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Reregistration Branch I, Health Effects Division (7509C) **Date** _____

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DATA EVALUATION RECORD

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

PC CODE: 000011 **DP BARCODE:** D294630
SUBMISSION NO.:

TEST MATERIAL (PURITY): Iodomethane (99.7% a.i.)

SYNONYMS: Methyl iodide

CITATION: Nemec, M. (2003) A Phased-exposure Prenatal Developmental Toxicity Study of Iodomethane in Rabbits. WIL Research Laboratories, Inc., Ashland, OH. Study No. WIL-418023, February 3, 2003. MRID 46077001. Unpublished

SPONSOR: Arvesta Corporation

EXECUTIVE SUMMARY:

In a developmental toxicity study (MRID 46077001) iodomethane (99.7% a.i., Batch# 02/Lot# 007403) was administered via the inhalation route (whole body) to 24 New Zealand White rabbits/group at concentrations of 0 or 20 ppm during GD 6-28 (Control and Group 2), GD 6-14 (Group 3), GD 15-22 (Group 4), GD 23-24 (Group 5), GD 25-26 (Group 6), or GD 27-28 (Group 7) for 6 hours/exposure day.[1] Does were observed twice daily for signs of toxicity and mortality as well as at the midpoint of exposure and within an hour after daily exposure ended. All surviving does were sacrificed on GD 29 and their ovaries and uteri examined.

Maternal Toxicity - No compound-related clinical signs of toxicity were noted in maternal animals. During the exposure period, overall body weight gain was decreased in all test groups relative to control during the same time frame (Group 2: ↓25%, Group 3: ↓45%, Group 4: ↓52%, Group 5: ↓197%, Group 6: ↓300%, and Group 7: ↓100%). The mean body weights on GD 29 and several other periods, however, were comparable among all groups including control. Gravid uterine weights were decreased for Groups 2, 3, and 6 (↓28%, 16%, and 12%, respectively). Similarly, food consumption in Groups 5,6, and 7 was decreased (non-statistically

[1] Abbreviations: GD = gestation day

significant) during the exposure period by 14-28% relative to control during the same time frame. Gross necropsy examination revealed a slight increase in the incidence of accessory spleens in treated animals (13-29% treated animals *vs.* 4% control) and cystic oviducts (13-29% *vs.* 8% control).

Developmental Toxicity - While some parameters (e.g. corpora lutea, implantation sites) were unaffected by treatment with the test article, Groups 2, 5, and 6 exhibited an increase in the incidence of late resorptions relative to concurrent controls (21%, 9%, and 11%, respectively *vs.* 2% control). Mean fetal weights in Groups 2 and 6 were reduced by 9% and 5%, respectively while all other groups were comparable to control. No evidence of visceral or skeletal abnormalities were evident after compound exposure.

The developmental toxicity study in the rabbit is classified **acceptable/non-guideline** and **does not** satisfy the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in rabbits. This study was not intended to fulfill the guideline requirement or establish NOAELs and LOAELs but rather was conducted to determine the critical period of exposure during gestation that resulted in fetal loss as observed in a previously evaluated guideline developmental toxicity study in rabbits.

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

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: Iodomethane

Description:	Technical, deep yellow translucent liquid
Lot/Batch #:	Lot# 007403/Batch#02
Purity:	99.7 % a.i.
Compound Stability:	Stable at room temperature
CAS #of TGAI:	Not available

2. Vehicle and/or positive control: None

3. Test animals:

Species:	Rabbits	
Strain:	New Zealand White	
Age/weight at study initiation:	Approx. 6 months at time of insemination. Body weight ranged from 2.9-4.0 kg	
Source:	Covance Research Products, Inc.	
Housing:	Housed individually in suspended stainless steel wire-bottom cages	
Diet:	PMI Nutrition International, Inc. Certified Rabbit LabDiet® 5322 *ad libitum*	
Water:	*ad libitum*	
Environmental conditions:	**Temperature:**	19 ± 3 °C
	Humidity:	50 ± 20%
	Air changes:	10/hr
	Photoperiod:	12 hrs dark/ 12 hrs light
Acclimation period:	21 days	

B. PROCEDURES AND STUDY DESIGN

1. In life dates - Start: 7/8/2002 End: 2/3/2003

2. Mating: Semen collected from 18 male rabbits of the same strain was used to artificially inseminate the females. Diluted semen (0.25 - 0.5 ml) from one male was used to inseminate one female in each group in each replicate (due to space constraints in the exposure chambers animals were divided into two replicates). Following insemination, each female received an intravenous injection of human chorionic gonadotropin. The day of insemination was designated as gestation day 0.

3. Animal Assignment: Using the WIL Toxicology Data Management System (WTDMS™) program, 24 animals were randomly assigned to each exposure group as indicated in Table 1. Rabbits were exposed to iodomethane in whole-body inhalation chambers for 6 hrs/day of exposure.

TABLE 1: Animal Assignment

Concentration Exposure Period	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7
	0 ppm GD 6-28	20 ppm GD 6-28	20 ppm GD 6-14	20 ppm GD 15-22	20 ppm GD 23-24	20 ppm GD 25-26	20 ppm GD 27-28
# Females	24	24	24	24	24	24	24

4. **Dose selection rationale:** This study was designed to determine the critical period of exposure during gestation that results in fetal loss as observed in a previously evaluated guideline developmental toxicity study in rabbits. Thus, the concentration selected was the concentration that elicited significant increases in fetal losses in the guideline Prenatal Developmental Toxicity study (MRID 45593811).

5. **Exposure conditions** - Whole-body inhalation chambers were used for delivery of the test substance. During exposure, rabbits were placed in a 1500L chamber and the chamber flow was maintained at 300-375 Lpm. After exposure, animals were transferred to their home cages.

6. **Generation of test atmosphere and chamber description** - Test substance was administered using a 1500 L whole-body inhalation chamber. Vapors of the test article were generated daily by using an ambient temperature bubbler-type vaporization system in which the carrier gas (air) was bubbled through the liquid test article. Thus the carrier gas picks up and vaporizes the test article as the fine air bubbles pass through the liquid and into the vapor phase above the liquid. Subsequently, the test article and regulated compressed were dispersed using a fitted disk and the test article vapor was then diluted by the chamber ventilation air flow to the desired concentration and carried to the exposure chamber. The airflow rate was monitored by compact rotameters. In the case of the control group, compressed air (without test article) was metered into the exposure chamber to simulate exposure conditions.

> **Test atmosphere concentration:** The test article atmosphere concentration was tested using a gas chromatograph. Every 35 minutes samples of the exposure atmosphere were collected using a computer-controlled gas-sampling valve. The actual exposure concentrations were 0 ppm for Group 1, 20 ppm for Group 2, and 21 ppm for Groups 3-7.

6. **Dosage administration:** Animals were exposed to the test article for 6 hours/day of exposure for 7 days/week (when applicable).

C. OBSERVATIONS

1. **Maternal Observations and Evaluations** - Maternal animals were checked twice daily for mortality and moribundity. Beginning on GD 0 through GD 29, animals were subjected to a "detailed" clinical examination (prior to compound exposure), halfway through the exposure

period (i.e 3 hrs after exposure initiation), and one hour after exposure. Animals were weighed on GD 0 and daily from GD 6-29. Body weight gains were calculated for various intervals including GD 0-6, 6-29, and intervals corresponding to the exposure periods in the different test groups. In addition, gravid uterine weight was obtained at the end of the study period (i.e GD 29) and net body weight gains were calculated. Food consumption was measured daily from GD 0-29 and reported as g/animal/day as well as g/kg bw/day. Does were euthanized on GD 29 by intravenous injection of sodium pentobarbital. Necropsy examination consisted of gross macroscopic examination of all internal organs, with emphasis on the uterus, uterine content (number of fetuses *in utero*, implantation sites, early and late resorptions), uterine weight, and number of corpora lutea. Uteri that showed no evidence of implantation were further evaluated by staining with 10% ammonium sulfide solution to detect early implantation losses.

2. Fetal Evaluations - The fetuses were removed from the uteri, euthanized by intrathoracic injection of sodium pentobarbital, weighed individually, and examined for gross external abnormalities (including examination of eyes, palate, and external orifices). Non-viable fetuses that had not been significantly autolized, were weighed and measured from crown to rump. In the case of late resorptions, the crown-rump length and extent of autolysis was recorded. The viable fetuses were subjected to visceral examinations that included evaluations of the development of the kidneys, heart, and blood vessels, as well as internal determination of fetal sex. In addition, the heads of all fetuses were examined by a midcoronal slice. The fetuses were then eviscerated, fixed in ethanol, placed in potassium hydroxide solution (for clearing) and stained with Alizarin red S to examine for skeletal abnormalities.

D. DATA ANALYSIS

1. Statistical analyses: A one-way ANOVA was used to determine the significance of intergroup differences for the mean maternal body weights, body weight changes, food consumption, gravid uterine weights, numbers of corpora lutea, implantation sites, viable fetuses, and fetal body weight. If ANOVA revealed statistical significance, a Dunnett's test was performed to compare treated vs. control groups. Mean litter proportions (percent/litter) of prenatal data were evaluated by a Kruskal-Wallis ANOVA test to determine intergroup differences. In the case of statistical significance, a Mann-Whitney U-test was performed to compare test *vs.* control groups. All statistical analyses were conducted using two-tailed tests for a significance of $p < 0.01$ or $p < 0.05$.

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

A. Group Mean Litter Basis:

$$\text{Post-implantation loss / litter} = \frac{\text{\# dead fetuses, resorptions (early \& late) / group}}{\text{\# gravid females / group}}$$

B. Proportional Litter Basis:

$$\text{Summation per Group (\%)} = \frac{\sum \text{Postimplantation Loss / Litter (\%)}}{\text{\# Implantation Sites / Litter}} \times 100$$

Where:

$$\text{Postimplantation Loss / Litter (\%)} = \frac{\text{\# dead fetuses, resorptions (early \& late) / Litter}}{\text{\# Implantation Sites / Litter}} \times 100$$

3. Historical control data: Historical control data were provided to allow comparison with concurrent controls. These data from Wil Laboratories consisted of 70 studies conducted from 1993-2001. Of the 70 studies, only four were conducted via the inhalation route and were used by the EPA reviewer as the "principal" source of comparison to the current study though data from the other 66 studies were also used.

II. RESULTS

A. MATERNAL TOXICITY

1. Mortality and Clinical Observations: No mortality or clinical signs of toxicity were reported during the study period. One female in Group 4 (exposure GD 15-22) aborted two fetuses on GD 27. For this female, dried red material was noted at the base of the tail and in the bottom of the cage.

2. Body Weight - Body weight gain data are summarized in Table 2. Briefly, in treated groups body weight gains appeared to be reduced during the exposure period (↓20-300%) relative to controls during the same time period. These decreases in body weight gain were particularly noticeable -and occasionally statistically significant ($p < 0.01$) - in animals exposed late in gestation (*i.e.* Groups 5,6, and 7). Though not statistically significant, does exposed during GDs 6-28, 6-14, and 25-26 exhibited a decrease (↓28%, 16%, and 12%, respectively) in gravid uterine weight relative to control while does exposed during GDs 15-22, 23-24, and 27-28 exhibited minimal changes (± 3%).

TABLE 2 Mean (±SD) Maternal Body Weight Gain (g) [a]

Interval	Concentration, Exposure Period						
	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7
	0 ppm GD 6-28	20 ppm GD 6-28	20 ppm GD 6-14	20 ppm GD 15-22	20 ppm GD 23-24	20 ppm GD 25-26	20 ppm GD 27-28
GD 0-6	356 ± 116.7	329 ± 101.6	322 ± 94.8	305 ± 103.3	269 ± 107.1	299 ± 85.5	334 ± 122.9
GD 6-29	376 ± 121.7	**281 ± 154.9**[b] (↓25%)[c]	333 ± 136.2	423 ± 145.5	413 ± 157.8	392 ± 162.7	426 ± 129.1
GD 6-15	142 ± 84.9	**114 ± 78.6** (↓20%)	**130 ± 70.2**38 (↓45%)	± 98.1**	245 ± 47.2**	265 ± 86.2**	229 ± 92.5**
GD 15-23	148 ± 61.1	**119 ± 70.2** (↓20%)	140 ± 91.6	**71 ± 73.6*** (↓52%)	111 ± 67.5	142 ± 117.9	155 ± 77.2
GD 23-25	36 ± 44.5	**41 ± 45.8**	25 ± 45.3	58 ± 57.1	**-35 ± 74.9**** (↓197%)	19 ± 38.2	21 ± 44.8
GD 25-27	24 ± 26.5	**1 ± 53.4**	9 ± 51.1	12 ± 85	33 ± 69.1	**-48 ± 58.8**** (↓300%)	20 ± 42.9
GD 27-29	27 ± 70.9	**6 ± 60.1**	29 ± 4124 ± 55.3		59 ± 35.3	14 ± 88.3	**0 ± 38.5** (↓100%)

a Data obtained from pages 51-54 in the study report.
b Bolded numbers represent weight gain during exposure interval assessed
c Numbers presented parenthetically represent % change from concurrent control during the same time period
* Statistically different ($p < 0.05$) from the control.
** Statistically different ($p < 0.01$) from the control.

3. <u>Food Consumption</u> - Food consumption of does exposed during the late stages of gestation (Groups 5, 6, and 7) was decreased by 14-28%. Food consumption was unaffected in the remainder of the test groups.

4. <u>Gross Pathology</u> - Necropsy examination revealed no changes in gross pathology between the treated and control groups with the exception of slight increases in the incidence of cystic oviducts in Groups 2, 3, 4, and 5 (13%, 25%, 21%, and 29%, respectively *vs.* 8% control) and accessory spleens in all treated groups (13-29% *vs.* 4% control),.

TABLE 3. Select Gross Pathology Findings

Observation	Concentration, Exposure Period						
	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7
	0 ppm GD 6-28	20 ppm GD 6-28	20 ppm GD 6-14	20 ppm GD 15-22	20 ppm GD 23-24	20 ppm GD 25-26	20 ppm GD 27-28
Cystic Oviduct	2/24 (8%)	3/24 (13%)	6/24 (25%)	5/24 (21%)	7/24 (29%)	1/24 (4%)	2/24 (8%)
Accessory Spleens	1/24 (4%)	3/24 (13%)	5/24 (21%)	4/24 (17%)	5/24 (21%)	7/24 (29%)	6/24 (25%)

5. Cesarean Section Data - Most of the parameters examined (*e.g.* pregnancy rate, corpora lutea, implantation sites) were comparable to the concurrent control. Iodomethane exposure during GD 6-28 elicited a statistically significant decrease (↓37%, $p < 0.05$) in live births/dam along with a concomitant increase in resorptions/doe (↑250%, $p < 0.01$). Though not statistically significant, the increases in the resorptions/doe noted in Groups 5 and 6 (exposures during GD 23-24 and 25-26, respectively) were considered biologically relevant.

TABLE 3 Cesarean Section Observations [a]

Observation	Concentration (ppm), Exposure Period						
	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7
	0 ppm GD 6-28	20 ppm GD 6-28	20 ppm GD 6-14	20 ppm GD 15-22	20 ppm GD 23-24	20 ppm GD 25-26	20 ppm GD 27-28
# Animals Assigned (Mated)	24	24	24	24	24	24	24
# Animals Pregnant	19	21	23	21	17	23	21
Pregnancy Rate (%)	79	88	96	88	71	96	88
# Nonpregnant	5	3	1	3	7	1	3
Maternal Wastage							
# Died	0	0	0	0	0	0	0
# Died Pregnant	0	0	0	0	0	0	0
# Died Nonpregnant	0	0	0	0	0	0	0
# Aborted	0	0	0	1	0	0	0
# Premature Delivery	0	0	0	0	0	0	0
Total # Corpora Lutea	204	194	204	187	178	215	192
Corpora Lutea/Dam	10.7 ± 2.49	9.2 ± 3.51	8.9 ± 2.44	9.4 ± 2.3	10.5 ± 3.0	9.3 ± 3.34	9.1 ± 2.99
Total # Implantations	135	119	132	140	127	150	140
(Implantations/Dam)	7.1 ± 3.04	5.7 ± 3.03	5.7 ± 2.79	7.0 ± 1.58	7.5 ± 3.36	6.5 ± 2.81	6.7 ± 2.17
Total # Litters	19	21	23	20	17	23	21
Total # Live Fetuses	127	89	119	131	108	127	131
(Live Fetuses/Dam)	6.7 ± 3.22	4.2 ± 2.66* (↓37%)	5.2 ± 2.61	6.6 ± 1.57	6.4 ± 2.89	5.5 ± 2.92	6.2 ± 2.61
Total # Dead Fetuses[b]	0	0	0	2	0	0	0
(Dead Fetuses/Dam)[b]	0	0	0	0.1	0	0	0
Total # Resorptions	8	30	13	9	19	23	9
Early	6	5	11	9	8	7	9
Late	2	25	2	0	11	16	0
Resorptions/Dam	0.4 ± 0.61	1.4 ± 1.75** (↑250%)	0.6 ± 1.47	0.5 ± 0.69	1.1 ± 1.8 (↑175%)	1.0 ± 1.57 (↑150%)	0.4 ± 0.93
% Early Resorptions[c]	4	4	8	6	6	5	6
% Late Resorptions[d]	2	23	2	0	9	11	0
Litters with Total Resorptions	0	0	0	0	0	0	0

Mean Fetal Weight (g)	45.5 ± 6.22	41.4 ± 8.19	48.3 ± 5.51	46.2 ± 4.41	45.9 ± 8.42	43 ± 7.37	47 ± 4.17
Males	46.2 ± 6.61	41.9 ± 8.04	48.2 ± 4.87	46.9 ± 4.62	46.8 ± 7.85	44.3 ± 8.31	46.7 ± 4.46
Females	45.2 ± 5.91	40.8 ± 8.17	46.6 ± 5.57	45.3 ± 4.94	44.3 ± 9.68	41.1 ± 5.80	47.3 ± 4.45
Sex Ratio (% Male)	50	53	49	54	66	53	42
Preimplantation Loss (%)[e]	34	39	35	25	29	30	27
Postimplantation Loss (%)[f]	4	25	10	6	15	14	4

a Data obtained from pages 67-68 and 223-229 in the study report.
b Two fetuses aborted on GD 27 were considered late resorptions by study authors but considered dead fetuses by EPA reviewer.

c Calculated by reviewer as % early resorptions $= \frac{\#\text{ early resorptions / litter}}{\#\text{ implantation sites / litter}} \times 100$

d Calculated by reviewer as % Late resorptions $= \frac{\#\text{ late resorptions / litter}}{\#\text{ implantation sites / litter}} \times 100$

e Calculated by reviewer as % Preimplantation Loss $= \frac{(\#\text{corpora lutea} - \#\text{ implantation sites}) / \text{group}}{\#\text{ corpora lutea / group}} \times 100$

f Calculated by reviewer as % Postimplantation Loss $= \frac{\#\text{ resorptions (early \& late) / group}}{\#\text{ implantation sites / group}} \times 100$

* Statistically different ($p < 0.05$) from the control.
** Statistically different ($p < 0.01$) from the control.

B. DEVELOPMENTAL TOXICITY

1. External Examination - Sporadic abnormalities were seen in all groups including the concurrent control. None of the findings could be attributed to compound-exposure.

2. Visceral Examination - The only visceral abnormalities observed were retroesophageal aortic arch in one fetus from Group 7 and agenesis of a lobule in the lung in one fetus each from Groups 4 and 5. These abnormalities were considered to be spurious findings.

3. Skeletal Examination - No skeletal findings were reported.

TABLE 4a. External Examinations [a]

Observations [b]	**Concentration (ppm), Exposure Period**						
	Group 1	**Group 2**	**Group 3**	**Group 4**	**Group 5**	**Group 6**	**Group 7**
	0 ppm GD 6-28	**20 ppm GD 6-28**	**20 ppm GD 6-14**	**20 ppm GD 15-22**	**20 ppm GD 23-24**	**20 ppm GD 25-26**	**20 ppm GD 27-28**
#Fetuses(litters) examined	127 (18)	89 (19)	119 (23)	131 (20)	108 (17)	127 (21)	131 (20)
#Fetuses(litters) affected	2 (2)	0	2 (2)	1(1)	1(1)	0	0
Mandibular Macrognathia	0	0	0	1(1)[c]	0	0	0

Hydrocephaly	0	0	1(1)	0	0	0	0
Astomia	0	0	0	1(1)	0	0	0
Spina Bifida	1(1)	0	1(1)	0	0	0	0
Short Tail	0	0	0	0	1(1)	0	0
Subcutaneous Hemorrhage	1(1)	0	0	0	0	0	0

a Data obtained from page 69 in the study report.
b Some observations may be grouped together.
c Fetal (litter) incidence

TABLE 4b. Visceral Examinations [a]

Observations [b]	Concentration (ppm), Exposure Period						
	Group 1	**Group 2**	**Group 3**	**Group 4**	**Group 5**	**Group 6**	**Group 7**
	0 ppm GD 6-28	**20 ppm GD 6-28**	**20 ppm GD 6-14**	**20 ppm GD 15-22**	**20 ppm GD 23-24**	**20 ppm GD 25-26**	**20 ppm GD 27-28**
#Fetuses(litters) examined	127 (18)	89 (19)	119 (23)	131 (20)	108 (17)	127 (21)	131 (20)
#Fetuses(litters) affected	0	0	0	1(1)	1(1)	0	1(1)
Retroesophageal Aortic Arch	0	0	0	0	0	0	1(1)[c]
Lung - Lobular Agenesis	0	0	0	1(1)	(1)	0	0

a Data obtained from page 69in the study report.
b Some observations may be grouped together.
c Fetal (litter) incidence

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS:

Since the purpose of this study was to establish the critical period of exposure during gestation that would elicit the fetal losses/late resorptions seen in a guideline Prenatal Developmental Toxicity Study in Rabbits, the authors did not identify a NOAEL for this study. The investigators identified GD 6-28, 23-24, and 25-26 as the gestational periods where increases in fetal losses were noted.

B. REVIEWER COMMENTS: The EPA reviewer concurs with the study authors in their assessment of the most vulnerable gestation period for the developmental endpoint of concern (*i.e.* fetal loss). The

increases in fetal loss/resorptions noted during GD23-24 and 25-26 though not statistically significant are considered to be compound-related. The timing of this finding is noteworthy considering that ontogeny of fetal thyroid function in rabbits occurs on GD 22 and iodine (critical to the chemistry of iodomethane) is essential to proper thyroid function. Given that both iodine deficiency and excess can have profound effects on thyroid function and thyroid hormone biosynthesis, there is a concern that iodomethane may cause perturbations of the fetal thyroid.[2] Taking into consideration that - unlike adults - fetuses and neonates cannot recover from the Wolff-Chaikoff effect (suppression of thyroid hormone caused by excess iodine), and that this effect has been linked to stillbirths, abortions, and other adverse pregnancy outcomes in a variety of species including horses, rats, rabbits, and humans, it is possible that the fetus may be specially susceptible to the potential thyroid toxicity of iodomethane.[3]

1. Maternal toxicity: Maternal toxicity was evident in the treated groups as decreases in body weight gain, gravid uterine weights, and food consumption. A slight increase in the incidence of cystic oviducts and accessory spleens was also noted. No other indications of maternal adverse effects after iodomethane exposure were observed.

2. Developmental toxicity:

a. Deaths/Resorptions: A statistically significant increase in late resorptions/fetal loss was noted after exposure to iodomethane during GD 6-28 (21% *vs.* 1% control). Though not statistically significant the increases in late resorptions/fetal loss noted during GDs 23-24 and 25-26 (9 and 11%, respectively) were also considered to be compound related and indicative of a particularly vulnerable time frame for iodomethane exposure during gestation.

b. Altered Growth: Growth was not affected by exposure to the test article.

c. Developmental Variations: Not affected by exposure to the test article.

d. Malformations: Not affected by exposure to the test article.

C. STUDY DEFICIENCIES No deficiencies were identified in this study given its objectives.

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[2] Salakhova, N.S. *et al.* "The functional state of the thyroid gland of the mother and fetus in the prenatal development of rabbits." *Sov. J. Dev. Biol.*(1975) **5**(4): 368-371

[3] Markou, K. *et al.* "Iodine-induced hypothyroidism." *Thyroid* (2001) **11**(5):501-510
Woeber, K.A. *et al.* "Iodine and Thyroid Disease." *Med. Clin. North Am.* (1991) **75**(1):169-178
Wemeau, J.L. "Hypothyroidism related to excess iodine." *Presse Med.* (2002) **31**(35):1670-1675
Drew, B *et al.* "The effect of excess dietary iodine on pregnant mares and foals." *Vet. Rec.* (1975) **97**(5):93-95
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Vorhees, C.V. *et al.* "Developmental toxicity and psychotoxicity of potassium iodide in rats: a case for the inclusion of behavior in toxicological assessment" *Food Chem. Toxicol.* (1984) **22**(12): 963-970
Poppe, K. and B. Velkeniers "Thyroid and infertility" *Verh K Acad Geneeskd Belg.* (2002) **64**(6):389-399

DATA FOR ENTRY INTO ISIS

Developmental Study - rabbits (870.3700b)

PC code	MRID	Study	Species	Duration	Route	Admin	Dose range ppm	Doses ppm	NOAEL ppm	LOAEL ppm	Target organ	Comments
000011	46077001	developmental	rabbits	various durations	inhalation	whole-body exposure	0-20	0, 20	Not identified	20	body weight gain decrease, food consumption decrease, gravid uterine weight decrease	Maternal
000011	46077001	developmental	rabbits	various durations	inhalation	whole-body exposure	0-20	0, 20	Not identified	20	Fetal loss	Developmental