential. Carbon dioxide was the major metabolite, and the major route of excretion. The major urinary metabolites were S-methyl glutathione and N-(methylthioacetyl) glycine.

B. REVIEWER COMMENTS: Toxicokinetic measurements in the blood demonstrated rapid absorption. The highest concentrations in blood occurred within 4 hours following oral administration (1.03 and 16.1 µg/g at the low and high doses, respectively) and within 0-2 hours following inhalation exposure (8.54 and 61.9 µg/g at the low and high concentrations, respectively). Concentrations in the blood were proportional to dose/concentration. In all treatment groups, the initial half-life was 5.1-7.2 hours, and the terminal half-life was 116-136 hours.

The supplementary test supported the Sponsor's conclusion in the interim report that poor recovery of radioactivity in the main test (65.4-82.6% dose) was due to poor recovery of carbon dioxide (2.75-34.99% dose). In the supplementary test, recovery of radioactivity improved (91.4-123.5% dose) due to improved recovery of carbon dioxide (39.40-60.81% dose). In the supplemental test, recovered radioactivity was found primarily as carbon dioxide (39.40-60.81%

dose) and in the urine (26.50-33.40% dose) in all treated groups, while feces accounted for <2% dose. Radioactivity remained in the carcasses (11.92-14.39% dose) of all treated animals 168 hours following treatment in the main test. The elimination half-lives were 17.8-22.3 hours for the urine and 29.7-38.0 hours for the feces in all treatment groups of the main test. The elimination half-life was 5.8-6.8 hours for carbon dioxide in all treatment groups of the supplementary test.

At 0-1 hour post-dose in the orally treated animals and the 233 ppm inhalation exposed rats, relatively high levels of radioactivity were observed in the liver (12.1 µg/g at 1.5 mg/kg and 187-204 µg/g at 24 mg/kg and 233 ppm) and GI tract (11.7 µg/g at 1.5 mg/kg, 78.8 µg/g at 24 mg/kg, and 192 µg/g at 233 ppm). Radioactivity was relatively high in the kidney (50.5 µg/g), lung (75.2 µg/g), and nasal turbinates (51.7 µg/g) of the 25 ppm inhalation exposed rats and in the kidney (319 µg/g), thyroid (198 µg/g), and lung (189 µg/g) of the 233 ppm inhalation exposed rats. At 6 hours post-oral dosing, tissue concentrations increased in the spleen (at 1.5 mg/kg only), kidney, brain, thyroid, lung, nasal turbinates, and fat (at 1.5 mg/kg only), and concentrations decreased in other tissues and in all tissues of the inhalation exposure animals. This reflected a decreased absorption and an increased distribution. At 168 hours post-dose, radioactivity was decreased in all tissues and was highest in the kidney and liver (0.377-0.406 µg/g at 1.5 mg/kg, 7.27-7.34 µg/g at 24 mg/kg, 3.15-3.70 µg/g at 25 ppm, and 23.9-24.1 at 233 ppm), and thyroid (18.7-21.7 µg/g at 24 mg/kg and 233 ppm). Thus, differences in tissue distribution were observed based on the route of exposure, but these differences were expected. For instance, the GI tract and the liver initially had relatively high levels of radioactivity in the orally treated animals, and the lungs had high concentrations in the animals treated via inhalation exposure. Because of the duration of exposure (5.5 hours) and route of exposure (inhalation), these animals were expected to generally have higher tissue concentrations at the initial measurement. Finally, the tissue distribution profiles were similar between the two routes of administration at 168 hours post-dose/exposure. Tissue concentrations increased (not proportionally) with dose. Substantial amounts of radioactivity (11.92-14.39% dose) remained in the carcass of each treated animal 168 hours following treatment. However, bioaccumulation was not evident in any sampled tissue. Therefore, the reviewers feel that this diffuse distribution of radioactivity is due to the methylating potential of iodomethane, and that further characterization of this radioactivity is unnecessary.

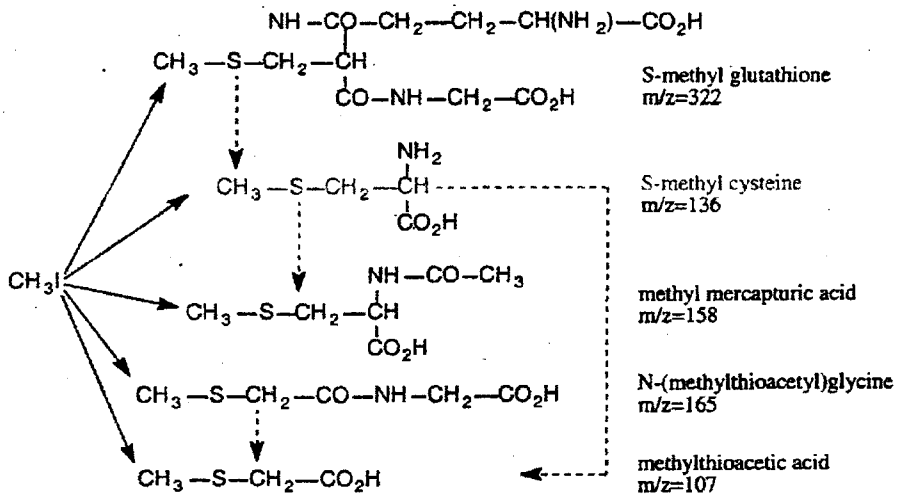
In addition to the major metabolite, carbon dioxide (39.40-60.81% dose), two major metabolites were found in the urine. At 1.5 mg/kg, N-(methylthioacetyl) glycine (4.23% dose) and S-methyl glutathione (8.49% dose) were isolated and quantified; these metabolites were present in the other dose groups at 10.12-15.67%. Minor metabolites were also found (methylthioacetic acid, methyl mercapturic acid, and S-methyl cysteine), but were not quantified.

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirement for a Tier 1 metabolism and pharmacokinetics study in rats (OPPTS 870.7485; OECD 417).

C. STUDY DEFICIENCIES: The study groups in the supplementary test should have included a minimum of four animals instead of three; however, this is a minor deficiency and would not change the conclusions of this review. No other deficiency was noted for a Tier 1 study.

APPENDIX

Proposed Metabolic Scheme for Iodomethane



Solid arrows represent metabolism to metabolites that were seen in this study. Broken arrows represent possible metabolic pathways.

DER #6

Iodomethane: Ames Assay
Sponsor Name: Arvesta Corporation (Formerly Tomen Agro, Inc.). Year of Study - 2001.
MRID Nos. 45593813

IODOMETHANE

BACTERIAL/MAMMALIAN ACTIVATION; GENE MUTATION (84-2)

EPA Reviewer: Irving Mauer, Ph.D.
Registration Action Branch 3, HED (7509C)
EPA Secondary Reviewer: Nancy McCarroll
Toxicology Branch, HED (7509C)

Date: 06/14/02

Date: 07/02/02

TXR NO.: 0050463

DATA EVALUATION RECORD

STUDY TYPE: Bacterial systems, *e.g.*, *Salmonella* and *Escherichia*/mammalian activation gene mutation assay; OPPTS 870.5100 [84-2]

DP BARCODE: D280895
P.C. CODE: 000011

SUBMISSION CODE: S609892
TOX. CHEM NO.: None

TEST MATERIAL (PURITY): Iodomethane (TM-425, 99.7% a.i.; Lot No. 007403)

SYNONYMS: TM-425

CITATION: Wagner, V.O., III and Dakoulas, G.W. (2001). Bacterial Reverse Mutation Assay (Ames) with Iodomethane, performed at BioReliance, Rockville (MD), Laboratory Study No. AA38UL.504004. BTL, dated March 14, 2001. MRID 45593813. Unpublished.

SPONSOR: Arvesta Corporation, San Francisco (CA).

EXECUTIVE SUMMARY: In repeat reverse gene mutation preincubation assays in bacteria, histidine-deficient strains (*his* $^-$) TA98, TA100, TA1535 and TA1537 of *Salmonella typhimurium* and trytophan-deficient (*try*)WP2 (uvrA) of *Escherichia coli* were exposed to iodomethane (99.7% a.i.; Lot No. 007403) in sterile distilled water (SDW) at twelve concentrations ranging from 0.015 to 5000 μg/plate. In a confirmatory assay, cultures were exposed to six concentrations ranging from 15 to 5000 μg/plate. In addition to cultures exposed to the vehicle, SDW, other cultures were treated with strain-specific mutagens. Following exposures, cultures were incubated at 37 ± 2°C for 24 - 72 hours, at which times reversions to prototrophy were determined.

Toxicity was observed at 5000 μg/plate +/-S9 in both assays, but no precipitation. At no concentration, however, were any increases in the number of revertant colonies (*his*$^-$ to *his*$^+$; *try*$^-$ to *try*$^+$) compared to vehicle control values observed. Therefore, **iodomethane is concluded to be non-mutagenic in these bacterial assays.**

This study is classified as acceptable/guideline. It does satisfy the requirements for FIFRA Test Guideline 84-2 for *in vitro* mutagenicity (bacterial reverse gene mutation) data.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: Iodomethane (TM-425)
Description: Clear to light yellow liquid
Lot/Batch No.: 007403
Purity: 99.7% a.i.
Stability of compound: Stable (Study Report, APPENDIX IV, p 57-59)
CAS No.: 74-88-4
Solvent used: Sterile, distilled water (SDW)
Other comments: Store at room temperature, in a tightly closed light-resistant container in a cool, dry, well-ventilated place.

2. Control Materials:
Negative: None
Solvent/Final Concentration: SDW/500 μL
Positive: Non-activated:

Sodium azide	1.0 μG/plate for T100, TA1535
2-Nitrofluorene	1.0 μg/plate for TA98
9-Aminoacridine	75.0 μg/plate for TA1537
Other (list):	
Methylmethane sulfonate	1000 μg/plate for WP2 (uvrA)

Activated:
2-Aminoanthracene (2-anthramine) 1.0 μg/plate for all *Salmonella* strains; 10.0 μg/plate for WP2 (uvrA)

Other (list): None.

3. Metabolic Activation: S9 was derived from male Sprague-Dawley rats.

x	Aroclor 1254	x	induced	x	rat	x	liver
	phenobarbital		non-induced		mouse		lung
	none				hamster		other
	other						other

If other, describe below.

Describe S9 mix composition:

Ingredient	Quantity (mL)
S9	10%
G-6-P	5 mM
NADP	4 mM
$MgCl_2$	8 mM
KCl	33 mM
in a 100 mM phosphate buffer at pH 7.4	

4. Test Organisms: *Salmonella typhimurium* strains:

	TA97	x	TA98	x	TA100		TA102
	TA104	x	TA1535	x	TA1537		TA1538

Source: Dr. Bruce Ames (University of California, Berkeley)
List any others: *Escherichia coli* WP2 (uvrA)
Source: National Collection of Industrial and Marine Bacteria, Aberdeen, (Scotland)

Properly maintained? Not stated.
Checked for appropriate genetic markers (rfa mutation, R factor)? Not stated.

5. Test Compound Concentration Used:

Cytotoxicity Test: (if performed): 0.015 - 5000 μg/plate

Main Assays:

Condition	ASSAY I	ASSAY II
Non-activated and activated conditions	0.015, 0.050, 0.15, 0.50, 1.5, 5.0, 15, 50, 150, 500, 1500, 5000 μg/plate	15, 50, 150, 500, 1500, 5000 μg/plate

B. TEST PERFORMANCE:

Overnight cultures were prepared by inoculating from the appropriate master plate or from the appropriate frozen permanent stock into a vessel containing ~50 mL of culture medium. To assure that cultures were harvested in late log phase, the length of incubation was controlled and monitored. Following inoculation, each flask was placed in a resting shaker/incubator at room temperature. The shaker/incubator was programmed to begin shaking at approximately 125 rpm at 37 ±2°C approximately 12 hours before the anticipated time of harvest. Each culture was monitored spectrophotometrically for turbidity and was harvested at a percent transmittance yielding a titer of approximately 10^9 cells per milliliter. The actual titers were determined by viable count assays on nutrient agar plates.

Initial Toxicity-Mutation Assay:

The initial toxicity-mutation assay was used to establish the dose-range over which the test article would be assayed and to provide a preliminary mutagenicity evaluation. Vehicle controls, positive controls and twelve dose levels of the test article were plated, two plates per dose, with overnight cultures of TA98, TA100, TA1535, TA1537 and WP2 uvrA on selected minimal agar in the presence and absence of Aroclor-induced rat liver S9.

Confirmatory Mutagenicity Assay:

The confirmatory mutagenicity assay was used to evaluate and confirm the mutagenic potential of the test article. A minimum of six dose levels of test article along with appropriate vehicle and positive controls were plated with TA98, TA100, TA1535, TA1537 and WP2 uvrA in the presence and absence of Aroclor-induced rat liver S9. All dose levels of test article, vehicle controls and positive controls were plated in triplicate.

Plating and Scoring Procedures

The test system was exposed to the test article via the preincubation methodology described by Yahagi *et al.* (1977).

On the day of its use, minimal top agar, containing 0.8% agar (W/V) and 0.5% NaCl (W/V), was melted and supplemented with L-histidine, D-biotin and L-tryptophan solution to a final concentration of 50 μM each. Top agar not used with S9 or Sham mix was supplemented with 25 mL of water for each 100 mL of minimal top agar. For the preparation of media and reagents, all references to water imply sterile, deionized water produced by the Milli-Q Reagent Water System. Bottom agar was Vogel-Bonner minimal medium E (Vogel and Bonner, 1956) containing 1.5% (W/V) agar. Nutrient bottom agar was Vogel-Bonner minimal medium E containing 1.5% (WV) agar and supplemented with 2.5% (W/V) Oxoid Nutrient Broth No. 2 (dry powder). Nutrient

Broth was Vogel-Bonner salt solution supplemented with 2.5% (W/V) Oxoid Nutrient broth N. 2 (dry powder).

Each plate was labeled with a code system that identified the test article, test phase, dose level, tester strain and activation, as described in detail in BioReliance's Standard Operating Procedures.

In the initial toxicity-mutation assay, two sets of test article dilutions were prepared immediately before use, one set was used for plating without S9 activation and the other set was used for plating with S9 activation. In the confirmatory mutagenicity assay, two sets of test article dilutions were prepared immediately before use, one set of dilutions for dose levels 5000, 1500 and 500 μg per plate in the presence and absence of S9 activation and the other set of test article dilutions for 150, 50 and 15 μg per plate in the presence and absence of S9 activation. One-half (0.5) milliliter of S9 or sham mix, 100 μL of tester strain and 500 μL of vehicle or test article were added to 13 X 100 mm glass culture tubes with Teflon®-lined screw caps preheated to 37 ± 2°C. The tubes receiving test article were capped during the preincubation period. After vortexing, these mixtures were incubated with shaking for 60 ± 2 minutes at 37 ± 2°C. Following the preincubation, 2.0 mL of selective top agar was added to each tube and the mixture was vortexed and overlaid onto the surface of 25 mL of minimal bottom agar. When plating the positive controls, the test article aliquot was replaced by a 50 μL aliquot of appropriate positive control. After the overlay had solidified, the plates were inverted and incubated for approximately 48 to 72 hours at 37 ± 2°C. For the confirmatory mutagenicity assay, the test article plates were placed in dessicators by dose level for 24 hours and then removed from the dessicator for the remainder of the incubation period. Plates that were not counted immediately following the incubation period were stored at 2 - 8°C until colony counting could be conducted.

The condition of the bacterial background lawn was evaluated for evidence of test article toxicity by using a dissecting microscope. Precipitate was evaluated by visual examinationn without magnification. Toxicity and degree of precipitation were scored relative to the vehicle control plate using the codes shown below.

Code	Description	Characteristics
1	Normal	Distinguished by a healthy microcolony lawn.
2	Slightly Reduced	Distinguished by a noticeable thinning of the microcolony lawn and possibly a slight increase in the size of the microcolonies compared to the vehicle control plate.
3	Moderately Reduced	Distinguished by a marked thinning of the microcolony lawn resulting in a pronounced increase in the size of the microcolonies compared to the vehicle control plate.
4	Extremely Reduced	Distinguished by an extreme thinning of the microcolony lawn resulting in an increase in the size of the microcolonies compared to the vehicle control plate such that the microcolony lawn is visible to the unaided eye as isolated colonies.
5	Absent	Distinguished by a complete lack of any microcolony lawn over ≥ 90% of the plate.
6	Obscured by Precipitate	The background bacterial lawn cannot be accurately evaluated due to microscopic test article precipitate.
NP	Non-Interfering Precipitate	Distinguished by precipitate on the plate that is visible to the naked eye but any precipitate particles detected by the automated colony counter total less than 10% of the revertant colony count (*e.g.*, < 3 particles on a plate with 30 revertants).
IP	Interfering Precipitate	Distinguished by precipitate on the plate that is visible to the naked eye and any precipitate particles detected by the automated colony counter exceed 10% of the revertant colony count (*e.g.*, > 3 particles on a plate with 30 revertants.)

Revertant colonies for a given tester strain and activation condition, except for positive controls, were counted either entirely by automated colony counter or entirely by hand unless the plate exhibited toxicity. Plates with sufficient test article percipitate to interfere with automated colony counting were counted manually.

1. Type of *Salmonella Assay*:

____ standard plate test
__x__ preincubation (__60__ minutes)
____ "Prival" modification
____ spot test
____ other (describe)

2. Protocol:

Both criteria for a valid test and evaluation of results were reported.

II. REPORTED RESULTS

A. SOLUBILITY:

Water was selected as the solvent (vehicle) of choice based upon the Sponsor's request, compatibility with the target cells and ease of solubility.

B. PRELIMINARY CYTOTOXICITY ASSAY:

The results of the initial toxicity-mutagenicity assay are presented in MRID 45593813, pp 15-24, and summarized in the Report, p 35, (ATTACHMENT, Table 21).

C. CONFIRMATORY MUTAGENICITY ASSAY:

The results of the repeat assay are presented in MRID 45593813 pp 25-34, and summarized in the Report, p. 36, (ATTACHMENT, Table 22). Although toxicity was evident the highest dose tested, 5000 μg/plate, no precipitation was observed at any dosage in either assay or was there any increase in revertant frequency. Thus, the investigators concluded that under the conditions of this Study, iodomethane was non-mutagenic in the presence and absence of S9 metabolic activation.

III. REVIEWER'S DISCUSSION/CONCLUSIONS

A. The EPA reviewer agrees with the investigators' conclusions that iodomethane assayed up to the limit dose/level of toxicity did not increase the frequency of revertants in *Salmonella typhimurium* or *Escherichia coli* deficiency mutants either in the presence or absence of S9 metabolic activation.

B. STUDY DEFICIENCIES

No major deficiencies would compromise the conclusions of this study.

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DER #7

Iodomethane: *In Vitro* Mammalian Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells
Sponsor Name: Arvesta Corporation (Formerly Tomen Agro, Inc.). Year of Study - 2001.
MRID Nos. 45593814

IODOMETHANE

IN VITRO CHROMOSOME ABERRATIONS [84-2]

EPA Review: Irving Mauer, Ph.D. Date: 06/24/02
Registration Action Branch 3, HED (7509C)
EPA Secondary Reviewer: Nancy McCarroll Date: 07/02/02
Toxicology Branch, HED (7509C)

TXR No.: 0050463

DATA EVALUATION RECORD

STUDY TYPE: *In Vitro* mammalian chromosome aberrations in Chinese hamster ovary (CHO) cells OPPTS 870.5375 [84-2], OECD 473

DP BARCODE: D280895 SUBMISSIONS CODE: S609892

P.C. CODE: 000011 TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): Iodomethane (TM-425, 99.7% a.i.; Lot No. 007403)

SYNONYMS: TM-425

CITATION: Gudi, R. and Brown, C. (2001). *In vitro* Mammalian Chromosome Aberrations Test with Iodomethane, performed at BioReliance, Rockville (MD), Laboratory Study No. AA38UL.331.BTL, dated August 21, 2001. MRID 45593814. Unpublished.

SPONSOR: Arvesta Corporation, San Francisco (CA)

EXECUTIVE SUMMARY:

In an *in vitro* cytogenetic (chromosome aberration) assay (MRID 45593814), cultures of Chinese hamster ovary (CHO) cells were exposed to iodomethanne (99.7% a.i.; Lot No. 007403) in sterile distilled water (SDW) for 4 hours at concentrations ranging from 25 or 50 to 350 μg/mL in the presence and absence of a mammalian activation system, then transferred to test article-free medium for a 16-hour recovery period, or exposed continuously for 20 hours at concentrations ranging from 25 to 250 μg/mL.

At 20 hours after initiation of exposure, cells were harvested following 2 hours treatment with the metaphase-arresting alkaloid, Colcemid, and both toxicity (mitotic indices) and frequency of aberrant metaphases determined. In addition to cultures exposed to the vehicle, SDW, other cultures were treated with the clastogens, mitomycin C (MMC, 0.1 - 0.2 μg/mL) and cyclophosphamide (CP, 10 - 20 μg/mL), to serve as positive controls for the non-activation and activation test series.

Substantial toxicity (at least 50% cell growth inhibition) was observed at dose levels of 426 μg/mL and above in both activated and non-activated 4-hour exposure groups, as well as in the 20-hour non-activated continuous exposure groups.

Dose-related and significant increases in structural chromosome aberrations were seen at 150 and 250 μg/mL -S9 (4-hour treatment), at 100 and 200 μg/mL +S9 (4-hour treatment) and at 50 to 250 μg/mL -S9 (20-hour treatment). In general, chromatid breaks and exchanges were the most frequently observed aberrations. Therefore, **iodomethane is positive for the induction of structural chromosome aberrations (clastogenesis), but negative for induction of numerical aberrations in CHO cells in this assay**.

This study is classified as acceptable/guideline and satisfies the requirements for Test Guideline OPPTS 870.5375 [84-2] for *in vitro* chromosome aberrations data.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: Iodomethane
   Description: Pale, yellow, clear liquid
   Lot/Batch No.: 007403/Batch: 02
   Purity: 99.7% a.i.
   Stability of compound: Not reported.
   CAS No.: 77-88-4
   Solvent used: Sterile distilled water (SDW)
   Other comments: Store at room temperature tightly sealed, and protected from exposure to light.

2. Control Materials:
   Negative: None
   Solvent/Final concentration: SDW/500 μL
   Positive: Non-activation (concentrations, solvent): Mitomycin C (MMC 0.1 - 0.2 μg/mL in SDW)
   Activation (concentrations, solvent): Cyclophosphamide (CP, 10 - 20 μg/mL in SDW)

3. Metabolic Activation: S9 derived from male Sprague-Dawley rats.

x	Aroclor 1254	x	induced	x	rat	x	liver
	phenobarbital		non-induced		mouse		lung
	none				hamster		other
	other						other

If other, describe below:
Describe S9 mix composition:

Cofactor Pool:	2 mM	$MgCl_2$
	6 mM	KCl
	1 mM	G-6-P
	1 mM	NADP
	20 μL	S9/mL medium (McCoy's 5A serum-free, supplemented with 100 units penicillin and 100 μg streptomycin + 2 mM L-glutamine)

4. Test Compound Concentrations Used: (for preliminary Cytotoxicity Test)

$5 \times 10^5/Cm^2$ flask were incubated at 37 ± 1 °C in 5 ± % CO_2 in air for 16 - 24 hours at 4 hours ± S9 and coninuously for 20 hours -S9. Presence of precipitate was assessed with naked eye, cell viability by trypton blue exclusion. Cell counts were made at 20 hours harvest. Concentrations: 0.142, 0.426, 1.42, 4.26, 14.2, 42.6, 142, 426, 1420 μg/mL.

5. Test Cells: CHO-K_1 (Repository No. CCL61)

Properly maintained? Yes.
Cell line or strain periodically for Mycoplasma contamination: Yes.
Cell line or strain periodically checked for karyotype stability? Yes.

B. TEST PERFORMANCE:

Cytogenetic Assay:

a. Cell treatment: Standard procedure:
Cells exposed to test compound, solvent, or positive control, for 4 or 20 hours (non-activated), 4 hours (activated).

b. Spindle inhibition:
Inhibition used/concentration: Colcemid, 0.1 μg/mL
Administration time: 2 hours (before cell harvest)

c. Cell harvest:
Cells exposed to test material, solvent or positive control for 4 hours were harvested 16 hours after termination of treatment (non-activated), 16 hours after termination of treatment (activated).

d. Details of slide preparation: standard cytological procedure

e. Metaphase analysis
Number of cells examined per dose: 200 (100/slide)
Scored for structural: Yes.
Scored for numerical? Yes.
Coded prior to analysis? Yes.

f. Evaluation criteria: Conventional criteria presented.

g. Statistical analysis: Data were evaluated for statistical significance at $p \leq 0.05$ using Fisher's Exact Test.

II REPORTED RESULTS:

A. Water was determined to be the solvent of choice based on information provided by Sponsor, the solubility of the test article, and compatibility with the target cells. The test article was soluble in water at a concentration of 14.2 mg/mL, the maximum concentration tested.

B. PRELIMINARY CYTOTOXICITY ASSAY:

The results of the toxicity tests reveal that extreme toxicity occurs at 426 μg/mL and above (MRID 45593814, pp, 17-20, 22 - ATTACHMENT Tables 1-4, 6.

C. CHROMOSOME ABERRATIONS ASSAYS:

Therefore, the high dose selected for the chromosome assays was 350 μg/mL +/-S9 (4-hour treatment) and 250 μg/mL -S9 (20-hour treatment). Dose-related and significant increases in structural aberrations (MRID 45593814, pp 23, 25, 26 - ATTACHMENT Tables 7, 9, 10) compared to concurrent controls as well as historical control data were seen in both the presence and absence of S9 activation. In general, chromatid breaks and exchanges were the most frequently scored structural aberrations (APPENDIX I, pp 28, 29). There was no consistent evidence of increases in numerical aberrations.

Therefore, the investigators concluded that iodomethane is positive for the induction of structural chromosome aberrations, but negative for the induction of numerical aberrations in this test system.

III. AGENCY DISCUSSION/CONCLUSIONS:

A. The EPA reviewer agrees with the investigators' conclusions that at concentrations producing minor toxicity (< 50% cell growth inhibition), iodomethane induces statistically significant increases in structural aberrations as compared to concurrent controls and historical control data.

B. DEFICIENCIES: None.

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DER #8

Iodomethane: *In Vivo* Mammalian Cytogenetics - Micronucleus Assay in Mice
Sponsor Name: Arvesta Corporation (Formerly Tomen Agro, Inc.). Year of Study - 2001.
MRID Nos. 45593816

IODOMETHANE

MICRONUCLEUS (84-2]

EPA Reviewer: Irving Mauer, Ph.D. Date: 07/05/02
Registration Action Branch 3, HED (7509C)
EPA Secondary Reviewer: Nancy McCarroll, Geneticist Date: 02/11/02
Toxicology Branch, HED (7509C)

TXR No.: 0050463

DATA EVALUATION RECORD

STUDY TYPE: *In vivo* mammalian cytogenetics - micronucleus assay in mice; OPPTS 870.5395 [84-2]; OECD 474

DP BARCODE: D280895
P.C. CODE: 000011

SUBMISSION CODE: S609892
TOX. CHEM NO.: None

TEST MATERIAL (PURITY): Iodomethane (TM-425, 99.7% a.i.; Lot No.. 007403)
SYNONYMS: TM-425

CITATION: Gudi, R. and Krsmanovic, L. (2001). Mammalian Erythrocyte Micronucleus Test With Iodomethane, performed at BioReliance, Rockville (MD), Laboratory Study No. AA38UL.123.BTL, dated 02 October 2001, MRID 45593816. Unpublished.

SPONSOR: Arvesta Corporation, San Francisco (CA)

EXECUTIVE SUMMARY:

In a cytogenetic (micronucleus) assay (MRID 45593816), groups of mice (5/sex/harvest) were injected once intraperitoneally with iodomethane (99.7% a.i.; Lot No. 007403) in sterile distilled water (SDW) at doses of 25, 50 or 100 mg/kg and bone marow collected 24 or 48 hours post-dose. In addition to animals treated with the vehicle, SDW, a group of mice (5M/5F) was injected i.p. with cyclophosphamide (CP, 2.5 mg/mL), to serve as positive control.

The highest dose selected for the study (100 mg/kg) was considered the maximum tolerated dose (MTD), based on the evidence of mortality and other clinical signs at ≥ 200 mg/kg, in the toxicity test. There was no clear evidence of a toxic effect in these animals or a cytotoxic effect in the target tissue. There was also no significant increase in micronucleated-PCE in iodomethane-treated groups relative to the respective controls in either males or females 24 or 48 hours after dose administration.

Therefore, iodomethane is considered to be negative in the mouse micronucleus assay.

This study is classified as acceptable/guideline and satisfies the requirement for FIFRA Test Guideline 84-2 for *in vivo* cytogenetic mutagenicity data.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: Iodomethane (TM-425)
Description: Pale, yellow, clear liquid
Lot/Batch No.: 007403/02
Purity: 99.7% a.i.
Stability of compound: Stable, according to report, APPENDIX III, p.34.
CAS No.: 74-88-4
Solvent used: Sterile, distilled water (SDW)
Other comments: Store at room temperature, protected from light and moisture.

2. Control Materials:
Negative/Route of Administration: None
Vehicle/Final Volume/Route of Administration: SDW/20 mL/kg/intraperitoneal injection
Positive: Final Dose(s)/Route of Administration: Cyclophosphamide/50 mg/kg/intraperitoneal injection

Test Compound Administration:
Volume: 20 mL/kg
Route of Administration: Intraperitoneal injection
Dose Levels: Toxicity Study: 50, 100, 200, 280 mg/kg i.p.

Because of deaths and clinical toxicity at 200 and 280 mg/kg, 100 mg/kg was set as the maximum tolerated dose for the main assay.
Main Assays: 25, 50, 100 mg/kg i.p.

3. Test Animals:
   a. Species: Mice Strain ICR Age 6 - 8 weeks
   Weight: Male 28.4 - 33.7 g female 25.8 - 29.3 g
   Source: Harlan Sprague-Dawley, Frederick (MD)
   b. Number of animals used per dose: 5 males 5 Fe,ales
   c. Properly maintained? Yes.

B. TEST PERFORMANCE:

1. Treatment and Sampling times:
   a. Test compound:
   Dosing: x once _____ twice (24 hours apart)
   _____ other (describe):
   Sampling (after last dose): ____6 hrs. ____12 hours x 24 hours
   x 48 hours _____72 hours (mark all that are appropriate)
   _____ other (describe):

b. Negative and/or vehicle control:
Dosing: __x__once _____twice (24 hours apart) _____ (describe):
Sampling (after last dose): _____6 hours _____12 hours __x__24 hours
__x__48 hours _____72 hours (mark all that are appropriate)
_____other (describe):

c. Positive Control:
Dosing: __x__once _____twice (24 hours apart) _____ other (describe):
Sampling (after last dose): _____6 hours _____12 hours __x__24 hours
_____48 hours _____72 hours (mark all that are appropriate)
_____other (describe)

2. Tissues and Cells Examined:
__x__bone marrow _____other (describe):

Number of polychromatic erythrocytes (PCE) examined per animal: 2000
Number of normochromatic erythrocytes (NCE; more mature RBCs) examined per animal: Per 1000 erythrocytes
Other (if other cell types examined, describe): None

3. Details of slide preparation:

Femoral bone marrow cells in fetal bovine serum were spread onto microscope slides (2/mouse). Slides were fixed in methanol, and stained with May-Gruenwald-Giemsa, then permanently mounted. Slides were coded prior to scoring.

4. Statistical Methods:

Incidence or micronucleated polychromatic erythrocytes (MPCE) per 2000 PCE was determined for each mouse and each treatment group. Statistical significance was determined using the Kastenbaum-Bowman tables (1970), which are based on the binominal distribution. Analyses were performed separately for each sex and sampling time at a p value ≤ 0.05.

5. Evaluation Criteria:

Criteria for the evaluation of results were presented.

6. Criteria for a valid test were also presented.

II. REPORTED RESULTS:

A. SOLUBILITY:

Water was determined to be the solvent of choice. The test article was soluble in water up to 14 mg/mL.

B. PRELIMINARY CYTOTOXICITY ASSAY:

Three-fifths of the males and four-fifths of the females died at 200 mg/kg; four-fifths of each sex at 280 mg/kg. Clinical signs were evident (lethargy, piloerection, tremors, crusty eyes/nose) at 200 and 280 mg/kg. Animals given 50 or 100 mg/kg manifested no clinical signs.

C. MICRONUCLEUS ASSAY:

Doses evaluated were 25, 50 and 100 mg/kg. No mortality occurred at any dose level during the course of the micronucleus assay; all mice appeared normal throughout the observation period.

The incidence of MPCE per 10,000 PCE scored (2000 PCE/animal), and the proportion of PCE per total erythrocytes indicate reductions of 2% to 20% in the ratio of PCE to total erythrocytes in some iodomethane-treated groups relative to their respective vehicle controls (MRID 45593816, pp. 19, 20, 21 - ATTACHMENT Tables 4, 5, 6). Since these reductions were sporatic and not dose-related, the investigators concluded that iodomethane did not inhibit erythropoiesis.

Further, **the number of MPCE per 2000 PCE in iodommethane-treated group was not statistically increased relative to their vehicle controls in either male or female mice, regardless of dose level or bone marrow collection time ($p > 0.05$, Kastenbaum-Bowman Tables).** The positive control, CP, induced a significant increase in MPCE in both male and female mice ($p \leq 0.05$, Kastenbaum-Bowman).

Therefore, the investigators concluded that iodomethane was negative in the micronucleus test in ICR mice.

III. REVIEWER'S DISCUSSION/CONCLUSIONS:

A. The EPA reviewer agrees with the investigators' conclusions that under the conditions of this assay, the test article, iodomethane, did not induce a significant increase in the incidence of MPCE in bone marrow of male and female ICR mice, and thus is negative in the micronucleus test in ICR mice.

B. DEFICIENCIES: None.

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DER #9

Iodomethane: Mammalian Cells in Culture Gene Mutation Assay in Chinese Hamster Ovary (CHO) Cells
Sponsor Name: Arvesta Corporation (Formerly Tomen Agro, Inc.). Year of Study - 2001.
MRID Nos. 45593815

IODOMETHANE

MAMMALIAN CELLS IN CULTURE; GENE MUTATION (84-2)

EPA Reviewer: Irving Mauer, Ph.D. Date: 06/24/02
Registration Action Branch 3, HED (7509C)
EPA Secondary Reviewer: Nancy McCarroll Date: 07/02/02
Toxicology Branch, HED (7509C)

TXR No.: 0050463

DATA EVALUATION RECORD

STUDY TYPE: Mammalian cells in culture gene mutation assay in Chinese hamster ovary (CHO) cells; OPPTS 870.5300 [84-2], OECD 476

DP BARCODE: D280895 SUBMISSION CODE: S609892

P.C. CODE: 000011 TOX. CHEM NO.: None

TEST MATERIAL (PURITY): Iodomethane (TM-425, 99.7% a.i.; Lot No. 007403)

SYNONYMS: TM-425

CITATION: San, R.H.C. and Clarke, J.J. (2001). *In Vitro* Mammalian Cell Gene Mutation Test (CHO/HGPRT Assay) with Iodomethane, performed at BioReliance, Rockville, (MD), Laboratory Study No. AA38UL.782.BTL, dated August 8, 2001. MRID 45593815. Unpublished.

SPONSOR: Arvesta Corporation, San Francisco (CA)

EXECUTIVE SUMMARY:

In a mammalian cell gene mutation assay (MRID 45593815), cultures of Chinese hamster ovary (CHO-K_1BH_4) cells were exposed for 5 hours to iodomethane (99,7% a.i.; Lot No. 007403) in sterile distilled water (SDW) at concentrations ranging from 100 to 500 (or 600) μg/mL in the presence and absence of metabolic activation. Following exposure, determinations of mutant frequencies (> 40 mutants per 10^6 clonable cells) were made. In addition to cultures exposed to the solvent, SDW, other cultures were treated with the mutagens, ethylmethansulfonate (EMS) and benzo(a)pyrene [B(a)P], to serve as positive controls for the non-activation (-S9) and activation (+S9) test series.

No visible precipitation was observed, but substantial toxicity (≤22%) occurred at ≥ 505 μg/mL ± S9. Cloning efficiency < 50% of the solvent control was observed at doses of ≥ 125 μg/mL -S9 and ≥ 150 μg/mL +S9. However, at no test dose in the presence or absence of activation was there any significant increase in mutant colonies. The positive controls responded appropriately with large increases in mutants.

Therefore, iodomethane is considered to be negative in this CHO/HGPRT Mutation Assay.

This study is classified as acceptable/guideline and satisfies the requirement for *in vitro* mutagenicity (mammalian cell forward gene mutation) data.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: Iodomethane (TM-425)
Description: Light yellow clear liquid
Lot/Batch No.: 007403, Batch: 02
Purity: 99.7% a.i.
Stability of compound: Stated to be the responsibility of the Sponsor.
CAS No.: 74-88-4
Solvent used: Sterile, distilled water (SDW)
Other comments: Store at room temperature, protected from exposure to light.

2. Control Materials:
Negative: None
Solvent/Final concentration: SWD/100μL
Positive: Non-activated (concentration, solvent): Ethyl methansulfonate (EMS, 0.2 μL/mL).
Activated: Benzo(a)pyrene B(a)P, 4.0 μg/mL)

3. Metabolic Activation: S9 derived from adult male Sprague-Dawley rats.

x	Aroclor 1254	x	induced	x	rat	x	liver
	phenobarbital		non-induced		mouse		lung
	none				hamster		other
	other						other

If other, describe below:
Describe S9 mix composition:

S9	100 μL
NADP	4 mM
G-6-P	5 mM
$MgCl_2$	10 mM
KCl	30 mM
$CaCl_2$	10 mM
Sodium phosphate buffer	50 mM

4. Test Organisms: Mammalian cells in culture.

	Mouse lymphoma L5178Y cells
x	Chinese hamster ovary (CHO) cells (CHO-K_1-BH_4)
	V79 cells (Chinese hamster lung fibroblasts)
	Other (list)

Properly maintained? Yes.
Periodically checked for Mycoplasma contamination? Yes.
Periodically checked for karyotype stability? Yes.
Periodically "cleansed" against high spontaneous background? Yes.

5. Locus Examined:

_____ thymidine kinase (TK)
Selection agent: _____ bromodeoxyuridine (BrdU)
(give concentration): _____ fluorodeoxyuridine (FdU)
_____ trifluorothymidine (TFT)

__x__ hypoxanthine-guanine-phosphoribosyl transferase (HPRT)
Selection agent: _____ 8-azaguanine (8-AG)
(give concentration): __10 μM__ 6-thioguanine (6-TG)

_____ Na^+/K^+ ATPase
Selection agent: _____ ouabain
(give concentration)

_____ other (locus and/or selection agent; give details):

6. Test Compound Concentrations Used:

Preliminary Toxicity Assay: ±S9: 0.15, 0.5 1.5, 5, 15, 51, 152, 505, 1430 μg/mL.
Mutation Assay: +S9: 25, 50, 100, 150, 175, 200 μg/mL.
-S9: 25, 50, 100, 125, 150, 175 μg/mL.

B. TEST PERFORMANCE:

1. Cell Treatment:

a. Cells exposed to test compound, negative/solvent or positive controls for: __5__ hours (± S9)

b. After washing, cells cultured for 7 - 9 days (expression period) before cell selection:

c. After expression, 2 x 10^5 cells/100 mM dish (4 dishes/group) were cultured for 7 to 9 days in selection medium to determine numbers of mutants and 100 cells/60 mM dish (3 dishes/group) were cultured for 7 to 9 days without selective agent to determine cloning efficiency.

2. Evaluation Criteria:

The minimum mutant frequency for a response to be considered positive was set at > 40 mutants per 10^6 clonable cells.

3. Criteria for a Valid Test:

The cloning efficiency of the solvent control must be > 50%. The spontaneous mutant frequencies in the solvent control must fall within 0-25 mutants per 10^6 clonable cells. The positive control must induce mutant frequencies at least 3 times that of the solvent control and must exceed 40 mutants per 10^6 clonable cells. There must be at least 4 analyzable test article concentrations with mutant frequency data.

II REPORTED RESULTS:

A. SOLUBILITY:

Sterile distilled water (SDW) was chosen by the Sponsor as the solvent for the test article. The test article was soluble in SDW at a concentration of 14.3 mg/mL, the maximum concentration prepared for this assay.

B. PRELIMINARY CYTOTOXICITY ASSAY:

Cloning efficiency (RCE) relative to the solvent controls was 1% at 1430 μg/mL for non-activated cultures and 0% at 1430 μg/mL for activated cultures. Therefore, doses chosen for the mutagenesis assay ranged from 100 to 500 μg/mL for +S9 cultures and 100 to 600 μg/mL for -S9 cultures.

C. MUTAGENICITY ASSAY:

The first two trials failed due to excessive toxicity (TRIAL 1) or contamination (TRIAL 2). The third trial (TRIAL 3) was assayed at 25 to 125 μg/mL in non-activated cultures (due to toxicity at 175 μg/mL and contamination at 150 μg/mL), and 25 to 200 μg/mL in activated cultures.

No test article precipitate was observed at any dose level. RCE was 41% and 19% at the highest dose tested in -S9 and +S9 cultures, respectively..

However, in none of the treated cultures were mutant frequencies greater than 40 mutants per 10^6 clonable cells. By contrast, both positive controls induced large increases in mutant frequencies.

Therefore, the investigators concluded that, under the conditions of this assay, iodomethane did not induce a positive response in the CHO/HGPRT system under both activated and non-activated conditions, and thus is negative for mutagenicity activity.

III. REVIEWER'S DISCUSSION/CONCLUSIONS:

A. The EPA reviewer agrees with the investigators that iodomethane, assayed up to toxic dose levels did not increase mutant frequencies in the CHO/HGPRT cell system and thus was negative for mutagenicity activity.

B. STUDY DEFICIENCIES: None.

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