Methyl Iodide (Iodomethane)

RISK CHARACTERIZATION DOCUMENT FOR INHALATION EXPOSURE

Volume I

Health Risk Assessment

CH_3I

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March 2009 Draft

A March 2009 draft (**Volumes I** to **III**) of the risk characterization document (RCD) was reviewed by the Office of Environmental Health Hazard Assessment of the California Environmental Protection Agency (OEHHA) and the U.S. Environmental Protection Agency (USEPA) as part of the Department of Pesticide Regulation (DPR) external review process. The registrant, Arysta LifeScience Corporation (Arysta) requested and was provided a copy.

August 2009 Draft

The August 2009 draft is a revision of the March 2009 draft of the RCD.

Volume IV contains DPR scientists' responses to comments from OEHHA, USEPA, and Arysta on the March 2009 Draft. It is divided: Part 1- OEHHA Comments, Part 2- USEPA Comments, and Part 3- Arysta Comments. The responses for the subjects are arranged in this order: toxicity and PBPK model (Medical Toxicology Branch), exposure (Worker Health and Safety Branch), and air modeling and environment fate (Environmental Monitoring Branch).

This draft was reviewed by the DPR Scientific Review Committee (SRC, also referred to as the External Peer Review Panel) convened to evaluate the DPR's risk assessment on methyl iodide. The Committee consists of: Dr. John R. Froines (Chair, University of California, Los Angeles), Dr. Paul Blanc (University of California, San Francisco), Dr. Katherine Hammond (University of California, Berkeley), Dr. Dale Hattis (Clark University), Dr. Edward Loechler (Boston University), Dr. Thomas McKone (University of California, Berkeley), Dr. Ronald Melnick (Former NTP/NIEHS Project Officer), and Dr. Theodore Slotkin (Duke University). DPR scientists presented the risk assessment to the SRC on September 24-25, 2009. The draft was also posted for public comment with comment period ended on Oct. 12, 2009.

December 2009 Draft

A December 2009 draft (**Volumes I** to **III**) was completed with revisions in response to the SRC comments (received November 18, 2009) on the August 2009 Draft. This draft was reviewed by the SRC who provided written comments (received January 21, 2010). DPR scientists met with the SRC on January 25, 2010 to discuss the comments and responses.

January 2010 Final Document

This final document (**Volumes I** to **III**) considered SRC written comments, an Errata, as well as comments from the January 2010 meeting. **Volume IV** contains responses to the SRC comments (Part 1) and public comments on the August 2009 Draft (Part 2).

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LIST OF ABBREVIATIONS
(for Volume I and Appendices to Volume I)

AAC	9-Aminoacridine
AAN	2-Aminoanthracene
ACGIH	American Conference of Governmental Industrial Hygienists
ADAF	Age-dependent adjustment factor
AIHA	American Industrial Hygiene Association
ALT	Alanine aminotransferase
ARB	Air Resources Board, California Environmental Protection Agency
Arysta	Arysta LifeScience North America Corporation
AST	Aspartate aminotransferase
ATSDR	Agency for Toxic Substances and Disease Registry
AUC	Area under the curve
B(a)P	Benzo(a)pyrene
BHT	Butylated hydroxytoluene
BMD	Benchmark dose
BMR	Benchmark dose response
BR	Breathing rate
BSO	L-Buthionine sulphoximine
BUN	Blood urea nitrogen
BW 755C	3-Amino-1-[m-(trifluoromethyl)phenyl]-2-pyrazoline
BWt	Body weight
CDC	Center for Disease Control and Prevention
CFR	Code of Federal Regulation
CHO	Chinese hamster ovary
CLTRANS1C	Placenta to fetus iodide transfer
CLTRANS2C	Fetus to placenta iodide transfer
CP	Cyclophosphamide
D1, 2, or 3	Deiodinase 1, 2, or 3
DF	Desferrioxamine mesylate
DPPD	N, N'-Diphenyl-p-phenylenediamine
DPR	Department of Pesticide Regulation, California Environmental Protection Agency
ED	Effective dose at a specified response level
EFH	Exposure Factors Handbook
EMS	Ethyl methanesulfonate
ERPG	Emergency Response Planning Guideline
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
F/M	Fetal-to-maternal
FOB	Functional observational battery
GABA	Gamma-aminobutyric acid
GD	Gestational day
GGT	Gamma glutamyltransferase
GI	Gastrointestinal
GSH	Glutathione
GST	Glutathione S-transferase

GW	Gestation week
HDL	High density lipoprotein
HEC	Human Equivalent Concentration
HGPRT	Hypoxanthine guanine phosphoribosyl transferase
IARC	International Agency for Research on Cancer
IDLH	Immediately Dangerous to Life or Health
IOM/NAS	Institute of Medicine, National Academy of Sciences
IPCS	International Programme on Chemical Safety
IP-GSH	Isopropyl ester of GSH
KI	Potassium iodide
LC50	Lethal concentration at 50% death
LD	Lactational day
LD50	Lethal dose at 50% death
LDL	Low density lipoprotein
LED	Lower bound of ED (e.g., LED_{05}: lower 95^{th} confidence bound of ED_{05})
LOEL	Lowest-observed-effect Level
LOQ	Limit of quantitation
ME	Microencapsulated
MeI	Methyl iodide (iodomethane)
MMC	Mitomycin
MMS	Methyl methanesulfonate
MNU	N-methyl-N-nitrosourea
MOE	Margin of exposure
MCL	Maximum Contamination Level
MF	Modifying factor
MOA	Mode of action
MRL	Minimal Risk Level
MTD	Maximal Tolerated Dose
NaI	Sodium iodide
NAZ	Sodium azide
NDGA	Nordihydroguaiaretic acid
NF	2-Nitrofluorene
NIOSH	National Institute of Occupational Safety and Health
NIS	Sodium/iodide symporter
NOAEL	No-observed-adverse-effect Level
NOEL	No-observed-effect Level
NTP	National Toxicology Program
ODP	Ozone depletion potential
OED	Olfactory epithelial degeneration
OSHA	Occupational Safety and Health Administration
PBPK	Physiologically Based Pharmacokinetic
PD	Pharmacodynamic
PD_{animal}	Pharmacodynamic difference between animals and humans
PD_{human}	Pharmacodynamic variation within human population
PEL	Permissible Exposure Level
PK	Pharmacokinetic

PK_{animal}	Pharmacokinetic difference between animals and humans
PK_{human}	Pharmacokinetic variation within human population
POD	Point of departure
QAC	Alveolar ventilation rate
RDA	Recommended Dietary Allowance
RDI	Recommended Daily Intake
REL	Recommended Exposure Limit
REM	Respiratory epithelial metaplasia
RfC	Reference Concentration
RfD	Reference Dose
RGDR	Regional gas dose ratio
rT3	Reverse T3
SB950	Senate Bill 950 (The Birth Defect Prevention Act), California
SDH	Sorbital dehydrogenase
SRC	Scientific Review Committee, an external panel of scientists charged with the review of DPR's draft risk assessments on methyl iodide
STEL	Short Term Exposure Limit
T3	Triiodothyronine
T4	Thyroxine
TAI	Tolerable additional iodide
TBG	Thyroxine-binding globulin
TIAF	Total interspecies adjustment factor
TLV	Threshold Limit Value
TSH	Thyroid stimulating hormone
TVol	Tidal volume
TWA	Time-weighted average
UDPGT	UDP-glucuronlytransferase
$UF_{additional}$	Additional uncertainty factor
UL	Tolerable Upper Intake Level
USEPA	U.S. Environmental Protection Agency
VFETC	Fetus weight as a fraction of maternal weight
VLDL	Very low density lipoprotein
WHO	World Health Organization
WOE	Width of the olfactory epithelium
WOX	Width of the olfactory exchange membrane with lamina propria

I. SUMMARY

Introduction (Section **II**.)

The Department of Pesticide Regulation (DPR) conducted a human health risk assessment on the proposed use of methyl iodide (MeI, iodomethane) as a new preplant fumigant in California. This volume (**Volume I**) presents the complete MeI inhalation exposure risk assessment, including the toxicity data for MeI and iodide. The appendices to this Volume include a review of the Physiologically Based Pharmacokinetic (PBPK) modeling of the data for use to establish the Human Equivalent Concentrations (HEC) for acute exposure (**Appendix A**), an explanation of the calculations (**Appendix B**), and a comparison of this risk assessment with the U.S. Environmental Protection Agency risk assessment for MeI (**Appendix C**). **Volume II** describes the data and methods used to estimate MeI exposures by workers, bystanders, and residents. **Volume III** discusses the environmental fate of MeI in the water, soil, and atmosphere. **Volume IV** contains comments and DPR scientists' responses to comments from the Scientific Review Committee (SRC), as well as written public comments.

Toxicology Profile and Hazard Identification (Section **III.** and **IV.A.**)

In the risk assessment process, one of the initial steps is hazard identification. The pharmacokinetic and toxicology studies are reviewed to establish the toxicity of the chemical of concern. For each toxicity study with sufficient data on the dose-response relationship, the highest dose which does not cause any toxicological effect, known as No-observed-effect Level (NOEL), or No-observed-adverse-effect Level (NOAEL), is established for relevant endpoints in the study. After the review, the toxicity studies are categorized into exposure durations such as: acute, subchronic, chronic, and lifetime, to match those determined in the human exposure assessment. The NOELs and effects, within each exposure duration, are then compared (in terms of mg/kg/day) to identify the most appropriate NOEL (critical NOEL) to address the toxicity endpoint of concern (critical endpoint) for that particular exposure duration. When the data can be modeled by benchmark dose software, the point of departure (POD) is based on benchmark levels based on a fixed response or multiplier of the standard deviation, instead of the critical NOELs. The PODs are converted to HECs, which account for factors such as intake, exposure duration, and pharmacokinetic (PK) differences between laboratory animals and humans using default methodology or PBPK modeling. With PBPK modeling, the HEC is linked to a dose metric for markers of exposure or toxicity, rather than to the external exposure concentration such as the NOEL.

The MeI pharmacokinetic and toxicology database is presented in the Toxicology Profile (Section **III.**). It consists of both laboratory animal studies and human case reports. In laboratory animals, the toxicity endpoints of concerns for inhalation exposure are fetal death, olfactory epithelial degeneration, neurotoxicity, reproductive toxicity (delayed development), salivary gland metaplasia, thyroid perturbation (including tumors), and other systemic effects. MeI also has mutagenic activities in laboratory studies. Humans exposed to high concentrations show neurotoxicity with delayed onset of psychiatric symptoms in some cases.

For MeI hazard identification (Section **IV.A.**), critical NOELs are derived from laboratory animal studies because human case reports do not provide sufficient dose-response information. In using laboratory animal data, the assumption is that effects observed in laboratory animals

may also be observed in humans. In the August 2009 draft of this document, the acute HECs for occupational (8 work hours and 16 non-working hours of exposure) and the general population (24-hours of exposure) exposures were determined by PBPK modeling. Due to different views between DPR scientists and the SRC regarding model application (discussion in Section **IV.A.1.a.**), all HECs in this document are calculated using DPR default methodology, and are determined for workers (8-work hours of exposure), and non-workers (24-hours of exposure; classified as adults, children, and infants) using default age-specific breathing rate adjustment and pharmacokinetic uncertainty factor. Potency factor estimated from linearized multistage model is also determined to address lifetime exposure. The HECs and potency factor used to estimate the risk of exposure are presented in Summary Table 1.

For acute exposure toxicity, relevant studies are selected from studies described in the Acute Toxicity, Subchronic Toxicity, and Developmental Toxicity sections. The critical endpoints are: fetal death in rabbits, olfactory epithelial degeneration in rats, and neurotoxicity in rats. The NOEL is 2 ppm and the benchmark LED_{01} is 0.5 ppm for the fetal death endpoint from a rabbit developmental toxicity study. Since it is the result of maternal exposure, it is applicable only for the risk assessment of women of child-bearing age exposed to MeI in the workplace or in the general population. Four possible MOAs are explored: thyroid perturbation from excess iodide, glutathione (GSH) depletion, direct alkylation, and altered cholesterol homeostasis. The conclusion is that the data do not support a single predominant MOA for fetal death.

The nasal effect and neurotoxicity endpoints with NOELs of 21 ppm and 27 ppm, respectively, are appropriate for the MeI risk assessment of all other age groups. Olfactory epithelial degeneration as a local effect was observed in rats from a 13-week study with GSH depletion as a marker for plausible MOA. Since the data cannot be adequately described by current benchmark dose models due to the large difference in response between the NOEL and the LOEL, the HECs are based on the NOEL. Neurotoxicity was indicated by decreased body temperature and motor activity in rats after a 6-hour inhalation exposure to MeI. The $LED_{0.36\sigma}$ for reduced ambulatory motor activity in female rats is 12.8 ppm.

For subchronic exposure, critical NOELs and endpoints are selected from subchronic toxicity, developmental toxicity, and reproductive toxicity studies. The critical endpoints considered are systemic effects (reduced body weight, increased cholesterol level, and neurotoxicity) and reproductive toxicity (reduced postnatal pup body weight and delayed development) in rats. The lowest benchmark dose levels are LED of 4.3 ppm for neurotoxicity, extrapolated from the acute $LED_{0.36\sigma}$ of 12.8 ppm with a modifying factor of 3-fold; and $LED_{0.36\sigma}$ of 3.0 ppm for reduced postnatal (21 day) pup body weight in rats from a reproductive toxicity study.

For chronic exposure, the critical NOEL and endpoint are selected from the chronic toxicity studies. The critical endpoint is salivary gland metaplasia in rats after a 2-year exposure to MeI, with a NOEL of 20 ppm and the LED_{05} is 3.4 ppm. In addition, the LED for potential neurotoxicity is 1.3 ppm extrapolated from the acute $LED_{0.36\sigma}$ of 12.8 ppm using a modifying factor of 10-fold.

For lifetime exposure, the endpoints are thyroid hyperplasia and tumors observed in rats and mice, astrocytomas in male rats, and cervical/uterine fibromas in female mice. The weight of the evidence analysis supports the consideration of MeI as an oncogen. With thyroid tumors in rats, two modes of action (MOA) are considered: genotoxic MOA and thyroid perturbation MOA.

Genotoxic MOA involves MeI alkylation to macromolecules. The potency factor is derived from non-threshold linear dose-extrapolation approach and is $5.0x10^{-3}$ mg/kg/day^{-1}, or human equivalent potency of 1.6×10^{-2} mg/kg/day^{-1}. Thyroid perturbation MOA involves excess iodide causing perturbation of thyroid function. The point of departure is based on the threshold approach using the benchmark dose to calculate the HEC. The lifetime HECs for thyroid tumors in rats are 1.2 ppm (workers) and 0.39 ppm (adult residents) for the LED_{01} of 2 ppm. Humans are assumed to be more sensitive to the oncogenicity of MeI than laboratory animals on a dose per body weight basis.

Summary Table 1. Critical endpoints, HECs and potency factor for MeI risk characterization.[a]

Duration	Toxicity endpoints	Point of Departure or Potency	HEC or Unit Risk	
			Worker/ Worker bystander (8 hours)	**Bystander/ Resident (24 hours)**
Acute	Fetal death in rabbits (*Nemec, 2002d)	0.5 ppm (LED_{01})	0.23 ppm	0.081 ppm (women of child-bearing age)
	Olfactory epithelial degeneration in rats (*Kirkpatrick, 2002b)	21 ppm (NOEL)	17.1 ppm	5.7 ppm (adult) 3.5 ppm (child) 2.7 ppm (infant)
	Neurotoxicity in rats (*Schaefer, 2002)	12.8 ppm ($LED_{0.36\sigma}$)	10.4 ppm	3.5 ppm (adult) 2.2 ppm (child) 1.9 ppm (infant)
Sub-chronic	Decreased body weight in day 21 rat pups (*Nemec, 2002a)	3.0 ppm ($LED_{0.36\sigma}$)	NA	0.51 ppm (child) 0.39 ppm (infant)
	Neurotoxicity in rats (*Schaefer, 2002)	4.3 ppm (estimated LED from 12.8 ppm and MF of 3)	3.5 ppm	1.2 ppm (adult) 0.7 ppm (child) 0.5 ppm (infant)
Chronic	Salivary gland metaplasia in rats (*Kirkpatrick, 2005)	3.4 ppm (LED_{05})	2.0 ppm	0.66 ppm (adult) 0.41 ppm (child) 0.31 ppm (infant)
	Neurotoxicity in rats (*Schaefer, 2002)	1.3 ppm (estimated LED from 12.8 ppm and MF of 10)	1.0 ppm	0.35 ppm (adult) 0.22 ppm (child) 0.16 ppm (infant)
Lifetime	Thyroid tumors in rats (*Kirkpatrick, 2005)	Non-threshold: Potency 5.0×10^{-3} mg/kg/day^{-1} (rat) 1.6×10^{-2} mg/kg/day^{-1} (human)	Unit risk: $6x10^{-6}$ per ppb	Unit risk: $2.5x10^{-5}$ per ppb
		Threshold: 2 ppm (LED_{01})	1.2 ppm	0.39 ppm (adult)

a/ Same as Table 59. MF=modifying factor. Under the "HEC or Unit Risk" column, all values are HECs except for unit risks from the non-threshold approach.

Exposure Assessment (Section **IV.B.**)

In conjunction with the hazard identification, potential human exposures are quantified in the exposure assessment (details in **Volume II**). The exposure levels and scenarios are established by the product labels, available studies on exposure, and information about the environmental fate of the chemical.

For MeI use in preplant fumigation, the exposure groups identified are: workers (involved in the fumigation), worker bystanders (working at fields adjacent to fumigated field), non-worker bystanders (present at the buffer zone), and residents (living adjacent to the application site). Air concentrations are based on MeI-specific studies using shallow shank injection or drip irrigation application methods. For workers directly involved in fumigation, the acute exposure is the upper-bound (95^{th} percentile) of measured air concentrations for an 8-hour work day. The arithmetic mean of the 8-hour time-weighted-average (TWA) air concentrations for each task represents the seasonal (subchronic) exposure of 3 months. The annual (chronic) exposure is the amortized seasonal exposure with a factor 3-month season/12 months. The lifetime exposure is the annual exposure amortized by a factor of 40 work year over a 75 year lifespan. The exposures of applicators, shovelmen, and tarp monitors include a 90% protection factor for the use of air-purifying respirators. Workers involved in shallow shank injections have higher exposures than those for drip irrigation application (Summary Table 2). Of all tasks, tarp monitors have the highest exposure.

For the bystanders and residents, the air concentrations are those at the 152-meter buffer zone after the MeI application, derived from modeling of MeI air monitoring data and the U.S. Environmental Protection Agency (USEPA) approved labels. For acute exposures (8 or 24 hours), an individual is assumed to be located downwind throughout the exposure interval at the maximum TWA air concentration for those durations. The 24-hour exposure duration for non-worker bystanders and residents living next to the field assumes that the indoor and outdoor air concentrations of MeI are the same. The seasonal exposure is 0.07 μg/L based on the 2-week average concentration with an adjustment for changing wind directions. For all bystanders, the highest exposure is from drip irrigation application (Summary Table 3). No chronic or lifetime exposure for bystanders is expected. The exposures for residents living next to the application site are based on those measured for drip irrigation, in the absence of actual monitoring data (Summary Table 3). The lifetime exposure is assumed to be the same as the annual exposure.

Summary Table 2. Acute and repeated exposures for workers engaged in pre-plant field fumigation with MeI.[a]

Application Methods/ Workers	Air concentration (ppm)			
	Acute	Seasonal	Chronic[b]	Lifetime
Shallow Shank Injection-tarped (broadcast and bedded)				
Applicator	0.27	0.06	0.015	0.008
Shovelman and shoveler	0.08	0.02	0.005	0.003
Tarp monitor	0.30	0.04	0.01	0.005
Tarp hole puncher, cutter	0.08	0.03	0.0075	0.004
Planter	0.006	0.004	0.001	0.001
Drip Irrigation- tarped (bedded)				
Applicator	0.003	0.001	0.0003	0.0002
Hole puncher	0.015	0.01	0.0025	0.001
Planter	0.004	0.001	0.0003	0.0002

a/ See Table 60 of this volume for details.

Summary Table 3. Acute and repeated exposures to MeI for bystanders and residents.[a]

Groups/ Application Methods	Air concentration (ppm)			
	Acute	Seasonal	Chronic	Lifetime
Worker bystanders				
Drip irrigation, raised bed	1.6	0.012	NA	NA
Shank injection, raised bed	0.6	0.012	NA	NA
Shank injection, flat-fume	1.0	0.012	NA	NA
Non-worker bystander adults				
Drip irrigation, raised bed	0.3	0.012	NA	NA
Shank injection, raised bed	0.2	0.012	NA	NA
Shank injection, flat-fume	0.2	0.012	NA	NA
Bystander children (3-5 years old)				
Drip irrigation, raised bed	0.3	0.012	NA	NA
Shank injection, raised bed	0.2	0.012	NA	NA
Shank injection, flat-fume	0.2	0.012	NA	NA
Bystander infants (<1 year old)				
Drip irrigation, raised bed	0.3	0.012	NA	NA
Shank injection, raised bed	0.2	0.012	NA	NA
Shank injection, flat-fume	0.2	0.012	NA	NA
Residents living next to application sites				
Adults	0.3	0.012	0.003	0.003
Children	0.3	0.012	0.003	NA
Infants	0.3	0.012	0.003	NA

a/ See Table 61 of this volume for details. NA=non-applicable.

Risk Characterization (Section **IV.C.)**

The risk is quantitatively expressed as a margin of exposure (MOE) with MOE = HEC÷ estimated human exposure, or probability for cancer risk from the product of potency factor and exposure. Potential age-depended sensitivity to oncogenic risk for the general population is also calculated. These risks for workers, bystanders, and residents are presented in Summary Table 4 and 5. The acute MOEs are the lowest of all MOEs.

Summary Table 4. Margins of exposure and lifetime risks for workers engaged in pre-plant field fumigation with MeI.[a]

Application Methods/ Workers	Acute MOE			Seasonal MOE	Chronic MOE		Lifetime	
	Fetal Death	Nasal Toxicity	Neuro-toxicity	Neuro-toxicity	Salivary metaplasia	Neuro-toxicity	MOE	Risk
Shallow Shank Injection-tarped (broadcast and bedded)								
Applicator	1	63	39	58	133	67	150	$5x10^{-5}$
Shovelman, shoveler	3	214	130	175	400	200	450	$2x10^{-5}$
Tarp monitor	1	57	35	88	200	100	225	$3x10^{-5}$
Tarp hole puncher, cutter	3	214	130	117	267	133	300	$2x10^{-5}$
Planter	38	2,850	1,733	875	2,000	1,000	2,250	$3x10^{-6}$
Drip Irrigation-tarped (bedded)								
Applicator	77	5,700	3,467	3,500	6,667	3,333	7,500	$1x10^{-6}$
Hole puncher	15	1,140	693	350	800	400	900	$8x10^{-6}$
Planter	58	4,275	2,600	3,500	6,667	3,333	7,500	$1x10^{-6}$

a/ See Table 62 of this volume for details.

Summary Table 5. Margins of exposure and lifetime risks for bystanders and residents exposed to MeI.[a]

Groups/ Application Methods	Acute MOE			Seasonal MOE		Chronic MOE		Lifetime	
	Fetal Death	Nasal Toxicity	Neuro-toxicity	Neuro-toxicity	Repro-toxicity	Salivary gland meta-plasia	Neuro-toxicity	MOE	Risk
Worker bystanders									
Drip, raised bed	0.1	11	7	292	NB	NA	NA	NA	NA
Shank, raised bed	0.4	29	17	292	NB	NA	NA	NA	NA
Shank, flat-fume	0.2	17	10	292	NB	NA	NA	NA	NA
Non-worker bystander adults									
Drip, raised bed	0.3	19	12	100	NB	NA	NA	NA	NA
Shank, raised bed	0.4	29	18	100	NB	NA	NA	NA	NA
Shank, flat-fume	0.4	29	18	100	NB	NA	NA	NA	NA
Bystander children (3-5 years old)									
Drip, raised bed	NB	12	7	58	43	NA	NA	NA	NA
Shank, raised bed	NB	18	11	58	43	NA	NA	NA	NA
Shank, flat-fume	NB	18	11	58	43	NA	NA	NA	NA
Bystander infants (<1 year old)									
Drip, raised bed	NB	9	6	42	33	NA	NA	NA	NA
Shank, raised bed	NB	14	10	42	33	NA	NA	NA	NA
Shank, flat-fume	NB	14	10	42	33	NA	NA	NA	NA
Residents living next to application sites									
Adults	0.3	19	12	100	NA	220	117	130	$8x10^{-5}$
Children (3-5 years old)	NB	12	7	58	43	137	73	NB	$1.4x10^{-4}$ (age-adjusted)
Infants (<1 year old)	NB	9	6	42	33	103	53	NB	

a/ See Table 63 of this volume for details.

Risk Appraisal (Section **V.**)

The uncertainties associated with the risk estimates in a risk assessment are due to limitations in the toxicology and human exposure data. Health protective assumptions and appropriate surrogate data are used to address deficiencies in the database. The appraisal of the calculated risk considers the data and approaches used in the risk assessment process, and makes recommendations regarding the risks associated with the exposure to the chemical. Calculated MOEs are compared with a benchmark MOE; exposures with MOEs at or higher than the benchmark MOE are considered to be health protective. When toxicity is represented by a HEC, which includes interspecies pharmacokinetic considerations, the conventional benchmark MOE is 30 (a 3-fold factor for interspecies pharmacodynamic differences, and a 10-fold factor for interindividual differences in humans). Additional uncertainty or modifying factor is considered when existing data are not sufficient to address toxicity or exposure issues. For oncogenic risk based on a non-threshold approach, the DPR default benchmarks are probability of risk of less than $1x10^{-5}$ and $1x10^{-6}$ for worker and general population, respectively. The HECs and appropriate uncertainty factors are used to calculate the reference concentrations. The resulting reference concentrations for MeI are presented in Summary Table 6.

For fetal death after MeI exposure, the benchmark MOE of 30 is increased because of issues related to MeI and iodide toxicity. While the toxicology database for MeI is complete with respect to registration requirements, the database indicates a need for a more thorough investigation of developmental neurotoxicity from pre- and post-natal exposure to MeI. These concerns include the potential serious and irreversible nature of neurodevelopmental effects from maternal exposure that may be manifested beyond the observed fetal death at the end of gestation, and the potential toxicity from post-natal exposure to MeI or the resultant excess iodide added to the background iodide intake (Section **V.C.**). This risk assessment recommends the application of the additional uncertainty factor of 10-fold to the conventional benchmark MOE resulting in a MOE of 300, and to the reference concentration (RfC) calculation for the fetal death endpoint. A MOE of 300 is also recommended for neurotoxicity due to database deficiency and for thyroid tumors when the risk is determined by the threshold approach.

Since the lowest MOEs were for acute exposure with fetal death as the endpoint, these determine the magnitude of exposure reduction in order to meet the risk benchmarks for acceptable exposure. Compared to the benchmark MOE of 300, the fetal death MOEs for most of the exposure scenarios are below this value for acute exposures of workers, bystanders, and residents (Summary Table 4 and 5)**.** For the adults as workers, bystander workers, other bystanders, and adult residents, the MOEs are 0.1 to 77. Significant exposure reduction, as much as 3000-fold for worker bystanders involved in drip irrigation, is needed to meet the benchmark. With respect to cancer concern, the lifetime exposure also needs to be reduced based on the higher risk determined by the non-threshold approach for thyroid tumor due to a genotoxic MOA. The risk levels for some workers ($2x10^{-5}$ to $5x10^{-5}$) associated with shallow shank injection method are higher than the $1x10^{-5}$ acceptable risk and would need to be reduced 2 to 5-folds. For residents, the oncogenic risk is $8x10^{-5}$ using only adult exposure level, but is 1.8-fold higher at $1.4x10^{-4}$ when potential increased sensitivity with childhood exposure is included. A 140-fold reduction is needed for the lifetime exposure of residents.

The risks associated with additional iodide added to the body burden from iodide in the water and from direct MeI inhalation are considered. There is a potential for iodide contamination of

the ground water where the soil is known to be vulnerable to ground water contamination and the ground water is shallow. An upper-bound estimate of 18 ppm iodide in the ground water results in iodide exposures in the drinking water far exceeded established iodide intake standards.

For non-cancer effects from MeI exposure, the recommended RfCs are based on the fetal death endpoint and an additional uncertainty factor of 10-fold for pre- and post-natal neuro-developmental concerns. They are 0.8 ppb and 0.3 ppb for women of child-bearing age in the workplace and in the general population, respectively. When applied for all durations, they are also protective of young children against excess iodide, which should not exceed 1 ppb based on available iodide intake standards. For potential cancer effects from lifetime exposure, the MeI RfCs is based on the genotoxic MOA, which are lower than those from the thyroid perturbation MOA. They are 1.7 ppb and 0.04 ppb for worker and general population, respectively.

Summary Table 6. Reference concentrations for MeI inhalation exposure.[a]

Duration	Toxicity endpoints	HECs	RfC[c]	
			UF=30	UF=300
Acute	Fetal death in rabbits[1]	Worker (8 hr)=0.23 ppm GP_W (24 hr)=0.081 ppm		0.8 ppb 0.3 ppb
	Olfactory epithelial degeneration in rats[2]	Worker (8 hr)= 17.1 ppm Adult (24 hr)= 5.7 ppm Child (24 hr)= 3.5 ppm Infant (24 hr)= 2.7 ppm	570 ppb 190 ppb 118 ppb 90 ppb	
	Neurotoxicity in rats[3]	Worker (8 hr)= 10.4 ppm Adult (24 hr)= 3.5 ppm Child (24 hr)= 2.2 ppm Infant (24 hr)= 1.9 ppm		35 ppb 12 ppb 7 ppb 6 ppb
Sub-chronic	Decreased day 21 body weight in rat pups[4]	Child (24 hr)= 0.51 ppm Infant (24 hr)= 0.39 ppm	17 ppb 13 ppb	
	Neurotoxicity in rats (extrapolated)	Worker (8 hr)= 3.5 ppm Adult (24 hr)= 1.2 ppm Child (24 hr)= 0.7 ppm Infant (24 hr)= 0.5 ppm		12 ppb 4 ppb 2 ppb 2 ppb
Chronic	Salivary gland metaplasia in rats[5]	Worker (8 hr)= 2.0 ppm Adult (24 hr)= 0.66 ppm Child (24 hr)= 0.41 ppm Infant (24 hr)= 0.31 ppm	66 ppb 22 ppb 14 ppb 10 ppb	
	Neurotoxicity in rats (extrapolated)	Worker (8 hr)= 1.0 ppm Adult (24 hr)= 0.35 ppm Child (24 hr)= 0.22 ppm Infant (24 hr)= 0.16 ppm		4 ppb 1 ppb 0.7 ppb 0.5 ppb
Lifetime	Thyroid tumors in rats[5]	Non-threshold: Worker (8 hr)= unit risk $6x10^{-6}$/ppb GP= unit risk $2.5x10^{-5}$/ppb		Risk benchmarks[b]: 1.7 ppb 0.04 ppb
		Threshold: Worker (8 hr)= 1.2 ppm GP_A= 0.39 ppm	 NA NA	 4 ppb 1 ppb

a/ See Table 66 of this volume for details. Abbreviations: GP=general population all ages, GP_W=women of child-bearing age in general population, GP_A=general population adult, NA=not applicable, UF=uncertainty factor.
b/ Based on cancer risk benchmarks of $1x10^{-5}$ for workers and $1x10^{-6}$ for residents, not UF of 300.

Conclusion (Section **VI.**)

This risk characterization document assesses the human health risk associated with the inhalation exposure to MeI from its proposed use in preplant field fumigation. The exposure groups examined are: workers directly involved in the application of MeI, workers in the adjacent fields, bystanders present at the buffer zone of 152 meters, and residents living next to application sites. Their exposures are estimated from MeI field monitoring studies. The toxicity of MeI is available from laboratory animal studies and human case reports. The main toxicity endpoints of concerns are: fetal death, nasal toxicity (olfactory epithelial degeneration), neurotoxicity, reproductive toxicity (delayed growth), salivary gland effect (metaplasia), and oncogenicity (thyroid tumors). These effects may be caused by MeI as a result of a direct effect or related to its effects on the thyroid in conjunction with iodide, a metabolite of MeI. Analysis of the database supports the need for a more thorough investigation on developmental neurotoxicity and neurotoxicity of MeI.

For non-cancer effects, the most sensitive endpoints are fetal death in rabbits and neurotoxicity in rats from acute exposure to MeI. The acute MOEs are 0.1 to 77 for adults (fetal death endpoint) and 6 to 7 for young children (neurotoxicity endpoint) exposures. For lifetime MeI exposure and cancer risk, the risks based on the genotoxic MOA for thyroid tumors in rats are $1x10^{-6}$ to $5x10^{-5}$ and $1.4x10^{-4}$, respectively, for workers and residents.

This risk assessment recommends the acute MOEs evaluated with a benchmark MOE of 300, an additional uncertainty factor of 10-fold applied to the conventional value of 30, because of concerns about MeI causing potential pre- and post-natal developmental neurotoxicity and adequacy of neurotoxicity testing. For some acute exposure scenarios, the calculated MOEs of these endpoints are well below this benchmark indicating that significant reduction of exposure, up to 3,000 fold, is needed. Exposure reduction is also necessary for some acute exposure scenarios evaluated using a benchmark of 30 for other endpoints as well as for repeated exposures. The recommended RfCs for human exposures based on the fetal death endpoint with the additional 10-fold uncertainty factor are 0.8 ppb and 0.3 ppb for women of child-bearing age in the workplace and in the general population, respectively. When they are applied for all durations, these levels are also protective of young children against excess iodide, which should not exceed 1 ppb based on available iodide intake standards. The lifetime cancer risks of worker and general population exposures, when compared to benchmarks of $1x10^{-5}$ and $1x10^{-6}$, respectively, exceed the benchmarks by 5- and 140-fold. The associated MeI RfCs are 1.7 ppb and 0.04 ppb for worker and general population, respectively. This risk assessment concludes that the application of MeI in field fumigation under the conditions evaluated could result in significant health risks for workers and the general population.

II. INTRODUCTION

This human health risk assessment is conducted by the Department of Pesticide Regulation (DPR) to evaluate the potential risks associated with the inhalation exposure to methyl iodide (MeI, iodomethane[1]) from its use as a new preplant fumigant in California. Risk assessment is the process used to evaluate the potential for human exposure and the likelihood that adverse effects of a substance will occur under specific exposure conditions. For MeI, these conditions are occupational, bystander, and residential inhalation exposures for acute, subchronic, and chronic durations. Dermal exposure to MeI is considered negligible and no dietary exposure is expected. The potential exposure risk to chloropicrin, a component in MeI formulations, is addressed in a separate DPR risk assessment document.

II.A. Chemical Identification

Methyl iodide is found in the air as a result of marine organism biogenic processes and anthropogenic activities. As a pesticide, MeI is a pre-plant fumigant to control soil-borne pests in fields intended for crops such as strawberries and tomatoes, trees and vine re-plants, and ornamental plants. It is considered a methyl bromide replacement because of its low ozone depletion potential (ODP of 0.0015 compared to 0.4 for methyl bromide). The industrial uses of MeI include microscopy, methylation reactions, and other chemical syntheses. Methyl iodide, a glutathione depleter in biological systems, has also been used to study the pharmacokinetics and mechanism of action for other compounds (for example, Priestly and Plaa, 1970; Schulze *et al*., 1976; Erich and Cohen, 1977; Di Simplicio *et al*., 1984).

II.B. Regulatory History

In October 2007, the U. S. Environmental Protection Agency (USEPA) granted a 1-year time-limited registration for MeI as a pesticide after the completion of the risk assessment process (USEPA, 2005a to d; 2006a; 2007; and 2008a). In the risk assessment, USEPA concluded that acute exposure, compared to repeated exposures, was of primary concern. The toxicity endpoints were developmental toxicity (fetal loss), port-of-entry toxicity (nasal lesions), and neurotoxicity. For the finding of thyroid tumors in rats, MeI was classified as "Not likely to be carcinogenic to humans at doses that do not alter rat thyroid hormone homeostasis." USEPA considered MeI a non-food use chemical and thus food tolerances were not needed. The rationale for the non-food use determination included MeI rapid metabolism, low iodide level produced and its incorporation into natural plant constituents, and difficulty associated with enforcement of a tolerance on iodide, which is also a natural element in the environment. USEPA concluded that MeI could be registered as a restricted use pesticide with the requirement of buffer zones, recording keeping, training and stewardship programs, entry restricted period, and respirators for some workers (tarp monitors, shovelers, tractor drivers and co-pilots). On September 29, 2008, USEPA granted conditional registration for all MeI products without time limitations (Erickson, 2008; USEPA, 2008a). Additional discussion of the USEPA risk assessment is in **Appendix C** of **Volume I**.

[1] The term iodomethane is used in some other DPR documents (*e.g*., Pesticide Use Report).

For industrial use of MeI, exposure limits and designations have been established, and they include:

- 5 ppm (28 mg/m^3) and skin effect- Permissible Exposure Level (PEL) 8-hour time-weighted-average (TWA), Occupational Safety and Health Administration (OSHA).
- 2 ppm (10 mg/m^3) and skin effect- 8-hour Threshold Limit Value (TLV), American Conference of Governmental Industrial Hygienists (ACGIH)
- 5 ppm (30 mg/m^3)- 15 minute Short Term Exposure Limit (STEL), American Conference of Governmental Industrial Hygienists (ACGIH)
- 25 ppm for EPRG 1 and 50 ppm for ERPG 2- Emergency Response Planning Guidelines (ERPGs[2]) for 60 minutes, American Industrial Hygiene Association (AIHA)
- 2 ppm (10 mg/m^3), skin effect, and potential carcinogen- Recommended Exposure Limit (REL) TWA, National Institute of Occupational Safety and Health (NIOSH). (Druckrey *et al.*, 1970), and lung tumors in mice (Poirier *et al*., 1975).
- 100 ppm (580 mg/m^3)- The Immediately Dangerous to Life or Health (IDLH) level based on acute LC50 (lethal concentration at 50% death) inhalation toxicity in animals
- A federal hazardous air pollutant, and a toxic air contaminant by the California Air Resources Board (ARB) under AB 2728 (ARB, 1997).

On the oncogenicity of MeI, the International Agency for Research on Cancer (IARC) initially concluded that there was limited evidence for carcinogenicity of MeI to experimental animals (subcutaneous sarcoma in rats, Druckrey *et al.*, 1970; lung tumors in mice, Poirier *et al*., 1975) and no evaluation was made for humans (IARC, 1986). Later, IARC revised the evaluation to conclude that MeI was not classifiable as to its carcinogenicity to humans (Group 3) (IARC, 1999). The National Toxicology Program (NTP) delisted MeI as a carcinogen in their recent Report on Carcinogens (NTP, 2005). The delisting was based on the IARC reevaluation conclusion that the data were equivocal. While the ACGIH does not list MeI as a carcinogen (Toxicology Data Network, 2009), NIOSH considers it as a potential occupational carcinogen based on the findings of Druckrey *et al.* (1970) and Poirier *et al.* (1975). In California, MeI was listed in 1988 under Proposition 65 as a chemical known to cause cancer, based on mutagenicity and the finding of sarcoma in the rat study (Druckrey *et al.*, 1970) (Scientific Advisory Panel, 1988).

II.C. Technical and Product Formulations

The MeI-containing products being considered for DPR registration include MeI technical, and in various amounts with chloropicrin (range from 2% as a warning agent to 75% as an active ingredient) (details of the label and proposed uses are in **Volume II**). The primary registrant is Arysta LifeScience North America Corporation (referred to as Arysta).

[2] ERPG 1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed up to one hour without experiencing other than mild transient adverse health effects or perceiving a clearly defined objectionable odor. ERPG2 addresses irreversible or other serious health effects that could impair individuals from taking protective action.

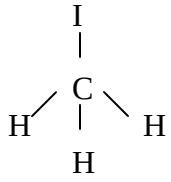
II.D. Usage

No information is available for MeI because it is not registered for use in California.

II.E. Illness Reports

Since MeI is not yet used in California, there are no illness reports in the DPR Pesticide Illness Surveillance Program Report. Case reports of human poisonings are discussed in Section **III.I. Human Exposure**.

II.F. Physical and Chemical Properties[a]

Chemical Name:	Methyl iodide
CAS Registry number:	74-88-4
Common Name:	Iodomethane
Trade Name:	Midas
Molecular formula:	CH_3I
Molecular weight:	141.95 g/mole
Chemical structure:	
Physical appearance:	Clear to light yellow liquid with an acrid odor
Solubility:	Slightly soluble in water (14.2 g/L at 25°C); soluble in acetone; miscible with diethyl ether and ethanol
Boiling Point:	42.5°C
Melting Point:	-66.5°C
Vapor Pressure:	398 mmHg at 25°C
Henry's Law Constant (Kh):	0.0054 atm-m^3/mol (25°C)
Octanol/Water Partition Coefficient:	log K_{ow}= 1.51
Ozone Depletion Potential:	0.0015
Atmospheric Lifetime:	5.2 days (average for all latitudes)
Air Conversion Factor:	ppm = 5.81 mg/m^3 at 25°C 760 mm Hg ppm = 5.65 mg/m^3 at 21°C 1 m^3 =1000 L

a/ References: ATSDR, 2004, **Volume II**, and **Volume III**.

II.G. Environmental Fate

Summary: After field application, MeI dissipates mainly by volatilization with rapid photolysis, with the release of iodine to the atmosphere. Other degradation routes, abiotic hydrolysis, aqueous photolysis, and biotransformation via soil microorganisms, appear minor when compared to volatilization of MeI. However, MeI in soil degrades to methanol and iodide ion. The fate of the iodide ion is unknown, but may potentially represent a substantial loading to ground water if all iodide leached. In field studies, MeI residues were below the detection limit or at low levels in strawberries and tomatoes grown on MeI fumigated soils because of environmental degradation and plant metabolism.

II.G.1. Dissipation and Degradation

The environmental fate of MeI in the water, soil, and the atmosphere is presented in **Volume III**. In summary, the sources of MeI in the environment are soil volatilization, marine organism metabolism, biomass burning, as well as soil microorganism and plant metabolism. The primary route of dissipation is volatilization with rapid photolysis, which releases active iodine with an atmospheric photolysis half-life of 5.2 days. The estimated ODP due to MeI photo-dissociation in the stratosphere is 0.0015, compared to 0.4 for methyl bromide. Other degradation routes are abiotic hydrolysis, aqueous photolysis, and biotransformation via soil microorganisms. Contamination of surface water is unlikely. DPR empirical modeling predicts essentially zero concentration of MeI in ground water under even extreme irrigation conditions. However, Florida required ground water monitoring of iodomethane as a condition of registration. The MeI in soil that doesn't volatilize degrades to methanol and iodide ion. The fate of the iodide ion is unknown, but may potentially represent a substantial loading to ground water if all iodide leached.

II.G.2. Residues in Soil and Plants

Residue studies were submitted to DPR to support the non-food use status of MeI based on these considerations: (1) the proposed pre-plant fumigation uses on strawberries, peppers, and tomatoes involved only a single application per season, (2) MeI is rapidly dissipated from the treated soil and there is little exposure for the transplanted seedlings, (3) the soil metabolite, iodide, declines with time due to uptake by microorganism or air oxidation to iodine, and (4) field studies with strawberry and tomatoes showed MeI residues at below the limit of quantitation (LOQ) of 0.005 ppm (Curry and Brookman, 2002). Descriptions of the studies are presented in this section.

Two studies were conducted to examine the nature of residues in the soil and fruits (strawberries and tomatoes). Bare-root strawberries were transplanted on four quadrants of a plot pretreated with ^{14}C-radiolabeled MeI at a maximum label rate of 235 pounds per acre (McFadden, 2002a). The first quadrant planting occurred on 7 days after the application, and the others occurred at 7-day intervals. Mature fruits were collected beginning 76 days after treatment and through a second crop from the first (oldest) plants. Soil samples were collected at the time of transplant. From the first week to the 4th week after application, MeI level in the soil declined from 0.09 ppm to 0.013 ppm. The radioactivity ranged from 1.05 ppm for fruits from the first planting (76 days after application) to 0.248 ppm for those collected 118 days after applications (second crop). Ninety-seven percent of the total radioactivity was found in the

glucose or glucose-related components due to incorporation of the ^{14}C-label. Iodide levels in the fruits of treated plots were below the LOQ (0.03 ppm).

Tomato seedlings were transplanted into plots 6 days after the soil had been injected with ^{14}C-MeI at a maximum labeled rate of 235 pounds per acre (30 ppm MeI) (McFadden, 2002b). Soil samples were collected at the time of transplant. Fruit samples were collected 104 (Group 1) and 115 days (Group 2) after soil treatment, respectively. The extractable radioactivity (as MeI) in the soil was less than 5% of total radioactivity, or less than 0.12 ppm. Analysis of the mature fruit showed MeI residue below the LOQ of 0.005 ppm. Most of the total residue was found in the glucose or glucose-related components, about 70% of the total radioactive residues. Iodide was detected in the 104-day samples at low levels (less than 0.13 ppm to 0.24 ppm), but not in the 115-day samples (LOQ of 0.03 ppm).

Field trials were conducted to determine the magnitude of the residues in strawberries and tomatoes grown on treated soils. Five field trials on strawberries were conducted in Florida, California, and Missouri with MeI at the maximum label rate of 235 lbs per acre (Cassidy *et al*., 2002). Strawberry transplants were planted through the tarping at 7 days after treatment. For all trials, fruits collected at earliest maturity showed no MeI residues (LOQ of 0.005 ppm). Iodide levels in strawberries from treated plots were below the LOQ (30 ppb) for two trials (Arroyo Grande, CA; Salinas, CA), and up to 62 ppb (control at <30 ppb) in two trials (Oxnard, CA; Clarence, MO). The result for the Hobe Sound, FL trial was not available due to analytical problems.

Five field trials with tomatoes were conducted in Florida and California with MeI at the maximum label rate of 235 lbs per acre (Cassidy, 2002). Tomato seedlings were planted through the tarping at 5, 7, and 11 days after treatment. For all trials, fruits collected at earliest maturity showed no MeI residues (LOQ of 0.005 ppm). Iodide levels in tomatoes from treated plots were below the LOQ (30 ppb) for two trials (Hobe Sound, FL; and Arroyo Grande, CA), up to 56 ppb (control at <30 ppb) in two trials (Boyton Beach, FL; Kettleman City, CA), and similar (37 to 48 ppb) to the control (42 ppb) for the fifth trial (San Ardo, CA).

III. TOXICOLOGY PROFILE

This section describes the toxicological database of MeI, which consists of pharmacokinetic and toxicity studies submitted to DPR and those published in scientific journals. All toxicity studies required under The Birth Defect Prevention Act of 1984 (SB 950)[3] have been submitted with adverse effects identified for the following study types (and indicated species): chronic toxicity (rat, dog), oncogenicity (rat, mouse), reproductive toxicity (rat), teratology (rabbit), and chromosome effects. These studies are considered in the hazard identification of MeI (**IV.A.**) and selected studies will also be referred to in the **Appendix A** of **Volume I** on the review of the Physiologically Based Pharmacokinetic (PBPK) model used to determine the Human Equivalent Concentrations (HECs). The toxicity of iodide, a metabolite of MeI, is discussed in this document only in the context of MeI toxicity in this section and risk characterization in the **RISK APPRAISAL** section (**V.C.1.**). Comprehensive reviews on iodine toxicity are available in the published literature (*e.g.*, Agency for Toxic Substances and Disease Registry; ATSDR, 2004).

Toxicity studies on MeI have been conducted in rats and rabbits by the inhalation route, the main route of human exposure, as well as mice and dogs by the oral route. Results show both port-of-entry and systemic effects. To compare the results among the studies, the doses are expressed in the same term (mg/kg/day) to account for differences in the intake of MeI due to breathing rate differences between species, routes of administration, and duration of exposure (see calculations in **Appendix B** of **Volume I**). This approach follows the dose calculation methods outlined in the USEPA Exposure Assessment guidelines, where the potential dose is a function of the concentration and intake rate (USEPA, 1992). It has generally been used for dietary exposure studies where the exposure concentration is expressed as the dose to account for consumption rate and duration of exposure. For each study, the no-effect level, if established, may be expressed as No-observed-effect Level (NOEL) or No-observed-adverse-effect Level (NOAEL). For the purpose of this document, either no-effect level designation is considered relevant for hazard identification. When available, the NOAELs established by the USEPA (USEPA, 2006a and 2007) are also cited[4].

DPR's external Scientific Review Committee (SRC) recommended the use of BMD approach, instead of the NOEL, for hazard identification because the approach uses all of the dose-response data and does not simply rely on statistical significance by pair-wise comparisons between small groups of control and exposed animals (**Volume IV Part 1-A**). Therefore, toxicity studies pertinent for hazard identification include results of BMD analysis for selected endpoints, including increased cholesterol levels and neurotoxicity from repeated exposures, as

[3] The required studies are: chronic toxicity (in two species), oncogenicity (in two species), reproductive toxicity (rats), developmental toxicity (in two species), genotoxicity, and neurotoxicity studies. For the SB 950 toxicity studies, the acceptability of studies (except genotoxicity studies) is based on the USEPA Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) guidelines. The acceptability of the genotoxicity studies is based on the Toxic Substances Control Act guidelines (Federal Register, 1985 and 1987). A study is considered supplemental information if the SB 950 data requirement for a certain study type is already fulfilled by an acceptable study or if the study is not part of the SB 950 data requirement. The Summary of Toxicology Data for this SB950 database is available online at http://www.cdpr.ca.gov/docs/risk/toxsums/toxsumlist.htm. Since MeI is not registered for use in California, the Summary is not posted yet.

[4] MRID numbers are study numbers assigned by the USEPA. They are provided in this document for cross-reference purposes.

recommended by the SRC. Benchmark dose concentrations are derived using either continuous or quantal benchmark dose models available from the USEPA (BMDS 2.0 software). The analysis involves fitting a mathematical model to the entire dose-response dataset for an endpoint, and allowing the model to estimate the threshold dose (benchmark dose, BMD) corresponding to a level of benchmark response (BMR). The BMD is either the model's best estimate of the effective dose (ED) at the BMR or the statistical 95th percent lower bound of ED (LED). The Akaike's Information Criterion (AIC) scores are provided for each model which is an indication of fit. In general, the lower the AIC value, the better the model fits the data. However, models with higher AIC scores but better fits visually around the ED and LED may be preferred. The BMR for the endpoint of interest can be set at a certain response level as a relative change in the mean response or a change in the mean relative to the standard deviation of the control (expressed as a multiplier of standard deviation[5]). Following the DPR guidelines (DPR MT-1, 2004; DPR MT-2, 2004), the MeI data are analyzed for 1 to 10% response as well as at 0.61σ or 0.36σ. The LED is used as the point of departure in this document.

III.A. Pharmacokinetics

Summary: In rats, the oral and inhalation absorption of ^{14}C-MeI was rapid and was considered complete (100% of the administered dose). After oral exposure, the peak blood radioactivity (^{14}C) level was reached by 6 hours after administration. The highest radioactivity levels were found in the liver and gastrointestinal (GI) tract, with lower amounts in the thyroid and other tissues. The routes of elimination were expired air as radiolabeled carbon dioxide (52-73% of dose), urine (30-40% of dose), and feces (2-4% of dose). For inhalation exposure, peak tissue levels were obtained immediately following exposure with the highest tissue radioactivity levels found in the thyroid, lungs, and nasal turbinates. Expired air (40 to 47% of dose) and urine (30-40% of dose) were also the main routes of elimination. Fecal elimination was 1-2% of the dose. For both routes of exposure, the major urinary metabolites were S-methyl glutathione and N-(methylthioacetyl) glycine. In rabbits given ^{14}C-MeI by subcutaneous injection, the highest radioactivity was detected in the brain, with subcellular distribution primarily to the mitochondria. In humans exposed to ^{132}I-MeI by inhalation, ^{132}I retention in the body ranged from 53% to 92% of the dose, and correlated with the respiratory rate (breaths/min) of the individuals. ^{132}I was detected in the thyroid, salivary gland, and saliva. The human inhalation absorption was considered 100%, the same value as for the rat. No pharmacokinetic study for dermal exposure has been submitted. Additional information on the pharmacokinetics of MeI, related to PBPK modeling, is presented in Section **III.J.** and **Appendix A** of **Volume I**.

[5] A hybrid approach is when the BMR is defined as a change of the mean response at a specified multiplier of the standard deviation, σ (Crump, 1995). The multiplier is determined based on both the pre-defined background probability (P_0) of "abnormal" (or "affected") individuals in the control population and the excess BMR risk (π) in the exposed population that is above P_0. The $LED_{0.61\sigma}$ approximates the LED at P_0 =0.05 and π = 0.1 (10% increase risk above background). The $LED_{0.36\sigma}$ approximates the LED at P_0 =0.05 and π = 0.05.

III.A.1. Absorption and Distribution

The pharmacokinetics of ^{14}C-MeI (TM-425, 99.7% pure; radiochemical purity 97%) after oral (single dose by gavage, 12/sex/group) and inhalation (5.5 hours whole-body, 12/sex/group) exposures were studied with Sprague-Dawley Crl:CD(SD)IGS-BR male rats (Sved, 2002) and female rats (Sved, 2003). Each exposure route and gender had a main test group. A supplemental test was conducted only in the males to address the inefficient trapping of expired carbon dioxide, which resulted in low recovery of the administered doses in the main test. For the oral main test, the doses were 1.5 mg/kg and 24 mg/kg for males, and 1.7 mg/kg and 21 mg/kg for females. Animals from each group were sacrificed at 1 hour, 6 hours, or 168 hours post-dosing. In the oral supplemental test, the males were given either 1 or 35 mg/kg, and all were sacrificed 48 hours post-dosing.

For whole-body inhalation exposure, the doses for the main test were 25 ppm (31 mg/kg) and 233 ppm (289 mg/kg) for males, and were 24 ppm (39 mg/kg) and 250 ppm (373 mg/kg) for females. They were sacrificed at 0 hour (immediately following the 5.5-hour exposure), 6 hours, or 168 hours post-dosing. In the inhalation supplemental test, the males were given 21 ppm (26 mg/kg) or 209 ppm (259 mg/kg). They were divided into two sub-groups with sacrifice time of 0 hour (immediately following the 5.5-hour exposure) and 48 hours post-dosing. Note that this study design resulted in differences in the amount of time allowed for tissue distribution. For example, the first sampling time was immediately after gavage dosing, while it was after 5.5 hours for inhalation exposure. Expired air, urine, feces, and blood samples were collected at intervals during the study. Expired air was trapped using 2% tripropylamine in dimethylsulfoxide to trap organic vapor and 0.2N NaOH to trap carbon dioxide[6]. Necropsy was performed only on the main test animals. MeI levels were quantified by ^{14}C-radioactivity (mean µg MeI equivalents/g tissue or medium) (Table 1 and 2) or % of dose recovered in different compartments (Table 3 and 4). Iodine levels were not measured.

Methyl iodide was readily absorbed by both routes and distributed to all tissues examined (Table 1 and 2). With oral exposure for both doses, the maximal concentration in the blood was achieved between 4 to 6 hours. The highest radioactivity was measured in the liver and GI tract, where peak levels occurred during the first hour after dosing. For other organs, highest levels were generally reached by 6 hours. For inhalation exposure, peak blood and tissue levels were measured immediately after exposure (Table 1 and 2). The blood radioactivity level remained relatively constant through 4 hours post dosing. Immediately after exposure, highest radioactivity was found in the thyroid and lung. At 233 or 250 ppm, high levels were also found in the kidneys and nasal turbinates.

[6] NaOH reacts with CO_2 to form a sodium carbonate solution.

Table 1. MeI equivalents (^{14}C-radioactivity) in male rat tissues after oral or inhalation exposures.[a]

Tissues		Tissue levels -mean µg MeI equivalents/g tissue			
		Oral		Inhalation	
		1.5 mg/kg	24 mg/kg	25 ppm, 31 mg/kg[b]	233 ppm, 289 mg/kg[b]
Blood	1 or 0 hr	0.861	11.7	8.54	61.2
	4 hr	1.03	16.1	7.87	60.0
	6 hr	0.963	15.8	6.76	54.2
	168 hr	0.175	2.91	1.95	12.9
Spleen	1 or 0 hr	1.24	29.0	43.4	152
	6 hr	1.40	24.7	12.6	66.7
	168 hr	0.319	5.50	2.49	16.3
Kidney	1 or 0 hr	1.28	17.3	50.5	319
	6 hr	2.40	36.8	19.7	134
	168 hr	0.406	7.34	3.70	24.1
Liver	1 or 0 hr	12.1	204	24.5	187
	6 hr	2.7	54.6	16.8	153
	168 hr	0.377	7.27	3.15	23.9
Brain	1 or 0 hr	0.471	5.97	21.9	121
	6 hr	0.680	10.3	12.6	93.5
	168 hr	0.154	2.62	1.30	9.12
Thyroid	1 or 0 hr	0.807	17.9	106	198
	6 hr	1.14	19.7	34.9	136
	168 hr	0.367	18.7	2.57	21.7
Lung	1 or 0 hr	0.752	11.1	75.2	189
	6 hr	1.05	18.0	21.5	85.9
	168 hr	0.258	4.28	2.40	16.5
Nasal	1 or 0 hr	0.549	9.9	51.7	138
turbinates	6 hr	1.02	16.0	14.3	72.4
	168 hr	0.342	5.85	3.01	18.6
Fat	1 or 0 hr	0.107	3.53	3.20	23.1
	6 hr	0.152	2.52	1.49	10.5
	168 hr	0.103	1.26	0.524	4.29
GI tract	1 or 0 hr	11.7	78.8	24.3	192
	6 hr	3.42	36.2	11.8	113
	168 hr	0.207	3.76	1.79	10.6

a/ Data from Sved (2002). The first sampling points were 1 hour after oral, and immediately (0 hour) after the 5.5 hours of inhalation exposures.

b/ Conversion of ppm to total dose:
ppm x 5.81 mg/m^3/ppm x 1000L/m^{3}x1.152 m^3/kg/day x hours exposed/24 hours. The 1.152 m^3/kg/day is the respiration rate used by the investigators. The DPR default value is 0.96 m^3/kg/day.

Table 2. MeI equivalents (^{14}C-radioactivity) in female rat tissues after oral or inhalation exposures.[a]

Tissues	Tissue levels -mean µg MeI equivalents/g tissue			
	Oral		Inhalation	
	1.7 mg/kg	21 mg/kg	24 ppm, 39 mg/kg[b]	250 ppm, 373 mg/kg[b]
Blood 1 or 0 hr	1.16	12.5	10.1	67.0
4 hr	1.61	18.6	8.19	63.0
6 hr	1.55	19.0	6.76	62.9
168 hr	0.193	2.61	1.58	9.15
Spleen 1 or 0 hr	1.94	30.7	53.2	168
6 hr	1.89	22.6	10.6	70.4
168 hr	0.384	5.70	2.42	13.4
Kidney 1 or 0 hr	1.67	17.4	57.0	336
6 hr	2.86	31.3	12.2	130
168 hr	0.467	6.99	2.25	17.8
Liver 1 or 0 hr	12.2	179	29.4	223
6 hr	3.80	54.8	19.8	140
168 hr	0.448	7.52	2.90	23.3
Brain 1 or 0 hr	0.684	5.68	24.8	123
6 hr	1.11	11.9	12.6	94.3
168 hr	0.225	2.97	1.42	8.61
Thyroid 1 or 0 hr	1.28	12.6	175	337
6 hr	1.63	26.6	32.8	172
168 hr	0.391	5.31	4.31	14.5
Lung 1 or 0 hr	1.57	14.8	92.7	200
6 hr	1.79	20.8	23.5	94.1
168 hr	0.354	5.21	2.27	13.2
Nasal 1 or 0 hr	1.16	6.95	53.0	152
turbinates 6 hr	1.88	16.8	15.5	77.4
168 hr	0.416	5.12	3.13	13.5
Fat 1 or 0 hr	0.169	3.46	5.59	31.5
6 hr	0.218	3.05	2.76	18.2
168 hr	0.073	1.45	0.87	5.39
GI tract 1 or 0 hr	11.8	77.5	30.3	219
6 hr	4.61	41.1	13.4	95.0
168 hr	0.220	3.44	1.70	7.85

a/ Data from Sved (2003). The first sampling points were 1 hour after oral, and immediately (0 hour) after the 5.5 hours of inhalation exposures.

b/ Conversion of ppm to total dose:
ppm x 5.81 mg/m^3/ppm x 1000L/m^{3}x1.152 m^3/kg/day x hours exposed/24 hours. The 1.152 m^3/kg/day is the respiration rate used by the investigators. The DPR default value is 0.96 m^3/kg/day.

The blood kinetics of MeI equivalents were considered similar regardless of route, dose, or gender[7]. The ^{14}C-elimination initial T1/2 ranged from 5.1 to 7.2 hours for males, and 3.8 to 7.7 hours for females. The ^{14}C-elimination terminal T1/2 ranged from 116 to 136 hours for males and 88 to 114 hours for females. The amount absorbed (% of dose for total recovery) was considered 100% for both routes based on results from the data for the supplemental tests in males (Table 3) and the main test for the females (Table 4).

Table 3. Group mean recovery (% of dose) of MeI equivalents (^{14}C-radioactivity) in male rats.[a]

	% of Dose							
	Oral				Inhalation in ppm (total dose)			
	Main Test		Supplement Test		Main Test		Supplement Test	
	1.5 mg/kg	24 mg/kg	1 mg/kg	35 mg/kg	25 ppm (31 mg/kg)	233 ppm (289 mg/kg)	21 ppm (26 mg/kg)	209 ppm (259 mg/kg)
All tissues	1.70	1.71	NE	NE	1.57	1.70	NE	NE
-brain	0.05	0.06			0.06	0.06		
-thyroid	<0.01	<0.01			<0.01	<0.01		
-lung	0.09	0.09			0.09	0.08		
-nasal	0.01	0.01			0.01	0.01		
-liver	1.23	1.23			1.10	1.26		
-others	0.34	0.34			0.33	0.31		
GI tract &contents	0.65	0.69	NE	NE	0.60	0.52	NE	NE
Blood	0.24	0.32	NE	NE	0.35	0.28	NE	NE
Organic vapor	0.13	0.22	NE	NE	0.12	0.14	NE	NE
Carbon dioxide[b]	34.99	12.77	51.71	60.81	2.98	2.75	46.95	39.40
Urine	29.02	35.27	30.04	33.40	34.68	33.63	28.73	26.50
Feces	2.66	2.47	1.74	1.73	1.58	1.40	1.32	0.74
Carcass	13.12	11.92	20.85	26.91	14.39	13.85	26.72	23.83
Cage Wash	0.06	0.05	0.53	0.62	0.06	0.18	1.10	0.96
Total Recovery	82.6	65.4	104.9	123.5	56.3	54.4	104.8	91.4

a/ Data from Sved (2002). "All tissues" values do not add up to the values of individual tissues and others due to rounding. Other tissues=fat, spleen, and kidney. Urine=sum of urine and cage rinse. Total recovery=sum of all components. NE=not evaluated.

b/ In the main test, there was inefficient trapping of expired carbon dioxide. Results from the supplemental test were used for total recovery.

[7] In the male study, radioactivity was measured only in whole blood. But in the female study, radioactivity was measured in plasma and blood cellular fraction. In order to compare these values, a cellular volume of 50% was assumed such that the average of plasma and cellular fraction values was equivalent to those for the whole blood.

Table 4. Group mean recovery (% of dose) of MeI equivalents (^{14}C-radioactivity) in female rats.[a]

	% of Dose			
	Oral		Inhalation in ppm (total dose)	
	1.7 mg/kg	21 mg/kg	24 ppm (39 mg/kg)	250 ppm (373 mg/kg)
All tissues	2.09	2.32	1.55	1.77
GI tract &contents	0.80	0.84	0.69	0.57
Blood	0.23	0.29	0.34	0.31
Organic vapor	2.90	1.42	2.35	1.04
Carbon dioxide[b]	53.47	73.29	39.98	46.61
Urine	38.11	42.99	33.84	35.85
Feces	3.15	3.88	2.59	1.29
Carcass	13.97	14.02	14.17	10.76
Cage Wash	0.10	0.13	0.10	0.05
Total Recovery	115	139	95.6	98.2

a/ Data from Sved (2003). Urine=sum of urine and cage rinse. Total recovery=sum of all components.

The disposition of MeI was studied in rabbits after a single subcutaneous injection of ^{14}C-MeI (53.5 to 57 mg/kg) (Hasegawa *et al*., 1971; Hasegawa, 1969). Peak tissue levels were obtained at 24 hours, with much lower levels at 48 hours and 72 hours after exposure. Detectable radioactivity levels were measured in the brain (highest level), blood, muscle, spleen, heart, and liver. The radioactivity in the brain persisted longer than other organs. Radioautographs showed the radioactivity associated with the gray matter, brain stem, and the cerebellar cortex. Subcellular analyses revealed that the highest radioactivity (on per 0.2 mL basis) was in the mitochondria of brain cells, and nuclei of liver cells.

In humans, the uptake of MeI is related to the respiratory rate. Human volunteers (17 males, 1 female) were exposed to ^{132}I-MeI vapor (3 mrem, dose not specified) by inhalation for 5 minutes via a mouth piece (Morgan and Morgan, 1967). Radioactivity in the exhaled air was trapped by charcoal, and used to calculate body retention. The retention ranged from 53% to 92%, and correlated with the respiratory rate (breaths/min). Individuals with the low respiration rates had the higher retention than those with higher rates[8]. Additional experiments conducted with two subjects confirmed this relationship and suggested negligible absorption in the conducting airways. The DPR Worker and Health Safety Branch evaluated this study for the determination of an inhalation absorption factor. Since the percent retention/absorption of MeI for individuals at rest or at work can vary widely, a default factor of 100% retention/absorption is assumed for the exposure assessment in **Volume II**.

Human volunteers were given ^{132}I-MeI (30 µg of unlabelled MeI as a carrier) by inhalation in a series of experiments (Morgan *et al*., 1967). Four subjects were exposed to MeI by inhalation for 5 minutes, and one subject inspired the vapor as a single deep breath and held

[8] The average breathing rate was 0.18 m^3/kg/day (range of 0.09 m^3/kg/day to 0.44 m^3/kg/day assuming body weights of 70 kg and 65 kg for males and females, respectively).

for 45 seconds. In the third experiment, one subject drank ^{132}I-sodium iodide (NaI, 10 µg unlabelled NaI as a carrier). For each experiment, thyroid uptake of ^{132}I was measured with a "NaI crystal" detector on the surface of the skin above the gland. Since the use of the detector is an indirect method, the potential sources of errors were: (1) extra-thyroidal radioactivity at the beginning of the experiment, (2) unknown size and location of the thyroid, and (3) low radioactivity at the end of the experiment. Radioactivity in the blood and urine was also measured. Following inhalation exposure, the uptake of ^{132}I in the thyroid was fitted with two exponential curves as one individual had much higher % of retention (34.1 mrem) than the other three subjects for all time points. The thyroid of the high retention individual showed 40% of the retained ^{132}I by 10 hours after administration. For the other subjects at the same time point, the retention was about 20-25%. The total thyroid dose ranged from 7.5 to 34.1 mrem for 5-minute inhalation exposure, 7.4 to 17.1 mrem for single breath inhalation, and 20.5 mrem for oral ingestion.

In the venous blood for all test subjects, ^{132}I levels generally showed rapid increase immediately after MeI exposure and decreased slowly with time. The maximum concentration of ^{132}I in blood was about 4% of the retained dose. At 150 minutes after exposure, the blood level was about 2.5%. The amount of radioactivity in the saliva was also measured in one subject who inhaled MeI over a 5-min period. The saliva showed a concentration of 90%/L during the first hour after inhalation exposure. This was much higher than the 2%/L, the average concentration in the blood at the same time. This result was consistent with the salivary gland as a site of bioaccumulation of iodide. In addition, the thyroid ^{132}I-uptake curve for NaI after oral ingestion was similar to that for inhalation exposure to MeI. Scan of the subject who ingested NaI showed "considerable" levels of radioactivity in the cardia and body of the stomach, the site of gastric glands, also known to bioaccumulate iodide.

III.A.2. Metabolism and Excretion

In rats, the major route of excretion was via the expired air for both oral and inhalation exposures in the studies described previously (Sved, 2002 and 2003). Post exposure, ^{14}C-carbon dioxide measured was 52 to 61% (male, oral exposure), 53-73% (female, oral exposure), and 40-47% (both genders, inhalation) of exposure dose (Table 3 and Table 4, Supplemental tests). Urinary elimination accounted for about 30 to 40% of the dose for all groups. Peak elimination time was between 6 and 12 hours. A small fraction of the dose (1-3%) was recovered in the organic vapor phase but the nature of the radioactivity was not identified. Fecal excretion was minor, at 2-4% and 1-2% of the dose for oral and inhalation exposures, respectively, and was diminishing by 24 or 48 hours. In the males, the urinary metabolites for both routes were S-methyl GSH and N-(methylthioacetyl) glycine (major metabolites), methylthioacetic acid, S-methylcysteine, and methylmercapturic acid (Figure 1). Additional metabolites (methylthiopyruvic acid, S-methylcysteine sulfoxide, and methylmercapturic acid sulfoxide) were identified in the female urine samples.

Kubic *et al.* (1974) showed that carbon monoxide was not a metabolite when rats were given MeI (dose not given) by intraperitoneal injection. Carbon monoxide in the blood was detected by gas chromatography. However there was little information about the MeI experiment since the main purpose of the study was concerned with dihalomethane metabolism.

Based on results from an earlier study (Johnson, 1965), the conjugation of MeI with GSH as a metabolic pathway was studied in female white rats (Porton strain) given a single oral dose of MeI (0, 50, 75, and 100 mg/kg) (Johnson, 1966). GSH levels were measured in tissues at various times from 15 minutes to 180 minutes after dosing. Liver non-protein thiols (predominantly GSH) were depleted at all doses tested; ranged from a loss of about 40% (compared to control) at 50 mg/kg to more than 90% at 100 mg/kg. Kidney, brain, and blood non-protein thiols were reduced to a smaller extent and only at 75 mg/kg and 100 mg/kg. Chromatography showed S-methyl-GSH in the liver extract as the result of an enzymatic methylation reaction. Additional experiments with cannulated rats showed that S-methyl-GSH was excreted in the bile. This compound was metabolized in the kidneys to yield glycine, glutamic acid and S-methylcysteine.

In rats, studies by Chamberlain *et al.* (1998b) show that no evidence of cytochrome P-450 oxidation of MeI to formaldehyde when MeI was incubated with rat liver or olfactory microsomes. Results by Bonnefoi *et al.* (1991) indicated that formaldehyde was formed via GSH conjugation instead of cytochrome P-450 oxidation. In the *in vitro* study, young mouse neuronal cell cultures containing mixed neuronal and glial cells were exposed to MeI. Increased formation of formaldehyde was detected with exposure to MeI, but its production was inhibited in the presence of sulfasalazine, a GSH-s-transferase inhibitor.

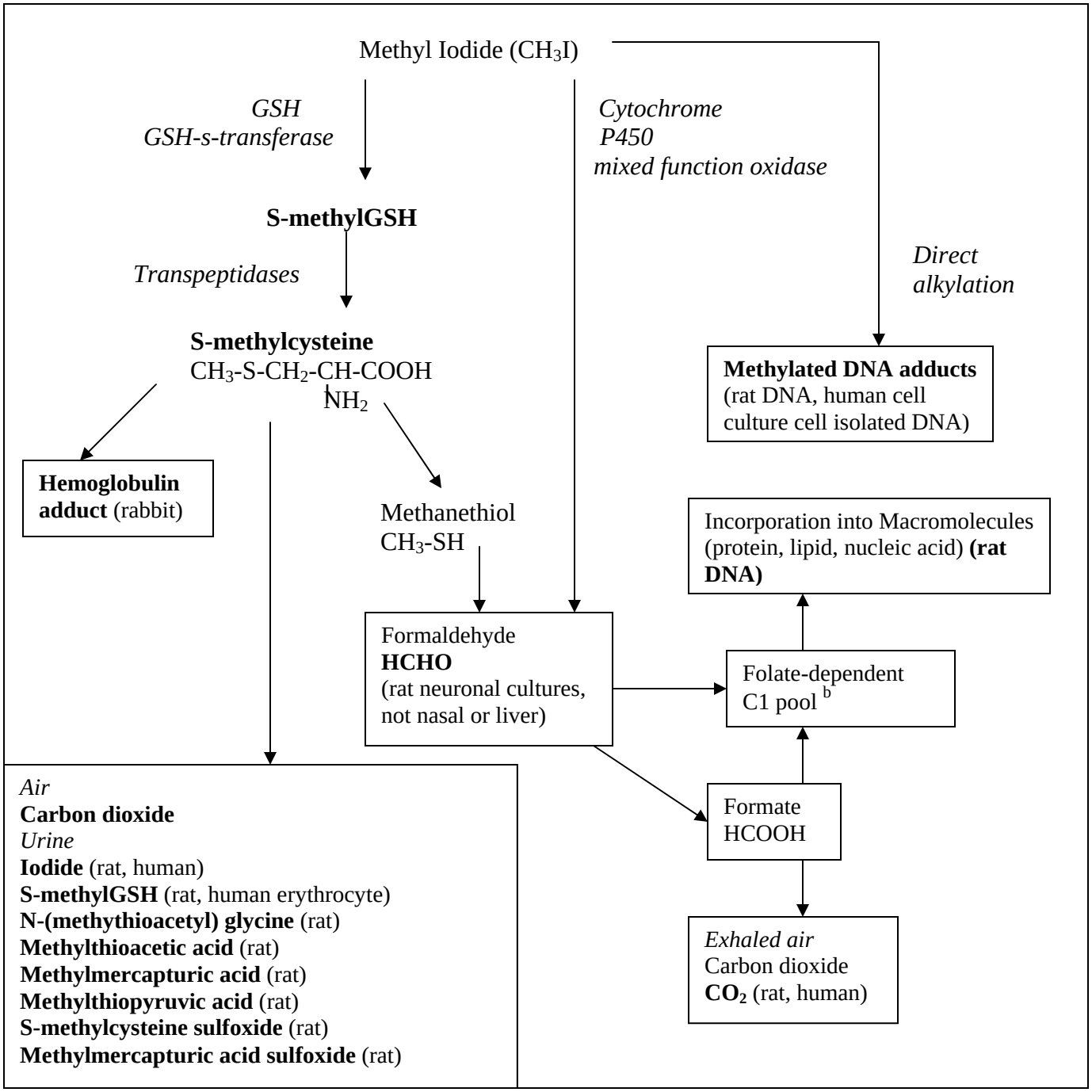
In the studies by Hasegawa *et al*. (1971) and Hasegawa (1969), the data suggested that some MeI was not metabolized in rabbits after a single subcutaneous injection of ^{14}C- MeI (53.5 to 57 mg/kg). This was based on the finding of toluene extractable tissue radioactivity (expressed as counts per minute/0.1 mL homogenate), which was assumed to be free MeI. At 24 hours after injection, all ^{14}C radioactivity in the heart, and about 50% for the other tissues, were in the toluene fraction. At 48 and 72 hours, 100% or more of the ^{14}C radioactivity in the homogenate of all tissues, were in the toluene fractions. There was no confirmation of the chemical identity in this study.

In the human study described previously (Morgan *et al*., 1967), the urinary excretion of ^{132}I was immediate after inhalation dosing with MeI. The excretion was described by two exponential decay curves indicating inter-individual differences. One individual had excretion rates faster than others, resulting in a cumulative excretion of 60% of the retained radioactivity, compared to 40% for the other subjects (values estimated from the graph in the report). For both groups, urinary excretion of ^{132}I increased with time with a peak at 40 minutes, and then decreased to a steady level at about 200 minutes. Urine samples analyzed by chromatography were found to contain only iodide, and not MeI. In comparison, the urinary excretion curve for NaI after oral ingestion was similar to those for MeI inhalation exposure. This result and the absence of MeI in the urine samples suggested that MeI was rapidly metabolized to iodide after inhalation exposure.

Heterogeneity in the metabolism of MeI and methyl bromide by GSH S-transferase in humans was studied using erythrocytes *in vitro* (Hallier *et al*., 1990). These compounds were incubated with GSH and fresh or boiled human erythrocyte cytoplasm, and activity was measured as chemical loss from the media. Two populations were present in the preparations: non-conjugators and conjugators. With the boiled preparations to measure non-enzymatic binding to GSH, MeI showed a more rapid decrease in concentration than methyl bromide. The reaction was spontaneous with the rapid formation of S-methyl GSH. A comparison of activities

between non-conjugator and conjugator preparations showed MeI conjugated both enzymatically and non-enzymatically to S-methyl GSH, but the non-enzymatic reaction was predominant. In contrast, methyl bromide is conjugated largely by an enzymatic reaction. An inhibitor study with sulfobromophthalein, a specific competitive inhibitor of a minor form of the erythrocyte GSH S-transferase, confirmed the involvement of this enzyme in the enzymatic conjugation reaction. Another study (Poet *et al*., 2009) on MeI and GSH depletion was conducted for PBPK modeling; it is described under **III.J.3. Glutathione and MeI Toxicity**. The result supports the finding of Hallier *et al.* (1990) that MeI reaction with GSH is largely non-enzymatic in the blood.

Figure 1. Metabolic pathways of methyl iodide.[a]



a/ This pathway is compiled from the general metabolic pathway for methyl halides described by Schwartz *et al.* (2005), Bolt and Gansewendt (1993), and Chamberlain *et al*. (1998 a and b). Chemicals in bold print are those identified in the pharmacokinetic studies (Sved, 2002 and 2003; Johnson, 1965 and 1966; Bonnefoi *et al*., 1991; Morgan *et al.*, 1967; Hallier *et al*., 1990) and adduct formation studies (Gansewendt *et al*., 1991; Sloter 2005a and b; Cloutier *et al*., 2001).

b/ Formaldehyde reacts with tetrahydrofolate to form N_5, N_{10} - methylene tetrahydrofolate, which results in the carbon atom derived from formaldehyde entering the one-carbon pool and can be incorporated into all major classes of macromolecules.

III.B. Acute Toxicity

Summary: At lethal doses, MeI treated laboratory animals showed clinical signs and port-of-entry effects. These signs included difficulties in breathing, salivation, gait problems, and urinary/fecal excretion changes. Histological studies indicated lesions of the olfactory epithelium (inhalation exposure), the GI tract (oral exposure), and the skin (dermal exposure). Technical MeI oral LD50s (lethal dose that causes death in 50% of the population) ranged from 79.8 mg/kg to 214.1 mg/kg (Toxicity Category II) in rodents. The acute dermal LD50 is >2000 mg/kg (Toxicity Category III). The inhalation 4-hour LC50 is 3.9 mg/L (691 ppm, Toxicity Category IV). It is a skin (Toxicity Category II) and eye irritant (Toxicity Category I), as well as a skin sensitizer. In comparison, formulation with 2% chloropicrin showed toxicity similar to technical MeI. Increasing chloropicrin concentration in these combinations resulted in greater toxicity with lower inhalation LC50s (0.18 and 0.24 mg/L), attributable to chloropicrin itself.

At non-lethal doses, rats given MeI by the inhalation route showed clinical signs involving gait and activity changes, breathing difficulties, and other effects. Functional observational battery testing of these rats reported clonic convulsion, lowered body temperature, reduced rotarod performance, and decreased total motor activity.

III.B.1. Acute Toxicity Category Studies

Acute toxicity category studies are summarized in Table 5. Those with clinical observations, which may be useful for hazard identification, are described further in the following sections categorized according to species tested and routes of exposure.

Technical MeI (TM-425) is relatively more lethal by the oral route in rodents compared to inhalation and dermal exposures (Table 5). The oral Toxicity Category was II with LD50s of 79.8 mg/kg and 131.9 mg/kg for rats (Bonnette, 2001a), and 155 mg/kg and 214.1 mg/kg for mice (Bonnette, 2001b). The acute dermal LD50 in rabbit and inhalation 4-hour LC50 in rats were in Category III and IV, respectively (Bonnette, 2001c; Kirkpatrick, 2000 and 2002a). The LC50 of 3.9 mg/L (691 ppm) is equivalent to 624 mg/kg/day (based on a default rat breathing rate of 0.96 m^3/kg/day and amortized for a single day exposure). Methyl iodide is an eye and skin irritant as well as a sensitizer (Bonnette, 2001d, e, and f).

The LD50, LC50, and irritation potential of the formulation containing MeI and a low level of chloropicrin as in TM-42501 (98.10% MeI and 2.19% chloropicrin) were similar to those for MeI only (Table 5). When the proportion of chloropicrin was increased to 75% as in TM-42503, the acute oral LD50 was similar to TM-425 and TM-42501. In contrast, the LC50 for TM-42503 was up to 20-fold lower than the other two formulations. This formulation also caused skin irritation and sensitization. As a comparison, Table 5 also includes the acute inhalation LC50s for chloropicrin; these values were all lower than those for MeI alone indicating greater inhalation lethality by chloropicrin.

The results of the above studies are consistent with the preliminary survey study of Buckell (1950). Male white mice were exposed to MeI by inhalation at 85 mg/L (15,000 ppm) to 0.5 mg/L (88 ppm). The lethal dose for 1 day of exposure was ≥ 5 mg/L (880 ppm for 80 minutes). Histological examination reported acute pulmonary congestion at 5 mg/L and degeneration of the renal tubular epithelium at 1 mg/L. With oral and subcutaneous injection in rats, the lethal dose was 0.15 to 0.22 g/kg. However, in another experiment, body weight reduction was reported at 300 and 500 mg/kg/day but not at 100-200 mg/kg in rats orally dosed daily with MeI. With dermal exposure, 1 ml of MeI applied on shaved skin of rats or human skin had no effect when MeI was allowed to evaporate. However, MeI caused slight redness on application area when MeI was soaked in a gauze pad which was then held in place for 0.5 hours with dressing. When MeI was applied with a gauze pad for 10 minutes, human skin showed reddening with erythematous patch with raised areas 6 hours later. Small vesicles appeared after the area was washed off with hot water.

Table 5. Acute toxicity category studies for MeI.[a]

Study Type	Result	References
TM-425 (99.7% MeI)		
Acute oral LD50-Rat	(M) 79.8 mg/kg and (F) 131.9 mg/kg (II)	*Bonnette, 2001a
Acute oral LD50-Mouse	(M) 155.0 mg/kg and (F) 214.1 mg/kg (II)	*Bonnette, 2001b
Acute dermal LD50-Rabbit	(M/F) >2,000 mg/kg (III)	*Bonnette, 2001c
Acute inhalation LC50-Rat	(M/F) 3.9 mg/L, 691 ppm (IV)	*Kirkpatrick, 2000 and 2002a
Eye irritation-Rabbit	Iritis, conjunctival irritation (I)	*Bonnette, 2001d
Dermal irritation-Rabbit	Erythema, edema (II)	*Bonnette, 2001e
Dermal sensitization-Guinea Pig	A sensitizer[b]	*Bonnette, 2001f
TM-42501 (98.10% MeI, 2.19% chloropicrin)		
Acute oral LD50-Rat	(M) 151 mg/kg and (F) 82 mg/kg (II)	*Bonnette, 2002a
Acute dermal LD50-Rat	(M/F) >2,000 mg/kg (III)	*Bonnette, 2002b
Acute inhalation LC50-Rat	(M) 2.85 mg/L (F) 4.13 mg/L (IV)	*Hilaski, 2002a
Eye irritation- Rabbit	Corneal opacity, iritis (I)	*Bonnette, 2002c
Dermal irritation-Rabbit	Erythema, edema (II)	*Bonnette, 2002d
Dermal sensitization-Guinea Pig	A sensitizer	*Bonnette, 2002e
TM-42503 (25% MeI, 75% chloropicrin)		
Acute oral LD50-Rat	(M) 119.7 mg/kg and (F) 77.4 mg/kg (II)	*Wilson, 2002a
Acute dermal LD50-Rat	3/10 dead at 2,000 mg/kg, highest dose tested (LD50 and toxicity category not determined)	Wilson, 2002b
Acute inhalation LC50-Rat	(M) 0.18 mg/L and (F) 0.24 mg/L (II)	*Hilaski, 2002b
Dermal irritation-Rabbit	Erythema, eschar, edema	*Wilson, 2002c
Dermal sensitization-Guinea Pig	A sensitizer	*Wilson, 2002d
Chloropicrin (Technical)		
Acute inhalation LC50-Rat (4 hours)	0.069 mg/L 0.097 mg/L 0.044 mg/L (nose only) (M) 0.11 mg/L and (F) 0.13 mg/L	Yoshida *et al*., 1987 Yoshida *et al*., 1991 Yoshida *et al*., 1991 Hoffman, 1999

a/ * indicates the study was acceptable according to FIFRA guidelines. Except noted, inhalation exposures were whole-body exposures. The lethal acute toxicity for chloropicrin is provided for comparison.

b/ The USEPA did not consider this formulation to be a sensitizer (MRID 45593809; USEPA, 2006a).

III.B.2. Rat - Inhalation

In an acute neurotoxicity study, Crl:CD(SD)IGS-BR rats (12/sex/group) were given MeI (purity 99.7%; reported analytical concentrations of 0, 27, 93, or 401 ppm, respectively; or 0, 0.15, 0.53, or 2.3 mg/L) by whole-body inhalation for 6 hours (Schaefer, 2002; Amendment in Schaefer, 2003). The equivalent dosages are: 0, 37, 126, and 544 mg/kg/day. One female at 401 ppm died on study day 6; no other mortalities occurred during the study. The mean body weight was reduced only in the 401-ppm males on day 7 and 14 (Table 6). Clinical observations were recorded daily for 14 days after exposure. The observation of dried red material around the nose or mouth occurred within 5 days after exposure, and the incidences were increased in the 93 (males only) and 401-ppm groups (Table 6 and 7). Decreased defecation was noted within 3 days after exposure at 93 ppm and 401 ppm, involving most or all the animals in the high dose group (Table 6 and 7).

Functional observational battery (FOB) testing was conducted before dosing ("pretest") and within 3 hours after treatment ("day 0"). Treatment-related effects were observed in both genders (Table 6 and 7). At 93 and 401 ppm, there was significant decrease in the body temperature. At these two doses, clonic convulsion as indicated by repetitive movement of mouth and jaws occurred in one male and female at 93 ppm, with higher incidences at 401 ppm. Other effects noted at 401 ppm included: sitting with head held low, eyelids closed or partially closed, salivation, hunched body, slight gait impairment, decreased rotarod performance. No treatment-related effects were observed when FOB assessments were conducted on days 7 and 14 post exposure. The NOEL was 27 ppm (37 mg/kg/day) based on these observations.

Test sessions of 60 minutes for motor activity assessments were conducted within 3 hours after MeI exposure. The activity was recorded in a measurement cage with 7 photobeam emitting/detecting units. Ambulatory motor activity was defined as the interruption of 2 or more consecutive beams while fine motor skills was defined as the interruption of the same beam (a stereotypic count). The total activity count was the sum of the ambulatory counts and the stereotypic counts. The study design and activity criteria most likely contributed to the unusually large data variability. In addition, combining the larger stereotypic counts to the ambulatory counts would dilute the latter which is a better representation of the actual movement from one location to another. The pretest data indicated no difference in baselines between test groups. However, the use of these pretest data in dose response analysis for delineating the NOEL is problematic because the control group on the day of test (day 0) showed a 20% reduction in ambulatory motor activity than the counts on pretest. Considerable variability between pretest and day 0 counts was also evident among individual animals within a given treatment group. For example, compared to the pre-test, 7 of 12 females at 27 ppm showed 37 to 81% reduced total motor activity on day 0 while the remaining 5 females had 113-177% increase. Thus, the evaluation of MeI effects on motor activity can only be based on the ambulatory activity data on day 0. These data analyses criteria do not impact conclusions about the effects at 93 and 401 ppm since they were at or above 75% inhibition. It is noted that in spite of the data variability, the reduction of ambulatory motor activity at 27 ppm was statistically significant compared to the same day controls (Table 7).

The BMD analysis for both sets of male and female ambulatory motor activity data necessitates the exclusion of the high dose response in order to obtain an adequate model fit within the

capacity of the USEPA BMDS (version 2.0). Below are the results of BMD analysis from linear model with homogeneous variance:

Gender	MeI ppm							
	ED_{05}	**LED_{05}**	**ED_{10}**	**LED_{10}**	**$ED_{0.61\sigma}$**	**$LED_{0.61\sigma}$**	**$ED_{0.36\sigma}$**	**$LED_{0.36\sigma}$**
Male	6.0	5.5	12.0	11.1	33.4	24.2	19.7	14.3
Female	5.5	5.3	11.0	10.5	29.6	21.8	17.5	12.8

The range of BMD at 0.36σ BMR in females is lower than the 27 ppm at which statistically significant reduction of ambulatory was reported. Thus, the $LED_{0.36\sigma}$ of 12.8 ppm can be used as the POD for acute neurotoxicity effect (Section **IV.A.2.c.**). In general, a 20% change in motor activity can be statistically identified in well-conducted FOB studies. The average motor activity at 12.8 ppm is approximately 12% reduction over the controls. No treatment-related effects were observed when motor activity assessments were conducted on days 7 and 14 post exposure.

After 15 days of observation, microscopic examination of central and peripheral nervous system tissues was limited to the control and high dose groups, and showed no treatment-related effects. These tissues included the brain (13 regions), spinal cord, trigeminal ganglia/nerves, lumbar and cervical dorsal root ganglia/fibers, lumbar and cervical ventral root ganglia/fibers, eyes, nerves (optic, sciatic, tibial, peroneal, and sural), and gastrocnemius muscle. However, the SRC questioned the conclusion that MeI did not cause neuropathology because the neuropathological examination was qualitative and lacked scientific rigor (full comments in **Appendix D** of **Volume IV Part 1-A**). This study was considered acceptable to DPR according to FIFRA guidelines.

The USEPA established a systemic NOAEL of 27 ppm based on FOB findings (clonic convulsions in 1/12 females, decreased body temperature), and decreased motor activity at 93 ppm (MRID 45593817; USEPA, 2006a).

Table 6. Clinical signs and functional observational battery results in male rats exposed to MeI by inhalation for 6 hours.[a]

Effects	Doses			
ppm	0	27	93	401
mg/kg/day	0	37	126	544
Mean body weight (g)				
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	244±15.8**
Day 14	314±31.2	316±31.4	307±26.3	290±15.6*
Clinical signs[b]				
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
FOB parameters- Observations on Day 0, within 3 hours after treatment				
Physiological Observations				
Mean body temperature (°C)	38.3±0.23	38.3±0.28	37.2±0.74**	34.2±1.07**
Home Cage Observations				
Sitting, head held low	0/12**	0/12	0/12	4/12*
Convulsions, clonic	0/12**	0/12	1/12	3/12
Eyelids not wide open	0/12	0/12	0/12	4/12
Handling Observations				
Salivation	0/12**	0/12	0/12	6/12**
Open-field Observations				
Gait, hunched body	0/12**	0/12	0/12	4/12*
Convulsions, clonic	0/12**	0/12	0/12	3/12
Neuromuscular Observations				
Rotarod performance (seconds, mean)	96.4	94.1	107.7	47.5**
Motor Activity Assessment (mean activity counts in a 60-minute test session)				
Total motor activity counts				
Pretest	969±513	809±438	777±396	1015±523
Day 0	800±323	637±288	201±78**	102±65**
Group Day 0/Control Day 0	800/800(100%)	637/800(80%)	201/800(25%)	102/ 800(13%)
Group Day 0/Group Pretest	800/989(83%)	637/809(79%)	201/777(26%)	102/1,015(10%)
Mean ambulatory motor activity counts (n=11 for control, n=12 for treated groups)				
Pretest	324±220	247±151	249±140	313±197
Day 0	260±116	194±102	58±32**	8±8**
Group Day 0/Control Day 0	260/260(100%)	194/260(75%)	58/260(22%)	8/260(3%)
Group Day 0/Group Pretest	260/324(80%)	194/247(79%)	58/249(23%)	8/313(3%)

a/ Data from Schaefer (2002). *, ** for statistical significance at $p<0.05$ and <0.01, respectively. Significance in trend by the Cochran-Armitage Trend test is denoted at the control value.

b/ # of occurrences/# of affected animals. First incidents for dried materials and reduced defecation were 3 to 5 days, and 1-3 days, respectively, after exposure.

Table 7. Clinical signs and functional observational battery results in female rats exposed to MeI by inhalation for 6 hours.[a]

Effects	Doses			
ppm	0	27	93	401
mg/kg/day	0	37	126	544
Mortality	0/12	0/12	0/12	1/12
Clinical signs[b]				
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
FOB parameters- Observations on Day 0, within 3 hours after treatment				
Physiological Observations				
Mean body temperature (°C)	38.4±0.33	38.3±0.32	37.1±0.67**	34.0±0.95**
Home Cage Observations				
Posture- sitting, head held low	0/12**	0/12	0/12	8/12**
Convulsions, clonic	0/12**	0/12	0/12	4/12*
Eyelids not wide open	0/12	0/12	0/12	7/12*
Handling Observations				
Salivation	0/12**	0/12	0/12	7/12**
Open-field Observations				
Gait, hunched body	0/12**	0/12	0/12	11/12**
Convulsions, clonic	0/12**	0/12	1/12	7/12**
Gait, slight but definite impairment	0/12**	0/12	0/12	7/12**
Neuromuscular Observations				
Rotarod performance (seconds, mean)	102.9	101.9	96.1	58.5*
Motor Activity Assessment (mean activity counts in a 60-minute test session)				
Total motor activity counts				
Pretest	1,038±867	831±265	1,033±345	855±349
Day 0	1,059±282	776±446*	204±45**	156±165**
Group Day 0/Control Day 0	1,059/1,059(100%)	776/1,059(73%)	204/1,059(19%)	156/1,059(15%)
Group Day 0/Group Pretest	1,059/1,038(102%)	776/831(93%)	204/1,033(20%)	156/ 855(18%)
Mean ambulatory motor activity counts (n=11 for control, n=12 for treated groups)				
Pretest	335±302	253±112	347±145	283±148
Day 0	393±99	248±159*	57±23**	18±19**
Group Day 0/Control Day 0	393/393(100%)	248/393(63%)	57/393(15%)	18/393(5%)
Group Day 0/Group Pretest	393/335(182%)	248/253(98%)	57/347(16%)	18/283(6%)

a/ Data from Schaefer (2002). *, ** for statistical significance at $p<0.05$ and <0.01, respectively. Significance in trend by the Cochran-Armitage Trend test is denoted at the control value.

b/ # of occurrences/# of affected animals. First incidents of dried materials and reduced defecation were 1-2 days after exposure.

The following study was conducted to generate data for PBPK modeling of MeI toxicity in the rat. Male Sprague-Dawley rats were exposed by whole-body inhalation to MeI (purity >99.8%; 0, 25, or 100 ppm) using two experimental protocols in a mode of action (MOA) study (Himmelstein, 2004). The results are published as separate studies: experiment #1 in DeLorme *et al.,* 2009; experiment #2 in Himmelstein *et al.,* 2009. No deaths resulted from any exposures. In Experiment #1 (respiratory function, serum iodide, and hemoglobin adduct), four males per group were exposed to MeI for one 6-hour exposure period (result also published in). The mean breathing frequency, tidal volume, and minute volume were similar for all three groups. The breathing frequencies (breaths per minute) were 195.6 ± 30.3, 191.0 ± 25.4, and 191.4 ± 29.3 for 0, 25, and 100 ppm, respectively. The tidal volumes were 1.5±0.1, 1.8±0.3, and 1.4±0.2 mL, respectively. The minute volumes (mL/min) were 223.8 ± 24.0, 271.9 ± 25.9, and 209.0 ± 32.9, respectively. The cause for the significant ($p<0.05$) minute volume changes (21% increase at 25 ppm and 7% decrease at 100 ppm) is unknown; irritancy was suggested as a possibility (DeLorme *et al*., 2009). Based on these values and average body weight (199 g to 211 g) for each group, the breathing rates were 1.53, 1.89, and 1.51 m^3/kg/day, for 0, 25, and 100 ppm, respectively. Note that these rates are higher than the Medical Toxicology default factor of 0.96 m^3/kg/day for all adult rats. Using the breathing rates determined in this experiment, the equivalent exposure concentrations were 0, 67, and 213 mg/kg/day for 0, 25, and 100 ppm, respectively. The data for serum iodide and adduct are discussed together with the two day experiment.

In Experiment #2, rats (3/time point) were exposed to MeI (0, 25 or 100 ppm) for 6 hours per day for two consecutive days. From 1 to 48 hours after the initiation of the first exposure, GSH was measured in the serum, liver, kidneys, and nasal olfactory and nasal respiratory epithelium; iodide was only measured in serum. Additional animals (10/group) with the exposure were sacrificed at 48 hours post study initiation to study MeI effect on hematology, clinical chemistry (including thyroid-associated hormone), hemoglobin adduct, and liver UDP-glucuronyl-transferase (UDPGT) activity. No histopathology was performed in any tissues.

At 25 ppm MeI, maximal GSH depletion (40 to 50% of control) was measured in the nasal epithelium, and about 30% in the other tissues, 3 to 6 hours after initiation of exposure (Table 8). For this time period, 100 ppm exposure caused greater GSH depletion, as the nasal epithelium GSH levels were only 15% (respiratory epithelium) to 25% (olfactory epithelium) of controls. For other tissues at 100 ppm, the additional GSH depletion was only about 10% more than those for 25 ppm. Depletion of the GSH levels in nasal epithelia was less apparent during the 2nd day of exposure than on the initial exposure, suggesting some compensatory response.

Serum iodide levels increased with exposure time (1 to 6 hours), and declined immediately after exposure (Table 8). Iodide was less than 10% peak level when measured 18 hours post exposure. The iodide levels for the 100-ppm group were 2- to 4-fold higher levels than the 25-ppm group.

Benchmark dose analysis of the GSH data (see footnote b of Table 8) for exposure time that caused maximal depletion was conducted. The results, using the continuous linear model, are shown in the following summary:

Endpoints	**MeI ppm**					
	ED_{10}	**LED_{10}**	**$ED_{0.61\sigma}$**	**$LED_{0.61\sigma}$**	**$ED_{0.36\sigma}$**	**$LED_{0.36\sigma}$**
GSH depletion, blood 3 hours	35.1	28.6	34.3	19.4	ND	ND
GSH depletion, OE 3 hours	13.7	11.7	10.2	7.0	ND	ND

Table 8. Glutathione and iodide concentrations in tissues of male rats exposed to MeI by inhalation.[a]

Hours	GSH Concentrations as % of Control					
	Blood		Olfactory Epithelium		Respiratory Epithelium	
	25 ppm	100 ppm	25 ppm	100 ppm	25 ppm	100 ppm
0 (1st dose)	100.0 ± 15.3	100.0 ± 15.3	100.0 ± 21.9	100.0 ± 21.9	100.0 ± 25.7	100.0 ± 12.5
1	101.7 ± 8.5	89.0 ± 7.0	84.8 ± 30.6	52.4 ± 18.3	90.6 ± 13.0	68.6 ± 3.3
3[b]	75.6 ± 8.5	62.1 ± 5.7	63.4 ± 10.8	27.6 ± 9.1	48.9 ± 8.0	17.2 ± 2.2
6	74.7 ± 11.7	81.6 ± 14.7	65.1 ± 14.0	24.2 ± 5.4	52.0 ± 11.4	14.3 ± 3.9
9[b]	73.8 ± 10.0	83.1 ± 12.5	85.6 ± 21.0	64.1 ± 25.3	86.8 ± 27.3	57.0 ± 18.0
24(2nd dose)	103.3 ± 13.1	106.3 ± 11.3	86.9 ± 26.8	114.3 ± 36.1	120.0 ± 29.4	157.8 ± 35.6
25	93.3 ± 16.7	87.2 ± 16.4	102.5 ± 13.7	92.3 ± 10.3	96.6 ± 12.9	93.1 ± 27.0
27	87.5 ± 9.6	65.3 ± 8.3	63.0 ± 13.5	55.5 ± 18.4	51.2 ± 15.9	54.6 ± 16.6
30	74.1 ± 19.3	64.2 ± 5.7	57.8 ± 14.3	44.4 ± 14.3	57.1 ± 14.6	43.2 ± 10.9
33	73.4 ± 15.5	76.2 ± 16.8	69.2 ± 13.4	74.6 ± 21.8	70.8 ± 26.5	77.4 ± 23.8
48	108.0 ± 16.5	114.7 ± 31.6	125.4 ± 23.0	143.6 ± 39.3	95.5 ± 33.0	129.1 ± 40.1
	Kidney		Liver			
0 (1st dose)	100.0 ± 2.4	100.0 ± 2.4	100.0 ± 12.5	100.0 ± 12.5		
1	89.4 ± 10.0	85.1 ± 9.1	91.7 ± 14.1	90.8 ± 15.8		
3	77.3 ± 13.9	66.3 ± 7.0	65.2 ± 18.2	63.1 ± 18.4		
6	95.6 ± 12.6	58.3 ± 10.9	106.5 ± 16.2	67.9 ± 20.5		
9	91.0 ± 18.5	91.8 ± 10.2	79.2 ± 20.5	53.3 ± 18.0		
24(2nd dose)	95.4 ± 14.4	97.9 ± 13.2	107.7 ± 16.3	117.5 ± 14.5		
25	88.4 ± 10.6	84.6 ± 11.2	112.1 ± 9.4	96.5 ± 39.0		
27	88.0 ± 8.1	71.6 ± 7.0	85.5 ± 19.6	96.5 ± 12.1		
30	77.0 ± 9.8	61.6 ± 8.0	86.1 ± 14.8	69.3 ± 14.2		
33	98.8 ± 9.2	91.8 ± 11.4	108.0 ± 26.9	82.6 ± 20.9		
48	83.6 ± 11.6	96.1 ± 12.8	111.3 ± 23.1	107.9 ± 22.4		

Hours	Mean Inorganic Serum Iodide (ng/mL)		
	0 ppm	25 ppm	100 ppm
0 (1st dose)	17	NA	NA
1	17	5,070 ± 721	22,900 ± 1,620
3	19	9,510 ± 3,800	60,300 ± 2,860
6	22	25,600 ± 1,940	53,800 ± 4,480
9	39	18,400 ± 1,550	52,500 ± 8,230
24(2nd dose)	19	1,260 ± 83.9	8,170 ± 1,850
25	14	5,960 ± 576	27,200 ± 13,700
27	14	10,800 ± 1,100	55,200 ± 3,050
30	4.1	34,100 ± 8,170	83,200 ± 7,840
33	13	24,700 ± 1,310	58,300 ± 6,520
48	14	742 ± 141	4,500 ± 396

a/ Data from Himmelstein (2004). The animals were exposed to MeI for 6 hours. Samples were taken during and after exposures. "0" hour=at the initiation of 1st day exposure. "24" hour=at the initiation of 2nd days exposure.

b/ At 3 hours after exposure, the blood GSH levels (n=3) were 0.931±0.084 mM (0 ppm), 0.703±0.047 mM (25 ppm), and 0.578±0.010 mM (100 ppm). At 3 hours after exposure, the olfactory epithelium GSH levels (n=3) were 2.309±0.204 mM (0 ppm), 1.463±0.213 mM (25 ppm), and 0.638±203 mM (100 ppm).

There was no treatment-related effect upon the hematology parameters. In the clinical chemistry evaluation, significant changes in three enzymes (aspartate aminotransferase, AST; sorbital dehydrogenase, SDH; gamma glutamyltransferase, GGT) and calcium were measured, with no clear dose response relationship (Table 9). Dose-related changes were evident with increased serum cholesterol, as well as high density and low density lipoproteins (HDL and LDL); decreased triglycerides; increased TSH (thyroid stimulating hormone); and decreased hormone levels (triiodothyronine, T3; thyroxine, T4; and reverse T3, rT3). UDPGT activity was unchanged, suggesting that thyroid hormone reductions were not due to enhanced T4 metabolism. Methylcysteine globin adducts were significantly increased only at 100 ppm, about 2-fold higher than the control for either 1 or 2 days of exposure. The adduct levels at 25 ppm were similar to controls. All the experiments in this study were considered supplemental information to DPR.

Table 9. Clinical chemistry in male rats exposed to MeI by inhalation.[a]

Parameters	Doses (ppm)		
	0	**25**	**100**
AST (unit/L)	71 ± 5	68 ± 7#	67 ± 17#
SDH (unit/L)	14.1 ± 2.3	10.0 ± 1.5#	11.1 ± 5.9#
GGT (unit/L)	0 ± 0	0 ± 1	1 ± 0#
Calcium (mg/dL)	10.7 ± 0.2	10.8 ± 0.3	11.0 ± 0.3*
Cholesterol (mg/dL)	83 ± 10	99 ± 9*	134 ± 24*
HDL (mg/dL)	30 ± 3	36 ± 3*	44 ± 6*
LDL (mg/dL)	53 ± 8	63 ± 7*	90 ± 19*
Triglycerides (mg/dL)	69 ± 11	49 ± 14*	33 ± 8*
TSH (ng/mL)	5.9 ± 1.4	10.9 ± 7.7#	21.1 ± 11.2#
T3 (ng/dL)	74.1 ± 11.4	65.9 ± 9.2	50.8 ±14.4#
T4 (µg/dL)	3.4 ± 0.5	3.1 ± 0.8	2.1 ± 0.9#
rT3 (mg/mL)	0.067 ± 0.049	0.119 ± 0.024	0.039 ± 0.037
UDPGT (nmol/min/mg)	16.1 ± 3.1	17.5 ± 2.0	17.8 ± 4.8
S-Methylcysteine (nmol/g globin)			
6 hours x 1 day	147.5 ± 13.1	220.0 ± 21.1	281.4 ± 9.0**
6 hours x 2 day	161.2 ± 23.8	201.6 ± 34.3	345.7 ± 50.4**

a/ Data from Himmelstein (2004). Clinical values with n=10 (except n=9 for rT3). *,** for statistical significance at $p<0.05$ and <0.01, respectively, by Dunnett/Tamhane-Dunnett test. # for statistical significance at $p<0.05$ by Dunn's test.

Crl:CD(SD)IGS-BR rats (5/sex/group) were exposed to MeI (purity 99.8%; reported analytical concentrations of 581, 710, 797 and 1,189 ppm, respectively) for 4 hours by whole-body inhalation exposure (Kirkpatrick, 2000 and 2002a). The equivalent dosages are: 525, 642, 720, and 1,075 mg/kg/day. Mortalities occurred as follows- males: 0/5, 4/5, 4/5, 5/5, respectively; females: 0/5, 4/5, 4/5, 5/5, respectively, for low to high doses. Clinical signs observed during or after exposure included hypoactivity, unkempt appearance, ataxia, labored respiration, rales, gasping, dried red or tan material around the mouth and/or nose, mucoid feces, wet or dried yellow material around urogenital area, decreased defecation, and decreased urination. Necropsy on the dead animals revealed distended or reddened stomach and distended intestine in some animals. Necropsy on the survivors showed no internal abnormalities. The LC50 (M/F) was 3.9 mg/L with the Toxicity Category of IV. The acute NOEL was < 581 ppm (< 525 mg/kg/day, <3.34 mg/L) for clinical signs and mortality at all doses. This study was considered acceptable to DPR according to FIFRA guidelines. The USEPA established a LC50 at 4 mg/L for both genders and a Toxicity Category of IV (MRID 45593806; USEPA, 2006a).

Two published studies examined the nasal epithelium damage with MeI exposure (Reed *et al.*, 1995 and Chamberlain *et al*., 1998a) (Table 10). These will be considered in the discussion of PBPK modeling for nasal toxicity in the rat. In Reed *et al.* (1995), male Wistar-derived albino rats were exposed to 0 or 100 ppm MeI by nose-only inhalation for 0.5 to 6 hours and sacrificed either immediately, or 6 to 24 hours afterward for examination of the nasal tissue. After 0.5 hour of exposure, the epithelium was described to show undulated appearance. With 1 hour of exposure, histology showed vacuoles in the sustentacular cell cytoplasm and pyknotic nuclei in the sensory cells, when the tissue was examined 24 hours later. Olfactory epithelial degeneration (OED) was noted as mild after 2 hours of exposure, and increased to moderate (4 hours) and marked (6 hours) with additional exposure duration. When the olfactory epithelium for the 3 hour and 6 hour groups was examined 2 weeks after exposure, it appeared to be completely regenerated, but with small foci of disorganized cells with pseudo-gland formation and reduction in apical cytoplasm. Methyl bromide (200 ppm for 6 hours) treated rats, as the positive control, showed similar damage to the olfactory epithelium as the 100-ppm (6 hours) MeI rats. The authors concluded that MeI appeared to be more toxic than methyl bromide perhaps due to the greater inherent chemical reactivity of iodide, compared to bromide.

In Chamberlain *et al.* (1998a), male Alpk:APfsD (Wistar-derived) rats (5 animals/group) were exposed to 0 or 100 ppm MeI by nose-only inhalation up to 6 hours and sacrificed immediately after exposure to study the relationship between GSH conjugation and tissue specific toxicity. Additional groups were pretreated with phorone and buthionine sulphoximine (GSH depletor), isopropyl ester of GSH (exogenous GSH), and cobalt protoporphyrin IX (cytochrome P-450 depletor). Methyl iodide treatment resulted in the depletion of non-protein sulfhydryls in tissues examined. The kidney and the nasal epithelium showed higher rates of depletion than other tissues. For kidneys, the GSH level was depleted to 20% of control within 15 minutes of exposure. The GSH levels in the respiratory and olfactory epithelium were below the detection limit, and 40% of control, respectively, by 1 hour after exposure. The GSH depletion was more gradual in the liver and brain (cerebellum and forebrain), and was 60%, and 30-40% of control, respectively, with 6 hours of exposure.

When animals were exposed to MeI, degeneration was noted only for the olfactory epithelium, and not the respiratory epithelium or other tissues (lung, liver, kidney, or brain). The degeneration was slight after 2 hours, but increased in severity (marked degeneration with

various degree of exfoliation) after 4 hours of exposures. Depletion of GSH with phorone and buthionine sulphoximine resulted in enhanced MeI toxicity. These animals showed markedly decreased activity with diarrhea, tremors and convulsions, and some displayed head and paw flicking, splayed gait and lacrimation. On the other hand, administration of isopropyl ester of GSH resulted in reduced severity (from marked to slight) in the damage to the nasal tissue by MeI. The depletion of cytochrome P-450 did not lessen the toxicity of MeI. Based on these results, the authors proposed that the selectivity of olfactory epithelium for MeI toxicity was due to extensive GSH depletion and slower GSH turnover rates. Maintenance of GSH level with the addition of exogenous GSH had a protective effect.

Table 10. Histological examination of rat nasal tissues after exposure to MeI by inhalation.

Exposure Time	**100 ppm (Reed *et al.*, 1995)**		**100 ppm (Chamberlain *et al.*, 1998a)**
	Killed 0-6 hours after exposure	**Killed 24 hours after exposure**	**Killed immediately after exposure**
0.5 hour	Not conducted	Undulated appearance	NP-SH as % of control OE 80% lung 50% RE 40%
1 hour	Not conducted	Vacuoles in sustentacular cell cytoplasm and pyknotic nuclei in sensory cells in OE (Fig 7 in report)	NP-SH as % of control OE, RE, lung 40%
2 hours	Not conducted	Minimal degeneration: exfoliation of OE with only the basal cell remained intact (Fig. 3, 5 in report)	Slight degeneration of OE
3 hours	Killed immediately after exposure: Vacuoles in sustentacular cell cytoplasm, pyknotic nuclei in sensory cells in OE, undulating appearance of OE	Slight degeneration: tags of degenerated cells attached to damaged OE (Fig 4 in report)	Not conducted
4 hours	Not conducted	Moderate degeneration of OE	Marked degeneration of OE
6 hours	Killed 0 to 6 hours after exposure: Degeneration of the OE, pronounced undulating appearance of OE (Fig. 8), epithelial necrosis	Marked degeneration of OE and transitional epithelium (Fig. 6 in report)	NP-SH lower than for 1 hour

Abbreviations: OE=olfactory epithelium, NP-SH= non-protein sulfhydryl, RE=respiratory epithelium

III.B.3. Rat - Oral

Sprague-Dawley SD rats (5/sex/group) were given MeI (purity 99.7%; 0 to 350 mg/kg) as a single gavage dose (Bonnette, 2001a). Mortalities in the males were: 0/5, 0/5, 5/5, 5/5, 5/5, respectively, for 0, 50, 75, 100, and 250 mg/kg. Mortalities in the females were: 0/5, 1/5, 4/5, 4/5, 5/5, respectively, for 0, 50, 100, 250, and 350 mg/kg. At 50 mg/kg, congested breathing was observed in 2 females and slight fecal staining and dark material around the nose were observed in 1 male. At higher doses, clinical signs observed included decreased activity; wobbly gait; breathing difficulties; prostration; tremors; salivation; piloerection; hunched posture; cool to the touch; decreased food consumption; irregular stools; urine staining; fecal staining; dark material around eye(s), nose, and/or mouth; pale skin; and eye problems (partially closed eyelids, dilated pupils, clear ocular discharge). Necropsy on the mortalities revealed abnormal contents in the GI tract, thickened stomach, dark red lungs, and blackish purple liver. The LD50 for males was 79.84 mg/kg and for females was 131.98 mg/kg, and Toxicity Category II. The acute NOEL was <50 mg/kg based on clinical signs observed in all treated groups. This study was considered acceptable to DPR according to FIFRA guidelines. The LD50 values and Toxicity Category are the same as those established by the USEPA (MRID 45593803; USEPA, 2006a).

Crl:CD(SD)IGS-BR female rats (5/group) were dosed by gavage with 100, 125 or 140 mg/kg of either microencapsulated (ME) MeI (MeI load: 2.35%, dose reported as equivalent MeI content) or MeI technical (purity 99.7%, Non-ME) in corn oil (Harriman, 2003a). For the ME MeI group, 2 died in the 100 mg/kg group and 4 each died in the 125 and 140 mg/kg groups. For the Non-ME MeI group, one died in the 125 mg/kg group due to an intubation error and 3 died in the 140 mg/kg group. Death occurred from day 1 to day 7 post-dose. Clinical signs were observed in all groups and included rales, labored respiration, abnormal excreta, hypothermia, clear or red material in facial area, hypoactivity and/or dehydration. These signs were cleared by day 7 post exposure. Lower body weight gains were noted for both 140 mg/kg treatment groups. Necropsy of dead animals showed dark red intestinal contents, reddened stomach mucosa, dark red areas in the stomach, and white and yellow areas of the liver. These findings were noted more frequently for the ME MeI group. Among the survivors, stomach adhesions were noted for four animals (3 at 125 mg/kg, and 1 at 140 mg/kg) in the ME MeI group. The LD50s were 105 mg/kg for ME MeI, and 139 mg/kg for Non-ME MeI. The acute NOEL for either form of MeI was <100 mg/kg. The study was considered supplemental information to DPR.

III.B.4. Mouse - Oral

CD-1 mice (5/sex/dose) were given MeI (purity 99.7%; 100, 175, 200, 225, and 250 mg/kg) as a single gavage dose (Bonnette, 2001b). Mortalities occurred as follows- males: 0/5, 2/5, 5/5, 5/5, 5/5, respectively; females: 0/5, 0/5, 1/5, 3/5, 5/5, respectively, for low to high doses. Clinical signs were observed at >100 mg/kg and included decreased activity, salivation, distended abdomen, wobbly gait, breathing difficulties (described as slow, labored, or shallow), tremors, urine staining, fecal staining, few feces, soft stools, hunched posture, piloerection, rough coat, eye problems (dilated, eyelids partially closed, or clear discharge), decreased food consumption, cool to touch, skin blue in color (entire body), and distended abdomen. Necropsy on the dead animals showed abnormal contents in the small intestine and stomach with reddened glandular mucosa. Necropsy on the survivors revealed thickened nonglandular portion of the stomach in some animals. LD50 for males was 155.0 mg/kg and for females was 214.1 mg/kg; the combined LD50 (M/F) was 179.2 mg/kg with the Toxicity Category II. The acute NOEL

(M/F) was 100 mg/kg based on clinical signs at 175 mg/kg and higher doses. This study was considered acceptable to DPR according to FIFRA guidelines. The USEPA established the same LD50s (MRID 45593804; USEPA, 2006a).

III.B.5. Rabbit - Dermal

The clipped skin of New Zealand white rabbits (5/sex/dose) was exposed to MeI (purity 99.7%; 500 and 2,000 mg/kg) for 24 hours using an occlusive dressing (Bonnette, 2001c). No mortalities occurred. Clinical signs in both treated groups included mucoid stools, soft stools, few feces, small (in size) feces, decreased food consumption, labored breathing, and dark material around mouth and/or nose. Erythema (grade 1-3), edema (grade 1-2), desquamation, and eschar were observed at the test sites. Signs of skin irritation persisted at Day 14. Necropsy revealed no treatment-related internal abnormalities. The LD50 (M/F) was > 2,000 mg/kg and a Toxicity Category III. The acute dermal NOEL was <500 mg/kg for clinical signs. This study was considered acceptable to DPR according to FIFRA guidelines. Same LD50 and Toxicity Category are established by the USEPA (MRID 45593805; USEPA, 2006a).

III.B.6. Rabbit - Subcutaneous

In the tissue distribution study by Hasegawa *et al*. (1971), MeI reduced phosphatidylserine and phosphatidylcholine, but not phosphatidylethanolamine or sphingomyelin, in treated rabbits (57 mg/kg by as single subcutaneous injection). These rabbits were reported to show abnormal gait. The blood showed increased turbidity indicating elevated total lipid in the serum. Fractional analysis of the lipid showed increased phospholipid, cholesterol, free fatty acid, estercholesterol and triglyceride. The β-lipoprotein, not α-lipoprotein, level was also increased.

Matsui *et al*. (1982a) showed that the hyperlipidemia induced by MeI (57 mg/kg by subcutaneous injection for two days) in rabbits were due to an increased lipid synthesis, and not reduced clearance of lipid from the plasma. The increase in triglyceride production was hypothesized to be a consequence of increased insulin resistance and hyperinsulinemia. Another report by Matsui *et al*. (1982b) showed that MeI-treated rabbits (57 mg/kg by subcutaneous injection for two days) were resistant to insulin with elevated serum glucose and glucagon levels.

III.B.7. Studies with TM-42501 (a combination of MeI and chloropicrin in 98:2 ratio; purity: MeI = 98.10%, chloropicrin = 2.19%).

Hsd: Sprague-Dawley SD rats were given a single gavage dose of TM-42501 (as a 10% w/v concentration in corn oil for the dose level below 91 mg/kg) using the up and down procedure: 70 mg/kg (1 female), 91 mg/kg (3 females), 118 mg/kg (1 male, 2 females), 154 mg/kg (2 males, 1 female), 200 mg/kg (2 males, 1 female), and 260 mg/kg (1 male) (Bonnette, 2002a). Mortalities occurred as follows- males: 0/1, 2/2, 1/2, 1/1, respectively; females: 0/1, 2/3, 2/2, 1/1, 1/1, respectively, for low to high doses. At the lowest dose tested, the 70 mg/kg female showed few feces and dark material around eyes. At higher doses, clinical signs observed included decreased activity, breathing difficulties (slow, shallow, congested, or labored; gasping), salivation, cool to the touch, eye problems (partially closed eyelids, dilated pupils, and ocular discharge), nasal discharge, and no or few feces. Necropsy on the dead animals showed abnormal contents in the GI tract and reddened lungs. Necropsy on the surviving animals

revealed body fat depletion in the 118 mg/kg male, but no abnormalities in the other 3 survivors. The LD50s were 151 mg/kg for males and 82 mg/kg for females with the Toxicity Category II. This study was considered acceptable to DPR according to FIFRA guidelines.

The clipped skin of Hsd:Sprague-Dawley SD rats (5/sex/dose) was exposed to TM-42501 (2000 mg/kg) for 24 hours using an occlusive dressing (Bonnette, 2002b). No animals died. Clinical signs observed included few feces and dark material around eyes, mouth, and/or nose. Erythema, edema, eschar, and desquamation were observed at the test site in all animals, and signs of irritation persisted at day 14. Necropsy revealed no treatment-related internal abnormalities. LD50 for both genders was > 2000 mg/kg with a Toxicity Category III. This study was considered acceptable to DPR according to FIFRA guidelines.

Sprague-Dawley Crl:CD(SD)IGS-BR rats (5/sex/dose) were exposed to TM-42501 by nose-only exposure for 4 hours (Hilaski, 2002a). The reported analytical concentrations of MeI:chloropicrin were 104:3 ppm, 310:7 ppm, 478:11 ppm, 689:40 ppm, and 986:50 ppm. The combined concentrations[9] were 0.59, 1.75, 2.70, 3.89, and 5.57 mg/L, respectively. Mortalities occurred as follows- males: 0/5, 0/5, 2/5, 5/5, 5/5, respectively; females: 0/5, 0/5, 0/5, 3/5, 5/5, respectively, for low to high doses. At 104 ppm MeI: 3 ppm chloropicrin, all animals appeared normal during exposure. However, clinical signs were reported 2 hours to 6 days post exposure and included skin cold to touch, rapid breathing, few/absent feces, and vocalization. At higher concentrations, clinical signs were reported during and post-exposure. They appeared in a dose-related manner and included skin cold to touch, no or few feces, soft feces, decreased activity, hunched posture, abnormal breathing, salivation, red material around nose and/or mouth, unkempt appearance, hair discolored (yellow), vocalization, and aggressive behavior. Necropsy revealed red, discolored lungs in some of the mortalities and in some of the survivors. The LC50 was 2.85 mg/L for males and 4.13 mg/L for females. The combined LC50 (M/F) was 3.55 (2.98-4.18) mg/L with a Toxicity Category IV. This study was considered acceptable to DPR according to FIFRA guidelines.

III.B.8. Studies with TM-42503 (a combination of MeI and chloropicrin in 25:75 ratio; purity: MeI = 25.15%, chloropicrin = 76.75%).

Hsd:Sprague Dawley SD rats were given a single gavage dose of TM-42503 (Wilson, 2002a). The dose levels (mg/kg) were based on the up and down procedure: 68 (1 males, 3 females), 88 (1 male, 3 females), 114 (1 male, 1 female), 148 (1 male, 1 female), 192 (1 male, 1 female), 250 (2 males, 1 female), 325 (1 male), and 500 (1 male, 1 female). Mortalities occurred at > 68 mg/kg and involved one 250 mg/kg female, and all animals in the higher doses. At the lowest dose tested, 68 mg/kg, the one male appeared normal while the females showed few or no feces, urinary stain, and dark material around the mouth and nose. For animals at higher doses, clinical signs observed included decreased activity, breathing difficulties (described as slow, shallow, congested, or labored; rales; gasping), salivation, cool to the touch, hunched posture, dark material around nose/mouth and/or eyes, partially closed eyelids, rough coat, piloerection, ocular discharge, nasal discharge, soft feces, and no or few feces. Necropsy on the dead animals revealed abnormal contents in the GI tract and reddened lungs. Surviving animals revealed thickened non-glandular portion of the stomach in the male and one female at 68 mg/kg, but no abnormalities in the other 3 survivors. The LD50s were 119.7 mg/kg for males and 77.4 mg/kg

[9] Combined concentration in mg/L= ppm iodomethane x 5.65/1000 + ppm chloropicrin x 6.70/1000.

for females with Toxicity Category II. This study was considered acceptable to DPR according to FIFRA guidelines.

The clipped skin of Hsd: Sprague Dawley SD rats was exposed to TM-42503 at the following dose levels (mg/kg): 500 (1 male, 5 females); 1,000 (1 male, 1 female); and 2,000 (5 males, 5 females) mg/kg for 24 hours using an occlusive dressing (Wilson, 2002b). Mortalities occurred as follows- males: 0/1, 0/1, 1/5, respectively; females: 0/5, 0/1, 2/5, respectively, for the low to high doses. For all dose groups, clinical signs observed included few feces and dark material around eyes, mouth, and/or nose. Prior to death, observed signs also included body cool to touch and decreased activity. Erythema, edema, eschar, and desquamation were observed at the test site in all surviving test animals, with signs of irritation persisted at day 14. Necropsy on the dead animals revealed abnormal contents in the small intestine, reddened mucosa of the jejunum, and subcutaneous edema at the test site. Necropsy on the survivors revealed no treatment-related abnormalities. The LD50 and Toxicity Category were not determined. This study was considered unacceptable and not upgradable to DPR according to FIFRA guidelines because only 1 female animal was used at 1,000 mg/kg despite the fact that 2 animals died at the 2000 mg/kg dose level (the limit dose).

Sprague-Dawley Crl:CD(SD)IGS-BR rats (5/sex/dose) were exposed to TM-42503 by nose-only inhalation exposure for 4 hours (Hilaski, 2002b). The reported analytical concentrations as MeI:chloropicrin were 3:20 ppm, 7:28 ppm, 14:47 ppm, and 23:69 ppm. The calculated combined doses were 0.15, 0.22, 0.39, and 0.59 mg/L. Mortalities were: 0/5, 5/5, 5/5, 5/5 for males, and 0/5, 1/5, 5/5, 5/5 for females, respectively, from low to high doses. At 3 ppm MeI: 20 ppm chloropicrin, breathing difficulty was noted for both genders. At higher concentrations, clinical signs appeared in a dose-related manner and included tremors, slightly impaired gait, skin cold to touch, fecal changes, decreased activity, hunched posture, breathing problems, salivation, red material around nose and/or mouth, unkempt appearance, hair discolored (red), vocalization, and aggressive behavior. Necropsy revealed red, discolored lungs in the mortalities and in 2 surviving males at 0.15 mg/L. The LC50s were 0.18 mg/L for males and 0.24 mg/L for females. The combined LC50 (M/F) was 0.22 mg/L with a Toxicity Category II. This study was considered acceptable to DPR according to FIFRA guidelines.

III.B.9. Other Studies

The following summaries of studies are based on translated abstracts and tables submitted by the registrant (Mézin, 2006).

Male CD-1 mice (5/group) were given a single dose of MeI (purity not specified; 0, 12.5, 25, 50, or 100 mg/kg for digestive system study, and an additional dose of 200 mg/kg for central nervous system study) by gavage. Charcoal meal was administered 30 minutes after dosing to assess intestinal transport and stomach emptying. All 200 mg/kg mice died within 2 hours, with clinical signs including sedation; decreased activity; prone or supine position; gait problems; incomplete eyelid opening, hypothermia, and bradypnea. At 100 mg/kg, all mice survived, but showed clinical signs. These changes disappeared within 24 hours after dosing. Intestinal transport of charcoal meal was retarded significantly only at 25 to 50 mg/kg.

Male CD rats (8/group) were given a single dose of MeI (purity not specified; 0, 12.5 to 100 mg/kg) by gavage. Na^+, K^+, and Cl^- concentrations and volumes of blood and urine were

measured, with the only statistically significant result for an increase in urinary Na^+ concentration at 100 mg/kg.

Male beagles (3/group) were given a single dose of MeI (purity not specified; 0, 15, 30, or 60 mg/kg) "intra-duodenally" prior to assessing respiratory rate; arterial blood measures of pH, oxygen tension (PaO_2), CO_2 tension ($PaCO_2$); hemoglobin oxygen saturation (SaO_2); blood pressure; heart rate; and echocardiogram. Dose-related increase in respiratory rate and decrease in $PaCO_2$ were measured with statistical significance ($p<0.05$) at 60 mg/kg. One 30 mg/kg dog had a nearly 2-fold increase in breathing over its pre-treatment condition; this was considered a treatment-related effect.

III.C. Subchronic Toxicity

Summary: Rats exposed to MeI by inhalation showed increased relative liver weight, decreased body weight gain, and nasal tissue lesions (olfactory epithelial degeneration and respiratory epithelial metaplasia). When given by the gavage, MeI treated rats were reported to have salivation, elevated relative liver weight, reduced body weight, some clinical chemistry parameter changes, and histological lesions (forestomach hyperplasia and hyperkeratosis, submandibular gland squamous metaplasia). After dermal exposure, both local (gross and histological skin lesions) and systemic effects (wet and yellow urogenital staining, reduced body weight and food consumption, altered hematology and clinical chemistry parameters) were reported in rats. Mice given MeI in microcapsules mixed in the feed showed decreased food consumption, body weight gain, and thyroid effects (increased organ weight and colloid[10]). Dogs given MeI capsules were observed to show injected sclera and salivation.

III.C.1. Rat - Inhalation

Crl:CD(SD)IGS-BR rats (20/sex/dose) were exposed to MeI (purity 99.7%; analytical concentrations of 0, 5, 21, and 70 ppm) by whole-body inhalation for 6 hours per day, 5 days per week for 13 weeks (Kirkpatrick, 2002b). The calculated exposure concentrations were 0.03, 0.12, and 0.40 mg/L, respectively, with equivalent dosages of 5, 20, and 68 mg/kg/day. Some animals (10/sex/group) were necropsied after 4 weeks with the remaining animals treated through week 13. Few treatment-related effects were shown with clinical observations, food consumption, serum chemistry, and hematology (Table 8 and 9). An increase in wet yellow material on the urogenital area for males and females following exposure at 70 ppm was noted. Slightly lower mean food consumption was noted for males at 5, 20, and 70 ppm for study weeks 0 to 1 and 4 to 12. There was no trend for treated females with values generally similar to those for the controls. Increased serum cholesterol levels were recorded for males and females at 70 ppm at weeks 4 and 13.

The mean weekly body weights of the 70 ppm group were lower than the control. Group mean body weight gains for the 70 ppm groups were significantly lower (67% of control) than those for the controls only for the first week (Table 8 and 9). For 13 weeks, the mean body weight gain for that dose was 83-85% of the control. Significantly higher mean relative liver weight/body weight ratios were reported at week 4 for 70 ppm females (108% of control), and at week 13 for 21 ppm females (110% of control) and 70 ppm both genders (115% and 122% of control).

Among the organs examined (brain, thyroid, and salivary gland), only the nasal tissue was affected (Table 8 and 9). Olfactory epithelium degeneration (OED)/regeneration and respiratory epithelial metaplasia (REM) were noted primarily in the 70-ppm groups. The degeneration was found in the dorsal meatus and on the dorsal septum and upper turbinates, with significantly increased incidences for some levels. Metaplasia was considered a regenerative response following degeneration of the olfactory epithelium. At 4 and 13 weeks, both types of lesions

[10] Colloid-proteinaceous material in the luman of the thyroid follicle, and contains several proteins including thyroglobulin (a protein when in the combination with iodine forms the mono- or di-units, which are then coupled to form the thyroid hormones, T3 and T4). When the gland is active, there may be increased colloid due to enhanced thyroid hormone synthesis, or depleted due to increased excretion of thyroid hormones.

were generally graded as minimal to mild. And at 13 weeks, few OED at Levels IV and V in the 70-ppm males were described as moderate. Since there was only a slight increase in severity but the NOEL remained the same, the OED was considered an acute effect for this risk assessment with a NOEL of 21 ppm (20 mg/kg/day). There was also no difference in the total number of animals affected between the two time periods. The lack of time-dose relationship was also demonstrated in the chronic toxicity study (**III.D.1. Rat- Inhalation**; Kirkpatrick, 2005). A dose-related increase in incidences of degeneration was reported, but the incidences and severity of degeneration at 104 weeks was reported to be similar to that at 52 weeks.

For other effects, the subchronic NOAEL was 21 ppm (20 mg/kg/day) based on increased liver weight/body weight ratio and decreased body weight gain. This study was considered acceptable to DPR according to FIFRA guidelines.

The USEPA established a NOAEL of 21 ppm based on initial decreases in body weights, body weight gains, and food consumption (males); and nasal degeneration at 70 ppm (MRID 45593810; USEPA, 2006a).

Benchmark dose analysis was conducted to determine the point of departure for systemic effects after subchronic exposure. The two endpoints of concern are body weight reduction and cholesterol increase in the blood. The results, using continuous linear model, are listed in the following summary:

Exposure duration/gender	**MeI ppm**					
	ED_{05}	**LED_{05}**	**ED_{10}**	**LED_{10}**	**$ED_{0.61\sigma}$**	**$LED_{0.61\sigma}$**
Body weight reduction in rats						
6 weeks/Males	29.6	18.2	59.2	36.4	24.1	13.0
Increased cholesterol level in rats						
4 weeks/Males	8.4	5.3	16.8	10.7	18.9	11.5
4 weeks/Females	6.7	4.8	13.4	9.7	19.4	14.4
13 weeks/Males	6.2	4.4	12.4	8.9	19.2	14.2
13 weeks/Females	8.5	5.9	17.0	11.7	23.7	16.8

Table 11. Effects in male rats exposed to MeI by inhalation for 4 and 13 weeks.[a]

Effects	**Doses**			
ppm	**0**	**5**	**21**	**70**
mg/kg/day	**0**	**5**	**20**	**68**
Urogenital staining (total occurrence/animals)	0/0	0/0	0/0	5/4
Food consumption (% decrease)				
Week 0-1	0%	4.5%	4.5%	13.6%**
Week 11-12	0%	4.2%	8.3%	8.3%
Cholesterol (mg/dL) (n=10)				
Week 4	44±6.3	55±9.5	51±11.9	68±17.6**
Week 13	48±14.9	50±13.7	55±9.3	75±12.7**
Cumulative group mean body weight changes (g) (% of control)				
Weeks 0-1	43±11	34±6* (79%)	36±10 (84%)	29±12** (67%)
Weeks 0-13	234±35	220±35 (94%)	212±50 (91%)	199±39 (85%)
Group mean body weight (g) (% control) (n=10)				
Week 6	418±19.2	392±25.5(94%)	376±38.4*(90%)	365±40.8**(87%)
Group mean relative liver weight/final body weight ratios x 100 (% of control)				
Week 4	2.90±0.29	2.97±0.54	2.92±0.16	2.99±0.20
Week 13	2.44±0.14	2.51±0.16	2.64±0.28	2.81±0.14** (115%)
Nasal microscopic findings- 4 weeks (affected/total animals examined)				
Total all levels	1/10	0/10	0/10	10/10**
Level II OED- minimal	1/10	0/10	0/10	1/10
REM- minimal	0/10**	0/10	0/10	2/10
Level III OED- minimal	0/10**	0/10	0/10	4/10*
REM- minimal	0/10	0/10	0/10	1/10
Level IV OED- minimal	0/10**	0/10	0/10	4/10*
- mild	0/10	0/10	0/10	1/10
REM- minimal	0/10	0/10	0/10	1/10
Level V OED- minimal	0/10**	0/10	0/10	9/10**
- mild	0/10	0/10	0/10	1/10
Level VI OED- minimal	0/10**	0/10	0/10	4/10*
- mild	0/10	0/10	0/10	1/10
Nasal microscopic findings- 13 weeks (affected/total animals examined)				
Total all levels	0/10	0/10	0/10	10/10**
Level II OED- minimal	0/10**	0/10	0/10	3/10
REM- minimal	0/10**	0/10	0/10	2/10
Level III OED- minimal	0/10**	0/10	0/10	4/10*
- mild	0/10**	0/10	0/10	4/10*
Level IV OED- minimal	0/10**	0/10	0/10	4/10*
- mild	0/10**	0/10	0/10	5/10*
- moderate	0/10	0/10	0/10	1/10
Level V OED- minimal	0/10**	0/10	0/10	3/10
- mild	0/10**	0/10	0/10	2/10
- moderate	0/10**	0/10	0/10	2/10
Level VI OED- minimal	0/10**	0/10	0/10	2/10
- mild	0/10**	0/10	0/10	2/10

a/ Data from Kirkpatrick (2002b). *, ** for statistical significance at $p<0.05$ and <0.01, respectively. Significance in trend by the Cochran-Armitage Trend test is denoted at the control value.

Table 12. Effects in female rats exposed to MeI by inhalation for 4 and 13 weeks.[a]

Effects	**Doses**			
ppm	**0**	**5**	**21**	**70**
mg/kg/day	**0**	**5**	**20**	**68**
Urogenital staining (total occurrence/animals)	0/0	0/0	2/2	13/6
Food consumption (% decrease)				
Week 0-1	0%	5.9%	0%	5.9%
Week 11-12	0%	0%	0%	5.9%
Cholesterol (mg/dL) (n=10)				
Weeks 4	49±9.8	62±16.4	62±11.3	82±13.0**
Week 13	70±22.0	73±17.1	83±14.6	100±13.2**
Cumulative group mean body weight changes (g) (% control)				
Weeks 0-1	25±6	22±6 (92%)	23±6 (96%)	18±5 ** (72%)
Weeks 0-13	101±20	105±13(104%)	102±27 (101%)	84±16 (83%)
Group mean body weight (g) (% control)				
Week 6	260±26.0	250±13.1(96%)	252±24.2 (92%)	242±14.5 (93%)
Group mean relative liver weight/final body weight ratios x 100 (% of control)				
Week 4	3.12±0.16	3.03±0.18	3.26±0.22	3.39±0.12** (108%)
Week 13	2.66±0.14	2.75±0.18	2.95±0.36* (110%)	3.24±0.27** (122%)
Nasal microscopic findings- 4 weeks (affected/total animals examined)				
Total all levels	1/10	0/10	1/10	9/10**
Level II OED- minimal	0/10**	0/10	0/10	3/10
REM- minimal	0/10**	0/10	1/10	5/10*
Level III OED- minimal	0/10**	0/10	1/10	4/10*
Level IV OED- minimal	1/10**	0/10	0/10	6/10*
Level V OED- minimal	0/10**	0/10	0/10	7/10**
Level VI OED- mild	0/10	0/10	0/10	1/10
Nasal microscopic findings- 13 weeks (affected/total animals examined)				
Total all levels	0/10	0/10	1/10	9/10**
Level II OED- minimal	0/10**	0/10	0/10	3/10
REM- mild	0/10	0/10	0/10	1/10
Level III OED- minimal	0/10**	0/10	0/10	6/10**
- mild	0/10	0/10	0/10	1/10
Level IV OED- minimal	0/10**	0/10	1/10	5/10*
- mild	0/10**	0/10	0/10	4/10*
Level V OED- minimal	0/10**	0/10	1/10	5/10*
- mild	0/10**	0/10	0/10	2/10
Level VI OED- minimal	0/10	0/10	0/10	1/10
- mild	0/10**	0/10	0/10	2/10

a/ Data from Kirkpatrick (2002b). *, ** for statistical significance at $p<0.05$ and <0.01, respectively. Significance in trend by the Cochran-Armitage Trend test is denoted at the control value.

III.C.2. Rat - Oral

Crj: SD (SD) IGS rats (10/sex/group) were given MeI (99.9% purity; 0, 5, 10, 25, or 50 mg/kg/day) by gavage daily for 13 weeks (Nishimura, 2002). Additional groups (10/sex) were dosed at 0, 25, or 50 mg/kg/day also for 13 weeks; but they were followed for 4 weeks afterward (recovery period). No treatment-related effects were observed for the following: food consumption, spontaneous motor activity, grip strength, sensorimotor reactions to auditory or visual stimuli, proprioceptive reaction, ophthalmology, urinalysis parameters, and hematology. Four 50 mg/kg/day females died on study days 81 and 86; they showed decreased activity, traces of reddish rhinorrhea, and urine staining prior to death.

Salivation was the most common clinical sign. With the exception of one 25 mg/kg/day female, signs of salivation were reported only at the 2-hours post-dosing period (other observation times were pre-dose, immediately after dosing, and 3 to 4 hours after dosing) (Table 13). Nearly all 25 and 50 mg/kg/day rats, and about half of 10 mg/kg/day rats were affected sporadically throughout the study. Salivation signs were first observed in high dose rats on days 4 (males) or 3 (females), with signs beginning to emerge in the two intermediate-dose groups by 1 week. None was observed during the recovery period.

Only the 50 mg/kg/day males showed a statistically significant decrease in body weight from week 1 to the end of the study (Table 13). However, their body weights after the recovery phase were not different than the control. Of the organs weighed, only the relative liver weight was significantly elevated in the 25 mg/kg/day (females only) and 50 mg/kg/day groups after the treatment phase (Table 13).

Some clinical chemistry parameters were affected by treatment (Table 13). These included statistically significant elevated alkaline phosphatase, albumin, and phospholipids for the 50 mg/kg/day males, as well as increased bilirubin, total protein, calcium, and sodium levels in the 25 and 50 mg/kg/day males. However, after the recovery phase, all values were similar to those for the concurrent control. For the females, the significant findings were increased sodium level, as well as α2- and β-globulin levels at the end of treatment phase. At recovery, α2-globulin remained elevated, while total protein and albumin levels were significantly reduced.

Gross examination found low incidences (involving 1 or 2 animals) of pathology in the liver and stomach. Histological examination showed lesions in the 25 and 50 mg/kg/day groups. They included: liver (hepatocyte necrosis, 50 mg/kg/day only), forestomach (hyperkeratosis, hyperplasia, and submucosal edema), glandular stomach (edema, 50 mg/kg/day females only), and submandibular gland (squamous metaplasia and decreased granulation) in the 25 and 50 mg/kg/day groups (Table 14). Rats in the recovery group showed significant recovery as the only lesion detected was very slight forestomach hyperplasia and hyperkeratosis in one female.

The subchronic NOEL was 5 mg/kg/day, based on hyperkeratosis and hyperplasia in the forestomach and submandibular gland ductal squamous metaplasia at 10 mg/kg/day. This study was considered acceptable to DPR under FIFRA guidelines.

Table 13. Effects of MeI in rats exposed by gavage for 13 weeks.[a]

Effects	Doses (mg/kg/day)									
	Males					Females				
	0	**5**	**10**	**25**	**50**	**0**	**5**	**10**	**25**	**50**
Salivation (2 hours post dose observation, number of animals affected during the study)										
Incidence First sign observed	0/20 NA	0/10 NA	5/10 day 7	18/20 day 8	20/20 day 4	0/20 NA	0/10 NA	4/10 day 10	19/20 day 6	19/20 day 3
Body Weight (g)										
Week 0	195	197	196	193	193	157	158	156	157	156
Week 1	248	248	249	243	233**	179	179	178	183	177
Week 5	438	437	431	417	402**	267	261	258	265	256
Week 13	582	587	582	555	534**	320	318	315	317	306
Relative Liver Weights (% body weight)										
End of treatment	2.88	2.84	2.95	3.07	3.36**	2.51	2.51	2.62	2.84**	3.19**
Clinical Chemistry (Treatment phase)										
Alkaline phosphatase (IU/L)	247	311	328	352	438**	168	133	124*	174	188
Total bilirubin (μg/dL)	39	52	67	54*	67**	63	61	54	63	64
Total protein (g/dL)	5.59	5.53	5.59	5.96*	5.99*	6.26	6.28	6.48	6.33	5.99
Albumin (g/dL)	4.14	4.09	4.02	4.42	4.47*	4.90	5.12	5.22	4.94	4.51
Phospholipid (mg/dL)	108	112	114	123	132*	142	143	151	143	149
Calcium (mg/dL)	9.41	9.23	9.43	9.78*	9.84*	9.73	9.64	9.75	9.76	9.63
Sodium (mEq/L)	141	140	142	146*	146*	143	143	144	145*	145
α2-globulin (% of protein)	8.84	8.82	9.51	9.19	9.66	6.45	6.45	6.21	6.54	8.69*
β-globulin (% of protein)	13.9	14.3	14.2	14.5	15.1	12.7	12.7	12.2	13.9	14.8**
Clinical chemistry (Recovery phase)										
Total protein (g/dL)	6.00	-	-	5.97	6.12	6.59	-	-	6.19	6.08*
Albumin (g/dL)	4.35	-	-	4.38	4.55	5.25	-	-	4.79	4.74*
α2-globulin (% of protein)	7.05	-	-	6.89	7.17	6.03	-	-	6.39	6.96**

a/ Nishimura (2002). *, ** for statistical significance at $p < 0.05$ and < 0.01, respectively based on analysis by investigators. "-" =no data because dose groups were not included in recovery phase study.

Table 14. Histopathology in survivor rats exposed to MeI by gavage for 13 weeks.[a]

Effects	Doses (mg/kg/day)									
	Males					Females				
	0	**5**	**10**	**25**	**50**	**0**	**5**	**10**	**25**	**50**
Terminal Survivors (N =)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(7)[b]
Liver hepatocyte necrosis, focal Grades 1 and 2, total affected	0	1	1	1	4	0	0	0	0	1
Forestomach										
Hyperkeratosis Grades 1 and 2, total affected	0	0	3	8**	10**	0	0	0	6*	7**
Hyperplasia Grades 1 and 2, total affected	0	0	3	7**	10**	0	0	0	6*	7**
Edema, submucosal, (Grade 1)	0	0	0	0	0	0	0	0	1	4*
Glandular stomach Edema, submucosal, (Grade 1)	0	0	0	0	0	0	0	0	0	2
Submandibular gland										
Squamous metaplasia, ductal Grades 1 and 2, total rats affected	0	0	1	10**	10**	0	0	2	10**	7**
Decreased granulation, granular duct Grades 1 and 2, total rats affected	0	0	0	2	5*	0	0	0	1	4*

a/ Nishimura (2002). *, ** for statistical significance at $p < 0.05$ and < 0.01, respectively based on analysis by investigators.

b/ Tissues were autolyzed in 3 animals that died prematurely.

III.C.3. Rat - Dermal

Crl:CD(SD)IGS-BR rats (10/sex/group) were exposed to MeI (purity 99.7%; 0, 30, 300, or 1,000 mg/kg/day) applied on clipped intact mid-dorsal skin (about 20% of total body surface area) and then covered with gauze and taped with plastic wrap for 6 hours per day over 21 consecutive days (Morris, 2002). All females survived to termination, but 4 males died or were humanely sacrificed prior to term with 3 deaths attributed to treatment.

Topical effect at 30 mg/kg/day was “very slight” erythema with desquamation in some animals (Table 15). The investigators considered the low dose results treatment-related. Almost all animals in the 300 and 1,000 mg/kg/day groups showed severe grades of skin responses such as erythema, edema, and eschar; and other skin damage. Ulceration was noted only for two 1,000 mg/kg/day males.

Several systemic effects were reported at both 300- and 1000-mg/kg/day groups: clinical signs, body weight, and food consumption (Table 16). Wet and yellow urogenital staining was noted with the 300 and 1,000 mg/kg/day females, but not the males. Body weights and food consumption were reduced at 300 and 1,000 mg/kg/day, with statistical significance mainly for the males. In addition, hematology parameters were significantly altered by treatment in both 300 and 1,000 mg/kg/day males and females (Data not shown in Table). They included: reduced

RBC, hemoglobin, hematocrit, and lymphocytes; and increased platelet and neutrophils. Clinical chemistry parameters were also affected: decreased albumin, A/G ratio (albumin/globulin ratio), and creatinine (females only); and increased globulin, blood urea nitrogen (BUN), alkaline phosphatase, alanine aminotransferase (ALT), AST, glutamyl transferase, cholesterol, and chloride.

Histological changes were also observed with the 300 and 1000 mg/kg/day groups, with higher frequency and/or severity at 1,000 mg/kg/day (Table 17). They included the skin and other organs (adrenal cortex cytoplasmic vacuolation, sternal marrow hypercellularity, liver and spleen extramedullary hematopoiesis, and thymus lymphoid necrosis). The severity was mainly minimal with few incidences noted as severe.

The NOEL for local effects was <30 mg/kg/day (lowest dose tested). The systemic NOEL was 30 mg/kg/day for multiple effects observed at 300 mg/kg/day. This study was considered acceptable to DPR according to FIFRA guidelines.

Table 15. Local skin effects in rats exposed to MeI dermally for 21 days.[a]

Effects (Total animals affected)	Doses (mg/kg/day)							
	Males				Females			
	0	30	300	1,000	0	30	300	1,000
Erythema	0	2	10††	9††	0	5	10††	10††
Edema	0	0	10††	9††	0	0	10††	10††
Fissuring	0	0	7**	7**	0	0	7**	10**
Desquamation	3	7	10**	9**	3	7	10**	10**
Eschar	0	0	10**	9**	0	0	10**	10**
Exfoliation	0	0	10**	9**	0	0	10**	10**
Atonia	0	0	9**	9**	0	0	9**	10**
Coriaceousness	0	0	4*	5*	0	0	8**	10**
Ulceration	0	0	0	2	0	0	0	0

a/ Data from Morris (2002). Total animals observed = 10. †, †† for statistical significance at $p < 0.05$ and < 0.01, respectively (Mann-Whitney) (Analysis by DPR Data Reviewer). *, ** for statistical significance at $p < 0.05$ and < 0.01, respectively (Analysis by DPR Data Reviewer using Fisher's exact test).

Table 16. Systemic effects in rats exposed to MeI dermally for 21 days.[a]

Effects	Doses (mg/kg/day)							
	Males				Females			
	0	30	300	1,000	0	30	300	1,000
Urogenital staining (affected/total examined)								
Wet and yellow	0/10	0/10	0/10	0/10	0/10	0/10	2/10	5/10
Body weight (g)								
Week 0	290	290	290	289	205	204	204	205
Week 1	305	307	282*	271*	219	219	214	208
Week 3	346	344	288*	280**	240	237	230	231
Food consumption (g/rat/day)								
Week 0-1	24	23	22**	19**	20	19	18	17**
Week 1-2	25	25	22**	24	21	21	21	21
Week 2-3	26	25	23**	22**	20	20	21	22

a/ Data from Morris (2002).*, **, for statistical significance at $p < 0.05$ and < 0.01, respectively (analysis by investigators).

Table 17. Histopathology of terminal survivor rats exposed to MeI dermally for 21 days.[a]

Effects	Doses (mg/kg/day)							
	Males				Females			
	0	30	300	1,000	0	30	300	1,000
Skin	Total animals affected							
exfoliation	0	3	8**	7**	0	0	10**	10**
epithelial hyperplasia	6	6	9**	7**	0	3	10**	10**
inflammation	0	1	9**	7**	0	1	10**	10**
necrosis	1	2	9**	7**	0	0	9**	10**
edema	0	0	2	6**	0	0	6*	8**
Adrenal cortex, vacuolation, cytoplasmic	0	0	1	6**	0	0	0	5
Bone marrow, sternum, hypercellular	1	0	7*	7**	0	0	4	6*
Liver, extramedullary hematopoiesis, minimal	0	0	1	2	0	1	6**	10**
Spleen, extramedullary hematopoiesis	0	0	1	6**	0	1	9**	10**
Thymus, lymphoid necrosis	0	0	8**	7**	0	0	9**	10**

a/ Data from Morris (2002). Total animals examined=10 for all groups, except for n=9 for 300 ppm males and 7 for 1000 ppm males. *,**, for statistical significance at $p < 0.05$ and < 0.01, respectively (analysis by DPR Data Reviewer using Mann-Whitney test).

III.C.4. Mouse - Oral

In a range finding study, Crl:CD-1(ICR)-BR mice (10/sex/group) received 0, 62.5, 250 or 1,000 ppm of microencapsulated MeI (2.2% active ingredient; 0, 11.3, 43.2, 154.0 mg/kg/day for males; 0, 13.5, 53.1, 168.0 mg/kg/day for females) in the diet for 3 weeks (21 or 22 days) (Harriman, 2003b). No treatment-related mortality, clinical observations, or gross examination changes were reported in the study. The mean body weights for the 1,000 ppm groups were significantly lower than that of the controls over the course of the study (Table 18). This difference was primarily due to significantly lower mean body weight gain at 250 ppm and 1,000 ppm, compared to the control, during the first week of the study. Mean food consumption of the 1,000 ppm groups was reduced for all weeks (Table 18). The mean absolute kidney, heart, and spleen weights of the 1,000 ppm groups and the mean ovarian weight of these females were lower than those of the controls (Table 18). However, their relative mean weights (to body weight) were not affected. The relative mean weights of the brain of 1,000 ppm groups were significantly greater than those of the control (Table 18). Other organ weights (including thyroid) were not affected. The NOEL was 62.5 ppm (11.3 mg/kg/day) based upon reduced body weight gain of the 250 ppm males. This study was supplemental information to DPR.

Table 18. Effects in mice exposed to microencapsulated MeI in the diet for 3 weeks in a range finding study.[a]

Effects	**Doses**							
	Males				**Females**			
ppm	**0**	**62.5**	**250**	**1,000**	**0**	**62.5**	**250**	**1,000**
mg/kg/day	**0**	**11.3**	**43.2**	**154.0**	**0**	**13.5**	**53.1**	**168.0**
Mean body weights (g)								
Day 0	27.0	27.3	27.4	27.4	22.5	22.3	22.3	22.4
Day 6	28.9	28.7	28.3	26.2**	24.6	24.5	24.2	21.5**
Day 14	29.8	29.5	28.8	26.4**	25.6	25.1	24.8	22.0**
Day 20	30.0	29.8	29.4	26.7**	26.2	26.3	25.2	22.6**
Mean body weight changes (g)								
Day 0 to 6	1.9	1.4	1.0*	-1.3**	2.0	2.2	1.8	-0.9**
Day 6 to 14	0.8	0.8	0.5	0.2	1.1	0.6	0.6	0.4
Day 14 to 20	0.3	0.3	0.6	0.4	0.5	1.2*	0.5	0.7
Mean food consumption (g/animal/week)								
Day 0 to 6	5.1	5.0	4.8	3.6**	5.2	5.1	5.0	3.2**
Day 6 to 14	5.1	5.4	5.0	4.2**	5.5	5.4	5.2	3.8**
Day 14 to 20	5.1	5.4	5.0	4.5	5.6	5.6	5.2	4.1**
Organ weights on Day 20 **(**Absolute weight g, and relative to body weight g/100g)								
Brain Abs.	0.463	0.470	0.467	0.469	0.496	0.485	0.486	0.481
Relative	1.505	1.521	1.543	1.682**	1.857	1.828	1.900	2.069**
Kidney Abs.	0.543	0.571	0.554	0.457*	0.410	0.401	0.406	0.361*
Heart Abs.	0.160	0.166	0.165	0.144*	0.153	0.150	0.143	0.129**
Spleen Abs.	0.089	0.087	0.097	0.074	0.114	0.116	0.102	0.081**
Ovaries Abs.	NA	NA	NA	NA	0.030	0.027	0.026	0.023*

a/ Data from Harriman (2003b). *, ** for statistical significance at $p<0.05$ and <0.01, respectively. Abs=absolute

Crl:CD-1(ICR)-BR mice (10/sex/group) received 0, 133, 400 or 1,200 ppm of microencapsulated MeI (active ingredient ranged from 2.32 to 3.81%; 0, 23.6, 65.3, 212.0 mg/kg/day for males and 26.8, 79.2, 221.6 mg/kg/day for females) in the diet for 13 weeks (Harriman, 2003c). One male and one female in the 1,200 ppm group died on days 60 and 7, respectively. The mean body weight gain of both genders in the 1,200 ppm group was reduced ($p<0.01$) during the first week of the study with no apparent treatment effect thereafter. Mean food consumption was likewise reduced during the first week for the 1,200 ppm group, indicating a possible palatability problem. The high dose animals demonstrated increased incidence of reduced defecation (male 0 ppm: 0 incidence versus 1,200 ppm: 22 times for 6 animals, female 0 ppm: 0 incidence versus 1,200 ppm: 25 times for 7 animals). No other treatment-related clinical signs were reported.

No treatment-related effects were noted in the hematology, clinical chemistry, ophthalmology and urinalysis. The mean absolute kidney weight for the 1,200 ppm males and the mean absolute adrenal and ovary weights for the 1,200 ppm females were lower than those of the control (Table 19). However, the mean relative weights for these organs were not statistically different from those of the control. The mean absolute and relative thyroid weights in all treated groups were greater than those for the controls with statistical significance reported only for the males. The lack of statistical significance for the female groups was attributed to larger standard deviations in the values.

Histopathology examination showed increased incidences of lesions in the thyroid, femur marrow, Harderian gland, and esophagus (Table 19). Other tissues (including nasal cavity, salivary gland, and brain) were normal. For the thyroid, increased colloid was noted for all treated groups with increasing incidences and severity (minimal to mild). Myeloid hyperplasia in the femur, and porphyrin pigments in the Harderian gland were found in the 1,200 ppm groups, the only treatment group examined. The esophagus of treated groups showed minimal hyperkeratosis. The subchronic NOEL for both genders was < 133 ppm (males 23.6 mg/kg/day, females 26.8 mg/kg/day) based upon increased colloid in the thyroid gland, and hyperkeratosis in the esophagus at 133 ppm. This study was considered acceptable to DPR according to FIFRA guidelines.

Table 19. Organ weights and histological lesions in mice exposed to microencapsulated MeI in the diet for 13 weeks.[a]

Effects	Doses			
	0	**133**	**400**	**1,200 ppm**
Males	**0**	**23.6**	**65.3**	**212.0 mg/kg/day**
Mean absolute (g) and relative organ weight				
Kidneys Absolute	0.617	0.587	0.572	0.498**
Adrenal Glands Absolute	0.0062	0.0054	0.0051	0.0049
Thyroid- Absolute (% Control)	0.0056 ±0.0011	0.0075 ±0.0012** (134%)	0.0079 ±0.00157** (141%)	0.0075 ±0.00143* (134%)
- Relative (% Control)	0.016 ±0.0026	0.022 ±0.0033** (138%)	0.024 ±0.0042** (150%)	0.025 ±0.0044** (156%)
Histopathological lesions				
Thyroid-Increased colloid				
-Minimal	1/9*	3/10	7/10*	6/9*
-Mild	0/9	5/10	2/10	2/9
Marrow, femur-Myeloid hyperplasia	0/10	NE	NE	0/9
Harderian Gland, porphyrin pigment				
-Minimal	1/10	NE	NE	2/9
-Mild	0/10			0/9
Esophagus- Hyperkeratosis				
-Minimal	0/10**	1/10	7/10**	8/9**
-Mild	0/10	0/10	0/10	1/9
Females	**0**	**26.8**	**79.2**	**221.6 mg/kg/day**
Mean absolute (g) and relative organ weights				
Kidneys Absolute	0.377	0.396	0.382	0.351
Adrenal Glands Absolute	0.0111	0.0110	0.0087	0.0086*
Thyroid- Absolute (% Control)	0.0049 ±0.00093	0.0116 ±0.0162 (237%)	0.0076 ±0.0017(155%)	0.0076 ±0.00223 (155%)
- Relative (% Control)	0.018 ±0.0035	0.043 ±0.0615 (239%)	0.029 ±0.0069(161%)	0.030 ±0.0095 (167%)
Ovaries Absolute	0.0333	0.0344	0.0299	0.0256*
Histopathological lesions				
Thyroid-Increased colloid				
-Minimal	1/10*	5/10	8/10**	6/9*
-Mild	0/10	4/10*	1/10	3/9
Marrow, femur-Myeloid hyperplasia	0/10	NE	NE	2/9
Harderian Gland, porphyrin pigment				
-Minimal	1/10	NE	NE	4/9
-Mild	0/10	NE	NE	1/9
Esophagus- Hyperkeratosis				
-Minimal	0/10**	2/10	7/10**	7/9**

a/ Data from Harriman (2003c). NE=not examined. *, ** for statistical significance at $p<0.05$ and <0.01, respectively. Significance in trend by the Cochran-Armitage Trend test is denoted at the control value.

III.C.5. Dog - Oral

In a range-finding study for the 13-week subchronic toxicity study, two groups of beagle dogs (2/sex/group) were dosed with MeI (purity 99.7%) in capsules according to the following regimen: 5 days at 3 mg/kg/day, 2 days of non-dosing, 2 days at 30 mg/kg/day, one day of non-dosing, 1 day of 15 mg/kg, 5 days of non-dosing and 5 days of 7.5 mg/kg/day (Mertens, 2002). Group I was offered feed only for two hours before dosing. Group II was offered food at least three hours after dosing and *ad libitum* until the time of dosing the next day. The report noted that the feed was found in the stomachs of both groups, in spite of the feeding protocol.

No treatment-related effect for the 15 mg/kg/day group was reported. At 30 mg/kg/day, body weight and food consumption decreased for 6/8 animals with all of the animals in Group I being affected. Emesis and decreased defecation were noted for this group. Clinical signs resulting from the 7.5 mg/kg/day treatment were infrequent occurrence of emesis and mucoid feces containing red material. Compared to the controls, increased incidences of injected sclera (bloodshot eyes, dilatation of the blood vessels in the eyes) affecting both eyes were noted for Group I animals at the 2-hour post dosing, as well as during the non-dosing days, compared to pre-dosing period. On the other hand, Group II animals were less affected, with occasional single incidence involving one dog. The author of the study suggested that this was a pharmacological effect rather than a toxicological effect but no explanation was given. It is unknown why there was a difference in response for the endpoint for the two groups. No treatment-related lesions were noted in the necropsy examination. A NOEL was not established due to the lack of a control group and use of different doses for different time periods. This study was considered supplemental information to DPR.

In the definitive study, beagle dogs (4/sex/group) were dosed orally with MeI (purity 99.7%; 0, 1.5, 6 or 15 mg/kg/day) in capsules for 7 days per week for 13 weeks (Harriman, 2003d). The animals were observed twice daily, as well as prior to and two hours after each dosing. Weekly physical examinations were also conducted on all animals, beginning one week before dosing to before the scheduled sacrifice. One male in the 15 mg/kg/day group was euthanized *in extremis* on day 48, exhibiting signs of emaciation, emesis, dehydration, and limited food consumption. For the survivors, there was no treatment-related effect upon body weight or food consumption.

Clinical signs included injected sclera of the eye and wet material around mouth at 1.5 mg/kg/day, with drooling, emesis, and head shaking at higher doses (Table 20). The excessive drooling and material around the mouth were considered indication of increased salivation. Overall, the data showed increased incidences and number of animals involved with increasing dose, but there was variability for the time of onset and incidences between animals within each dose group. The interpretation of the dose-response relationship was complicated by no change or paradoxical reduction in the number of incidences 2-hours after dosing compared to prior to dosing for these signs. For example, the total incidence/animal affected for injected sclera in the left eye of 1.5 mg/kg/day males was 5/1 prior to, and 5/2 at 2 hours after dosing. However, in the 6.0 mg/kg/day male group, they were 10/3 prior to, and 3/3 after dosing at 6.0 mg/kg/day. The authors attributed the finding of injected sclera to treatment but did not consider it as an adverse effect since ophthalmic examination showed no treatment-related findings.

There were no treatment-related effects on the hematology or urinalysis. For serum chemistry, the mean albumin serum concentrations of the 15 mg/kg/day males and females at 6 and 12 weeks and the 6-mg/kg/day females at 12 weeks were less than those of the controls (Table 20). The total protein concentrations in the serum were likewise affected in these groups (Table 20). These two parameters were also decreased for the males, but were not statistically significant. Serum hormone analysis (TSH, T3, and T4) and organ weights did not show any treatment-related effect.

Histopathological evaluation showed increased incidence (3 of 4 animals) of minimal degeneration of the olfactory epithelium in the nasal level IV section of the 6 and 15 mg/kg/day females but not in males (Table 20). Other organs (including brain, salivary gland, and thyroid) were found to be normal. The NOEL was < 1.5 mg/kg/day for males and 1.5 mg/kg/day for females for injected sclera and salivation. The study was considered acceptable to DPR according to FIFRA guidelines.

Table 20. Effects in dogs exposed to MeI capsules via the oral route for 13 weeks.[a]

Effects	Doses (mg/kg/day)							
	0		1.5		6		15	
Males								
Clinical signs (No. of events/no. of animals affected, prior to and 2 hours post each dosing)								
	prior	**2-hr**	**prior**	**2-hr**	**prior**	**2-hr**	**prior**	**2-hr**
Marked injected sclera - left eye	0/0	0/0	5/1	5/2	10/3	3/3	42/2	29/2
- right eye	0/0	0/0	17/1	8/2	33/4	11/4	25/3	9/2
Excessive drooling	0/0	0/0	0/0	0/0	1/1	1/1	55/4	25/3
Wet, clear material around mouth	2/1	5/3	28/3	20/4	122/4	87/4	143/4	90/4
Emesis, small amount of food	1/1	0/0	4/3	2/1	12/4	4/3	21/4	32/4
Head shaking	0/0	0/0	0/0	0/0	9/2	0/0	64/4	7/2
Clinical chemistry (mean values)								
Albumin (g/dL) -week 6	3.4±0.22		3.3±0.05		3.3±0.29		2.9±0.31*	
-week 12	3.7±0.21		3.6±0.17		3.5±0.15		2.9±0.46**	
Total protein (g/dL) - week 6	5.8±0.24		5.6±0.13		5.8±0.49		5.3±0.57	
- week 12	5.9±0.05		5.9±0.37		5.8±0.15		4.9±0.47**	
Histopathology								
Nasal Level IV – degeneration of olfactory epithelium, minimal	2/4		2/4		2/4		0/4	
Females								
Clinical signs (No. of events/no. of animals affected, prior to and 2 hours post each dosing)								
	prior	**2-hr**	**prior**	**2-hr**	**prior**	**2-hr**	**prior**	**2-hr**
Marked injected sclera- left eye	1/1	0/0	2/1	1/1	70/3	55/4	53/3	28/3
- right eye	0/0	0/0	1/1	0/0	62/4	50/4	7/3	3/2
Excessive drooling	0/0	0/0	0/0	0/0	0/0	0/0	22/3	5/2
Wet, clear material around mouth	3/2	5/2	2/1	2/1	21/4	21/2	132/4	52/4
Emesis, small amount of food	4/3	4/2	8/4	3/3	4/3	9/3	12/4	34/4
Head shaking	0/0	0/0	2/2	0/0	0/0	0/0	40/4	0/0
Clinical chemistry (mean values)								
Albumin (g/dL) - week 6	3.4±0.24		3.4±0.15		3.0±0.22		2.9±0.16*	
- week 12	3.8±0.13		3.6±0.13		3.3±0.08**		3.0±0.23**	
Total protein (g/dL) - week 6	5.8±0.50		5.8±0.48		5.2±0.21		5.1±0.06*	
- week 12	6.0±0.25		5.9±0.42		5.2±0.34*		5.3±0.13*	
Histopathology – Nasal Level IV								
Nasal Level IV- degeneration of olfactory epithelium, minimal	1/4		1/4		3/4		3/4	

a/ Data from Harriman (2003d). *, ** for statistical significance at $p<0.05$ and <0.01, respectively. NE=not evident. Clinical observations were made prior to dosing for the day and two hours after the dosing.

III.D. Chronic Toxicity and Oncogenicity

Summary: In rats after inhalation exposure, MeI caused reduced food consumption as well as reduced body and organ weights. The primary target organs were the thyroid (hyperplasia and atrophy), nasal tissues (olfactory epithelium degeneration), and salivary gland (metaplasia). At the doses studied, reduced body weight gain and food consumption were also observed in treated mice given MeI by gavage. Dogs ingesting MeI in capsules showed injected sclera, excessive drooling and effects on the thyroid (reduced organ weight, colloid depletion, and follicular cell hypertrophy). For all three species, TSH level was elevated with MeI treatment. Increased incidences of thyroid adenomas and/or carcinomas were reported for rats and mice.

III.D.1. Rat - Inhalation

Crl:CD(SD)IGS-BR rats (60/sex/group, except for 70/sex/group for 60 ppm were exposed to MeI (purity 99.7% for all but 36 exposures, during which the purity was 97.9% with 2% dichloromethane; analytical concentrations of 0, 5, 20, or 60 ppm) by whole-body inhalation for 6 hours per day, 5 days per week for 1 (interim sacrifice) or 2 years (main group) (Kirkpatrick, 2005; interim reports in Kirkpatrick, 2003a and b). Ten (for 0, 5, and 20 ppm groups) or 20 (for 60 ppm groups) animals were removed from each group at 51 weeks for interim sacrifice. The equivalent dosages were 5, 19, 58 mg/kg/day for 0.03, 0.11, and 0.34 mg/L, respectively. Excess deaths in the 60 ppm rats occurred during months 5 and 6 of the study. Engineering corrections and changing cage placements stopped the mortality. By week 91, survival between control and the treated groups were comparable and represented about 50% or higher rates (Table 21). The terminal survival rate for the control was lower (38-39%) than the treated groups (43-51%). Pituitary adenomas and "undetermined" accounted for almost all cases of death with similar number of animals affected between the control and treated groups.[11]

There were no treatment-related effects reported for clinical signs and hematology. Clinical chemistry data showed comparatively few indicators of treatment effects. The mean cholesterol levels at week 26 were significantly elevated for 60 ppm males (134 mg/dL, $p<0.05$), and 20 and 60 ppm females (104 and 109 mg/dL, respectively, $p<0.05$ and <0.01) when compared to controls (74 and 78 mg/dL). The sodium levels were 144, mEq/L for the control, and significantly increased for all male groups (146 to 147 mEq/L, $p<0.05$) and 60 ppm females (147 mEq/L). At week 52, both cholesterol and sodium levels were not different than control values. The phosphorus levels in the 60-ppm females, not the males, were increased (145%, 127% of control, respectively) at both 6 and 12 months.

Mean body weights were significantly reduced in the 60 ppm group throughout the study, starting on study week 5 (Table 21). They were 91-95 (male-female) % of control on week 5, and were 80-82% (male-female) of control at 24 months, which suggested that the 60 ppm exceeded the Maximal Tolerated Dose (MTD). The % of reduction corresponded to that for food consumption, except for the week 0-1 value 60-ppm female.

[11] Pituitary adenoma was listed as the cause of death in the majority of the animals with no gender difference; the total animals affected were 28, 28, 26, and 20 animals for control, 5, 20, and 60 ppm groups. The undetermined were 15, 10, 7, and 12 for control and treated groups.

The main target organs were stomach, thyroid, nasal tissue, and salivary gland. At gross examination, the stomach showed dark red areas, reddened mucosa, dark red contents, and distension (Table 21). In the thyroid (including the parathyroid), both the absolute and relative mean organ weights of the 60 ppm males were significantly greater than those of the controls (Table 21). This was consistent with the increased incidence of enlarged thyroids (Table 21) and histological changes (Table 22) in these males. Thyroid hormones and TSH levels showed variable changes over time, with overall dose-related increase in T4, TSH, and rT3, but a reduction in T3 (Table 21).

Microscopic examination of the thyroid revealed increased incidences of follicular cell hyperplasia (significant for both genders), and adenoma/carcinoma (significant for the males only) in the 60 ppm groups (Table 22). The overall incidences for adenomas and carcinomas were attributed to animals in the main groups, with few adenomas from the interim group (3 and 1 adenomas for males and females, respectively, of the 60 ppm groups). In the 60 ppm males, the total incidences (all animals) for adenomas (18.6%) and combined adenomas/carcinomas (21%) were significantly increased compared to the control (6.7%), and historical control of 2.21% at the conducting laboratory. While incidence for follicular carcinomas (5.7%) in the 60 ppm females (all animals) was not significantly elevated compared to the control (3.3%), it was higher than the historical control of 0.88%. Table 19 also showed findings of cyst, vacuolation, cystic hyperplasia, and ultimobranchial cyst[12] in the thyroid follicular cell. The increased incidences were statistically significantly elevated at 60-ppm, primarily in the males. Cytoplasmic vacuolation of follicular cells was described as "appeared to be a form of follicular cell degeneration." While considered a common congenital finding, increased incidence of cysts was considered to be treatment-related.

Examination of individual data for male rats showed a wider range of TSH, and higher mean TSH levels for animals with thyroid changes (enlargement, tumors, and hyperplasia) than those not affected (Table 23). However, within this affected male subgroup, there was no obvious relationship between TSH level and the formation of tumors. For example, the TSH levels were between 3.04 and 13.80 ng/mL, respectively, for the animals (#3222, 3442, 3509) with adenomas at 52 weeks. On the other hand, animal #3484 had no adenomas and its TSH was 26.02 ng/mL. The lack of correlation was also noted for the 104-week data. The TSH levels in animals with carcinomas ranged from 2.27 to 36.86 ng/mL. The TSH level was 10.53 ng/mL in the most affected animal (#3338) with enlarged thyroid, adenoma, carcinoma, and hyperplasia. The animal (#3331) with highest TSH level (50.40 ng/mL) did not have any carcinoma. The female individual data for 104 weeks also did not show any correspondence between TSH and adenoma formation (Table 21). This lack of direct relationship with TSH, as well as T4, suggested that, instead of terminal values, changes in hormone levels over the course of treatment might be a better predictor of tumor outcome. However, the current study lacked the data for such an analysis because there were only a few animals with hormone levels measured more than once, and were only at week 26 and 52 (Table 23 and 24). As pointed out by the SRC, the on/off MeI dosing regimen of 6 hours per day may also contribute toward the fluctuations in the TSH levels (**Volume IV Part 1-A)**. Nasal olfactory epithelial degeneration showed dose-related increase in incidences with the majority of 60 ppm rats affected (Table 22). The severity of the lesion

[12] Ultimobranchial cysts were considered a common finding in rats, representing embryological rests from the ultimobranchial body. The study investigators considered the increases noted in the male rats as likely random occurrences rather than exposure related.

progressed from mild at 0 and 5 ppm, to minimal and mild for 20 ppm, and up to severe at 60 ppm. However, the incidence and severity of degeneration at 104 weeks was reported to be similar to that at 52 weeks. Cyst formation, considered an indication of regeneration, affected up to half of the 60-ppm animals, depending on the nasal tissue level.

Squamous metaplasia of ductal epithelium and atrophy of the acinar structures in the mandibular salivary gland showed dose- and duration increased incidences and severity in the treated groups (Table 22). They were found in all treated groups with statistically significant increases at 20 ppm for metaplasia (both genders) and 5 ppm for atrophy (male). The severity of these lesions ranged from mild/minimal for the 5-ppm group, to moderate in the 20 ppm and 60 ppm groups.

One notable finding was significantly ($p<0.05$ or <0.01) reduced brain weights (absolute and relative) for the 60 ppm groups during interim and terminal sacrifices. However, it was less than 10% at both intervals (89% and 95% of control at interim, 94% and 92% of control at terminal). Brain histological examination was conducted for all animals in the control and 60 ppm groups. In the 5 and 20 ppm groups, it was performed only on those that died prior to scheduled sacrifice. The groups and incidences were: control (none), 5 ppm males only (1/27 malignant), 20 ppm (none), 60 ppm males (1/69 benign, 2/69 malignant), and 60 ppm females (1/69 benign). When the interim sacrifice group and those that died before day 218 when the first tumor was detected were excluded, the incidences of astrocytomas for males were: 0/48, 1/25, 0/25, and 3/44 (6.8% incidence) for control to 60 ppm. These incidences are incomplete to establish dose-response relationship because microscopic examination of the brain was not conducted on the remaining animals, about 50%, of the 5 and 20 ppm groups, which survived to terminal sacrifice. Data from the 60 ppm group showed that while the first astrocytoma was observed on day 218, the remaining two incidences were found at terminal sacrifice. Thus, without actual data for astrocytoma at 5 and 20 ppm at terminal sacrifice, the existing data are not suitable for dose-response analysis.

The NOELs were “slightly below” 5 ppm for salivary gland atrophy for both genders, and 5 ppm for metaplasia. The latter NOEL of 5 ppm (5 mg/kg/day) was considered for risk assessment since it showed a clearer dose-response relationship, and atrophy is generally an age-related finding. This study was considered acceptable to DPR according to FIFRA guidelines.

The USEPA established a systemic NOAEL of 5 ppm for increased incidence of salivary gland squamous cell metaplasia (USEPA, 2006a). The NOAEL for port of entry effects was 20 ppm based on olfactory epithelial degeneration and cysts at 60 ppm.

Benchmark dose analysis was conducted for several endpoints in this study to be used in point of departure considerations for subchronic and chronic exposures. The results are listed in the following summary:

Exposure duration/gender	**MeI ppm**					
	ED_{05}	**LED_{05}**	**ED_{10}**	**LED_{10}**	**$ED_{0.61\sigma}$**	**$LED_{0.61\sigma}$**
Increased cholesterol level in rats (continuous liner model)						
26 weeks/Males	4.0	3.0	7.9	6.0	12.4	9.6
26 weeks/Females	9.4	5.7	18.8	11.3	29.7	18.9
Other endpoints						
Salivary gland metaplasia, both genders (loglogistic model)	4.9	3.4	Not determined			
Enlarged thyroid, males (probit model)	18.8	14.2	Not determined			
Thyroid hyperplasia, males (gamma model)	46.4	25.7	Not determined			
Thyroid hyperplasia, females (logistic model)	32.7	25.2	Not determined			
	ED_{01}	**LED_{01}**	**ED_{05}**	**LED_{05}**	**Potency slope**	
Thyroid tumors, males (multistage cancer model)	18	2	33	10	0.005 mg/kg/day^{-1}	

Table 21. Effects in rats exposed to MeI by inhalation in a two-year study.[a]

Effects	Doses							
	Males				Females			
ppm	0	5	20	60	0	5	20	60
mg/kg/day	0	5	19	58	0	5	19	58
Survival (% alive)[b]								
Week 52	90	90	98	84	98	96	96	74
Week 78	64	70	80	70	78	80	82	60
Week 91	50	52	62	54	48	62	66	46
Week 103	34	46	48	36	38	46	48	36
Mean body weight (g)								
Week 5	400	397	397	363**	250	252	252	237**
Week 104	717	725	665	577*	456	449	439	375*
Food Consumption (g/rat/day)								
Week 0-1	26	26	25	24**	18	18	19	19
Week 102-103	28	27	26	23*	21	20	19	18
Cholesterol (mg/dL) (n=10)								
Week 26	74±18	85±23 (115%)	92±12 (124%)	134±26** (181%)	78±14	88±18 (113%)	104±25* (133%)	109±29** (140%)
Week 52	106±29	106±37 (100%)	111±25 (105%)	112±26 (106%)	116±35	96±18 (83%)	106±15 (91%)	134±19 (116%)
Stomach lesion[c]	5/33	5/27	10/26*	11/33	3/31**	4/27	5/27	22/32**
Thyroid								
Absolute weight[b] (mg)								
Week 52	35	35	34	65**	35	34	28	29
Week 104	42	55	55	126**	60	37	34	58
Relative to body weight								
Week 52	0.005	0.005	0.005	0.011**	0.010	0.009	0.007	0.009
Week 104	0.007	0.008	0.009	0.023**	0.014	0.009	0.008	0.017
Enlarged glands– Week 52	0/10**	0/10	0/10	5/20	0/10	0/10	0/10	1/20
– Week 104	2/17**	1/23	6/24	7/17	3/19	1/23	1/23	0/18
- all[c]	4/50**	2/50	7/50	14/50**	3/50	2/50	1/50	3/50
T3 (ng/dL) – Week 26	58±6	51±19	57±21	38±16	68±28	55±17	80±22	49±20
– Week 52	43±11	39±16	51±40	38±11	82±33	79±20	60±10	73±16
– Week 104	50±21	53±21	50±21	44±16	73±32	71±19	66±24	65±22
T4 (µg/dL) – Week 26	3.9±1.0	3.4±0.4	3.2±0.5	1.7±1.4**	2.0±0.6	1.7±0.6	1.9±0.5	1.8±0.7
– Week 52	2.6±0.8	2.4±0.9	3.4±0.7	3.4±0.8*	2.0±0.7	2.2±0.5	1.7±0.3	2.2±0.6
– Week 104	2.2±0.7	2.3±0.7	2.2±1.0	2.5±0.6	1.6±1.0	1.6±0.7	2.0±0.8	2.5±1.0**
TSH (ng/mL) – Week 26	2.5±1.2	3.8±1.9	4.9±3.9	30.5 ±13.7**	1.8 ±0.6	1.8 ±0.5	2.1 ±0.7	12.9 ±13.4**
– Week 52	2.2±0.9	2.3±0.6	3.6±2.8	9.1 ±11.4	2.6 ±0.7	3.3 ±1.9	2.9 ±1.3	5.5 ±6.4
– Week 104	2.4±1.1	3.3±1.6	3.5±1.8	11.3 ±14.9**	2.5 ±1.0	2.9 ±1.8	3.8 ±2.9	4.0 ±6.3
rT3 (ng/mL) – Week 26	0.13 ±0.05	0.12 ±0.05	0.11 ±0.05	0.15 ±0.03	0.10 ±0.05	0.11 ±0.03	0.15 ±0.05	0.19 ±0.09
– Week 52	0.09 ±0.03	0.09 ±0.05	0.09 ±0.04	0.19 ±0.05**	0.12 ±0.04	0.14 ±0.06	0.09 ±0.02	0.33 ±0.16**
– Week 104	0.03 ±0.03	0.04 ±0.03	0.04 ±0.03	0.07 ±0.05**	0.05 ±0.03	0.09 ±0.04	0.20 ±0.12**	0.24 ±0.12**

a/ Data from Kirkpatrick (2005). *, ** for statistical significance at $p<0.05$ and <0.01, respectively. Significance in trend by the Cochran-Armitage Trend test is denoted at the control value.

b/ Includes only in the main group (104 week and unscheduled deaths), not those in the interim sacrifice group.

c/ Total incidences noted for dark red area, mucosa reddened, dark red contents, and distended and number of rats examined.

Table 22. Histopathological findings in rats exposed to MeI by inhalation after 2 years.[a]

Effects	Doses							
	Males				Females			
ppm	0	5	20	60	0	5	20	60
mg/kg/day	0	5	19	58	0	5	19	58
Thyroid Follicular Cell-								
Main Group[b]								
Hyperplasia	0/50**	1/49	0/50	13/50*	0/50	2/49	1/50	10/48*
Main Group[c]								
Adenoma	2/45**	2/45	4/49	10/42**	1/50	1/48	0/48	2/38
Carcinoma	2/45*	0/45	0/49	4/42	1/50	0/48	1/48	2/38
Adenoma plus carcinoma	4/45**	2/45	4/49	12/42*	2/50	1/48	1/48	3/38
Thyroid Follicular Cell-								
Cyst	1/60*	4/60	4/60	8/70*	1/60	2/59	1/60	1/70
Vacuolation	0/60**	1/60	0/60	16/70**	0/60	1/59	0/60	1/70
Hyperplasia, cystic	1/60*	5/60	4/60	8/70*	0/60	3/59	2/60	2/70
Cyst, ultimobranchial	9/60**	10/60	11/60	28/70**	14/60*	16/59	23/60	27/70*
Olfactory epithelium								
Degeneration all levels	2/60**	3/60	8/60*	68/70**	0/60**	2/59	5/60*	63/70**
Level III								
-Degeneration	0/60	0/60	1/60	41/70**	0/60**	1/59	4/60	20/70**
-Cysts	0/60	1/60	0/60	16/70**	0/60**	0/59	0/60	9/70**
Level IV								
-Degeneration	0/60	2/60	4/60	59/70**	0/60	1/59	3/60	43/70**
-Cysts	0/60	0/60	0/60	21/70**	1/60	0/59	1/60	22/70**
Level V								
-Degeneration	0/60	1/60	4/60	63/70**	0/60	0/59	4/60	60/70**
-Cysts	0/60	0/60	0/60	35/70**	0/60	0/59	1/60	35/70**
Level VI								
-Degeneration	1/60	0/60	3/60	54/70**	0/60	0/59	2/60	51/70**
-Cysts	1/60	0/60	0/60	19/70**	0/60	0/59	0/60	28/70**
Salivary gland –								
All animals								
Squamous metaplasia	1/60**	4/59	25/59**	63/70**	0/60**	3/59	25/60**	58/68**
Atrophy	0/60**	5/59*	5/59*	22/70**	0/60**	2/59	5/60*	10/68**
Main Group[b]								
Squamous metaplasia	1/50**	4/49	22/49**	47/50**	0/50**	3/50	22/50**	40/48**
Atrophy	0/50**	5/49*	5/49*	14/50*	0/50**	2/50	5/50*	9/48*

a/ Data from Kirkpatrick (2005). *, ** for statistical significant at $p<0.05$ and <0.01, respectively. Significance in trend by the Cochran-Armitage Trend test is denoted at the control value. For thyroid tumors, single and multiple occurrences of a given tumor type are combined per rat in this table. Incidences were analyzed by using 1-tailed Fisher's exact test. Incidences for olfactory epithelial degeneration according to severity were given in the report with primarily minimal to mild grades for 0, 5, and 20-ppm groups, and the addition of moderate to severe grades at 60 ppm.

b/ Data for all animals in the main group regardless of when they died or sacrificed.

c/ Data for animals died or sacrificed after week 53. First tumors were detected on week 59 (adenoma) and 90 (carcinoma), both in the 60 ppm groups. Two animals had both an adenoma and a carcinoma. NA=not applicable. Significant in trend is noted at the control values. Salivary gland of one animal each (5 ppm male and 20 ppm female) was not examined.

Table 23. Individual animal data on thyroid hormone levels and lesions in 60 ppm male rats exposed to MeI by inhalation for 52 weeks and 104 weeks.[a]

Animal number	T3 ng/dL	T4 µg/dL	TSH ng/mL	rT3 ng/mL	En-larged	AD	CA	HYP
52 weeks-Animals with thyroid gland effects								
3222	40.50	3.62	3.04	QNS		x		
3244	QNS	3.15	18.12	QNS	x			x
3269	53.70	3.50	13.52	QNS				x
3322	55.62	4.86	2.72	QNS				x
3344	43.68	2.97	1.18	QNS	x			
3369	40.92	2.29	9.92	QNS				x
3438	23.12	4.42	3.20	QNS				x
3442	37.96	1.91	48.40	QNS	x	x		x
3484	QNS	2.33	26.02	0.18	x			x
3509	27.04	2.43	13.80	QNS	x	x		x
52 weeks- Animals without thyroid gland effects (values are presented as ranges)								
n=10	12.80-48.56	2.54-4.27	0.88-11.20	0.12-0.24	No effects reported			
104 weeks-Animals with thyroid gland effects								
3234	41.36	2.88	2.27	0.05	x	x	x	
3282	47.61	2.88	36.86	0.14	x		x	
3283	31.50	3.04	6.23	0.11	x			x
3286	37.48	1.49	32.33	0.02				x
3331	54.93	2.24	50.40	0.13	x	x		x
3338	44.54	3.29	10.53	0.12	x	x	x	x
3350	56.76	2.47	20.41	0.03	x			
3371	24.00	1.88	2.62	0.04		x		
3374	32.58	2.27	2.30	0.05		x		
3412	58.02	3.36	11.24	0.18	x	x		x
104 weeks-Animals without thyroid gland effects (values are presented as ranges)								
n=7	23.84-91.45	1.48-3.09	0.92-7.95	0.02-0.09	No effects reported			
Comparison of week 26[b] and 52 hormone and TSH levels for three rats								
No. 3479								
wk 26	36.52	1.47	20.24	QNS				
wk 52	28.96	4.27	3.38	0.24	No effects reported			
No. 3509								
wk 26	QNS	QNS	QNS	QNS				
wk 52	27.04	2.43	13.80	QNS	x	x		x
No.3484								
wk 26	27.42	0.75	52.88	0.13				
wk 52	QNS	2.33	26.02	0.18	x			x

a/ Data from Kirkpatrick (2005), and do not include unscheduled death animals whose thyroid hormone levels were not measured. Abbreviations for thyroid pathology: ENL=enlarged, AD=adenoma, CA=carcinoma, HYP=hyperplasia, QNS=quantity not sufficient for analysis, x=present.

b/ Animals were not sacrificed, therefore no histopathology data.

Table 24. Individual animal data on thyroid hormone levels and lesions in 60 ppm female rats exposed to MeI by inhalation for 52 weeks and 104 weeks.[a]

Animal number	T3 ng/dL	T4 μg/dL	TSH ng/mL	rT3 ng/mL	ENL	AD	CA	HYP
52 weeks-Animals with thyroid gland effects								
3680	98.69	1.75	2.74	0.11				x
3708	QNS	2.06	11.20	QNS		x		
3742	50.02	1.13	28.20	QNS	x			x
52 weeks- Animals without thyroid gland effects (values are presented as ranges)								
n=17	50.28-92.18	1.49-3.48	0.98-11.14	0.23-0.61	No effects reported			
104 weeks-Animals with thyroid gland effects								
3729	71.72	2.55	4.17	0.24				x
3763	31.29	2.81	1.11	0.23		x		
3813	63.95	1.75	3.69	0.13				x
3817	67.55	1.92	28.37	0.23		x		x
104 weeks-Animals without thyroid gland effects (values are presented as ranges)								
n=14	32.31-94.31	1.32-4.66	0.85-6.85	0.09-0.49	No effects reported			
Comparison of week 26[b] and 52 hormone and TSH levels								
No.3825								
wk 26	QNS	2.63	2.60	0.24				
wk 52	70.98	2.23	2.54	0.23	No effects reported			
No. 3849								
wk 26	85.74	2.91	6.22	0.20				
wk 52	QNS	3.48	2.18	0.61	No effects reported			

a/ Data from Kirkpatrick (2005), and do not include unscheduled death animals whose levels were not measured. Abbreviations for thyroid pathology: ENL=enlarged, AD=adenoma, CA=carcinoma, HYP=hyperplasia, x=present.

b/ Animals were not sacrificed, therefore no histopathology data.

III.D.2. Mouse - Oral

Crl:CD-1(ICR) mice (50/sex/group) were given microencapsulated MeI (purity 99.7% 0, 60, 200 or 600 ppm) daily mixed in the diet for 18 months (Harriman, 2005a; pathology report in Hardisty, 2005; interim reports in WIL Research Laboratories, 2004). The mean dosages for males were 0, 8, 28, and 84 mg/kg/day; and for females were 0, 10, 35, and 100 mg/kg/day. MeI treatment had no effect on survival, clinical signs, or hematology.

Mean body weight was significantly reduced at 600 ppm starting on study week 1 and continued to week 78 for all male groups, but only the 600 ppm females (Table 25). The reduction in body weight was dose and time-related, and was associated with food consumption decrease, suggesting a palpability problem and/or irritation in the GI tract (Table 26 and 27).

The target organs were thyroid, GI tract and reproductive system. The thyroid was assessed only at termination with significant changes in the hormones for males only (Table 25). These included elevated TSH at 200 to 600 ppm, reduced T4 at 600 ppm, and increased incidences of enlarged thyroids at 600 ppm. However, significantly increased thyroid/parathyroid weights were reported for both genders in all treatment groups. Histological examination showed increased incidences of colloid[13], vacuolation, cysts, hyperplasia, and tumors in the treated groups (Table 26 and 27). With increased colloid, vacuolation, and cyst, high incidences of similar magnitude were reported for 200 and 600-ppm groups. There were two forms of follicular cell hyperplasia[14], with lack of dose-response relationship as well as no change in severity noted for "hyperplasia", where low and minimal incidences were reported for all treated groups. "Hyperplasia, follicular cell" data, on the other hand, showed a gender difference with high incidences and mostly minimal severity for all female treated groups, but very low incidences for all male treated groups. The investigators considered the non-significant increase in follicular cell tumors in 600-ppm males (2 adenomas and 1 carcinoma) to be treatment-related. Single follicular cell adenoma was observed in a 200-ppm male, a 600-ppm female, and a control female; this finding was not attributed to treatment. Basophilic hypertrophy of the pituitary (plausibly associated with enhanced TSH production) was statistically significantly elevated in all groups of females. The lack of dose-response relationship, however, could represent a secondary treatment response or a random low control value. For the latter, the male control showed an incidence (37/49) higher than all values for the female groups (13/48 to 35/50).

For the GI tract, hyperkeratosis was reported for the esophagus, pharynx, and non-glandular stomach at all doses, with statistically significant increases at 60 ppm (females and esophagus only), 200 ppm and 600 ppm (Table 26 and 27). The investigators considered hyperkeratosis a local irritation effect since MeI was given in the diet and the lesion was limited to the squamous

[13] "Increased colloid" determination was made when 3 or fewer follicles could span a 40x microscopic field. "Cytoplasmic vacuolation" was applied to cells which appeared to be follicular-type cells (and specifically did not appear to be C-cells), but which did not surround follicles. The vacuoles were described as "distinct and clear."

[14] There were two forms of follicular cell hyperplasia: "hyperplasia"- nests of cells similar to that described for cytoplasmic vacuolation, except the foci were larger (more cellular), and follicular lumens were infrequently observed; and "hyperplasia, follicular cell"- higher numbers of cells lining the thyroid follicles, which contained discolored (gray) colloid. For the two types of hyperplasia, the foci were described as small, mild in the majority of the incidences, and involving only an estimated 1-3% or less of the total thyroid gland area.

regions of the upper GI tract. Stomach squamous cell carcinoma (one at 600 ppm) or papilloma (one at 200 ppm) was found in the males, but none in the females.

The investigators noted a positive trend in incidences of cervical fibroma, and combined cervical and uterine fibroma (Table 27). The fibromas were described as small bundles of fibers without evidence of mitotic activity. They were not grossly evident, and appeared not to be growing appreciably nor advancing toward malignancy. The incidences did not show any statistical significance by pair-wise comparisons. The reported historical incidences of benign fibromas in the uterus or cervix are very low (Charles River Laboratories, Inc. compilation in March 2000 reported 2/2812 cases in uterus, and 0/2724 cases in cervix). However, this historical incidence may not be an appropriate comparison to the results in the present study, which is based on reevaluation of the original sections, and additional sections for the Pathology Working Group (Hardisty, 2005). The Group concluded that proliferative mesenchymal lesions (fibroma and leiomyoma) of the uterus or cervix were not treatment-related because of the following reasons:

1. Low incidence for fibromas in the treated mice, compared to that for the concurrent controls
2. No precursor cytotoxic lesions or non-neoplastic proliferative changes were observed
3. Increased incidences only in this study, and not in the rat two-year oncogenicity study
4. Proliferative changes detected after extensive examination, not comparable with historical ranges
5. No known clinical or biological significance for these fibromas in animals or humans.

The study NOEL was < 60 ppm (< 8 mg/kg/day in males) with a Lowest-observed-effect Level (LOEL) of 60 ppm for decreased body weight; markedly elevated thyroid/parathyroid weights, increased colloid and cytoplasmic vacuolation in thyroid; follicular cell hyperplasia; and hyperkeratosis as evidence of upper GI tract local irritation. The Medical Toxicology Branch Reviewer found that, at present, there was insufficient information to determine whether the observed incidences of fibromas, particularly in the cervix, were an indication of oncogenicity. Neither associated histopathology nor any evident mechanism was available to explain the findings. However, the possibility that the fibroma in the cervix in high dose females was treatment-related cannot be dismissed at this time. This study was considered acceptable to DPR according to FIFRA guidelines. While the 18 month study duration met the FIFRA oncogenicity study protocol for mice, the SRC commented that higher incidences of thyroid tumor may be found if the study had been conducted for 2 years, the duration in the rat inhalation study (Kirkpatrick, 2005) (**Volume IV Part 1-A**).

The USEPA did not establish a NOEL for this study (USEPA, 2006a and 2007). The results on the thyroid, uterus, and cervix were discussed in the cancer assessment review (USEPA, 2005d). USEPA noted that the thyroid tumors were treatment related and were consistent with perturbations of thyroid function. However, the uterine and cervical fibromas were not considered treatment-related for reasons similar to those put forth by the Pathology Working Group.

Table 25. Chronic toxicity in mice exposed to microencapsulated MeI in the diet in an 18-month study .[a]

Effects	Doses							
	Males				Females			
ppm	0	60	200	600	0	60	200	600
mg/kg/day	0	8	28	84	0	10	35	100
Mean body weight (g, % of control)								
Week 1	30.0	29.8	29.6	27.3** (9%)	23.6	23.4	23.1	22.3** (6%)
Week 78	41.3	38.5** (7%)	38.4** (7%)	36.6** (11%)	34.0	34.0	32.9	31.1** (9%)
Food Consumption (g/mouse/day)								
Week 0-1	5.1	4.8	4.9	4.1**	4.7	4.8	4.7	3.9**
Week 102-103	5.4	4.9**	4.8**	4.8**	5.3	5.9*	5.2	4.6**
Thyroid Effects								
T3 (ng/dL)	71	70	75	75	62	59	67	69
T4 (µg/dL)	2.7	2.6	2.6	1.9**	1.8	1.9	1.9	1.8
TSH (µg/mL)	0.45	0.54	0.69*	0.86**	0.28	0.45	0.47	0.39
Enlarged thyroid gland at terminal sacrifice	0/43	0/37	2/41	8/40**	1/42	2/39	3/42	5/44
Thyroid/parathyroid organ weight (mg)	8.7	20.4**	20.7**	20.3**	8.6	17.9**	16.5**	16.3**
relative to body weight	0.021	0.053**	0.054**	0.056**	0.025	0.053**	0.050**	0.053**

a/ Data from Harriman (2005a). *, ** for statistical significance at $p<0.05$ and <0.01, respectively.

Table 26. Histopathological findings in male mice exposed to MeI in the diet in an 18-month study.[a]

Effects	Doses			
ppm	0	60	200	600
mg/kg/day	0	8	28	84
Thyroid Follicular cell				
Vacuolation	0/50**	12/50**	22/50**	15/49**
Increased colloid	3/50**	28/50**	37/50**	44/49**
Cyst, ultimobranchial	23/50	24/50	30/50	31/49
Hyperplasia, follicular cell	0/50*	1/50	3/50	6/50*
minimum	0	1	3	6
mild	0	0	0	0
Hyperplasia	0/50**	4/50	2/50	8/49**
minimum	0	2	1	7
mild	0	2	1	1
Adenoma	0/50*	0/50	1/50	2/49
Carcinoma	0/50	0/50	0/50	1/49
Adenoma & carcinoma	0/50*	0/50	1/50	3/49
Pituitary hypertrophy	37/49	11/13	5/8	44/49
GI tract				
Esophagus				
Hyperkeratosis	3/50**	4/50	28/50**	38/49**
Epithelial hyperplasia	0/50**	0/50	0/50	4/49
Pharynx hyperkeratosis	1/50**	3/50	11/48**	26/49**
Stomach, non-glandular				
Hyperkeratosis	5/49**	11/50	32/50**	38/49**
Squamous cell carcinoma	0/49	0/50	0/50	1/49
Squamous cell papilloma	0/49	0/50	1/50	0/49

a/ Data from Harriman (2005a). *, ** for statistical significant at $p<0.05$ and <0.01, respectively. Significance in trend by the Cochran-Armitage Trend test is denoted at the control value. Incidences were analyzed by DPR Data Reviewer using 1-tailed Fisher's exact test.

Table 27. Histopathological findings in female mice exposed to MeI in the diet in an 18-month study.[a]

Effects	Doses			
ppm	0	60	200	600
mg/kg/day	0	10	35	100
Thyroid Follicular cell				
Vacuolation	0/49	15/50**	14/50**	12/50**
Increased colloid	8/49**	35/50**	31/50**	36/50**
Cyst, ultimobranchial	33/49**	32/50	41/50	45/50**
Hyperplasia, follicular cell	1/49**	25/50**	22/50**	26/50**
minimum	1	18	17	22
mild	0	7	4	3
moderate	0	0	1	1
Hyperplasia	1/50	2/50	5/50	5/50
minimum	1	1	5	5
mild	0	1	0	0
Adenoma	1/50	0/50	0/50	1/50
Carcinoma	0/50	0/50	0/50	0/50
Adenoma & carcinoma	1/50	0/50	0/50	1/50
Pituitary hypertrophy	13/48**	30/49**	28/49**	35/50**
GI tract				
Esophagus Hyperkeratosis	0/50	5/50*	27/50**	45/50**
Pharynx hyperkeratosis	1/49**	5/50	16/49**	31/50**
Stomach, non-glandular Hyperkeratosis	19/50**	20/50	34/50**	36/50**
Cervix/Uterus				
Cervical fibroma	0/49*	1/50	0/47	3/50
Uterine fibroma	0/50	1/50	0/50	1/50
Combined	0/50**	1/50	0/50	4/50

a/ Data from Harriman (2005a). *, ** for statistical significance at $p<0.05$ and <0.01, respectively. Incidences were analyzed by using 1-tailed Fisher's exact test. Significance in trend by the Cochran-Armitage Trend test is denoted at the control value.

III.D.3. Dog - Oral

Beagle dogs (4/sex/group) received gelatin capsules containing MeI (purity 99.7%; 0, 1.5, 6.0, or 12.0 mg/kg/day) daily for 52 weeks (Harriman, 2004; interim report in WIL Research Laboratories, 2003). One male in the 6.0 mg/kg/day group and one female in the 12.0 mg/kg/day group were euthanized *in extremis* after 41 weeks. Clinical observations were made twice daily, as well as 2-hours prior to and after dosing. Clinical signs included head shaking, clear material around the mouth, excessive drooling, and injected sclera (Table 28 and 29). As with the results from the subchronic toxicity study (Table 20; Harriman, 2003d), the incidences generally increased with dose, but lower incidences were recorded for 2-hours after dosing than before dosing. Examination of the individual data for the 12-month study showed that the high incidence for the low dose and control groups was attributed to a few dogs in these groups with high incidences (Harriman, 2005b). The ophthalmic examination was normal for all groups.

There were no apparent treatment-related effects on mean body weight, body weight gain or food consumption. Hematology and serum chemistry showed some changes related to treatment affecting one or both genders at 6.0 and 12.0 mg/kg/day during either the 25 or 52-week measurements (Table 28 and 29). These included: increased mean numbers of platelets and cholesterol levels, and reduced albumin and total protein.

Organ weight changes were noted for the treatment groups (Table 28 and 29). The mean absolute and relative liver and thyroid/parathyroid weights were increased at 12.0 mg/kg/day groups with the values statistically significant for some relative weights. While the total T3, T4, and rT3 levels were not affected by treatment, the average TSH levels in the 12.0 mg/kg/day groups were higher (not statistically significant) than those in the control. The large standard deviations were attributed to the increased TSH level of one male (1/4) and one female (1/4) in each group. These two animals demonstrated mild to severe colloid depletion and moderate follicular cell hypertrophy of the thyroid gland, and minimal to mild hyperplasia of basophilic cells in the pars distalis of the pituitary gland.

Gross examinations of the tissues showed thickening and discoloration of the esophagus, firmness and enlargement of the mandibular salivary gland, and thickening of the stomach from the 6.0 and 12.0 mg/kg/day groups. Microscopic examination showed extensive ulceration of the esophagus, mucous cell hypertrophy and/or decreased secretion of the mandibular salivary gland, and hyperplasia and/or decreased secretion of the stomach. The author attributed the effects on these tissues to the irritative property of MeI. For males, there was dose-related increased incidences and severity of seminiferous tubular degeneration (Table 28). No significant microscopic findings were reported in other tissues (including brain and nasal cavity).

The chronic NOEL was < 1.5 mg/kg/day based upon the increased incidence of clinical signs (clear material around mouth, excessive drooling, and marked injected sclera) in the 1.5 mg/kg/day group. This study was considered acceptable to DPR according to FIFRA guidelines.

Table 28. Chronic toxicity in male dogs exposed to MeI capsules via the oral route in a one-year study.[a]

Effects	Doses (mg/kg/day)							
	0		1.5		6.0		12.0	
Clinical signs (No. of events/no. of animals affected, prior to and 2 hours post each dosing)[b]								
	prior	**2-hr**	**prior**	**2-hr**	**prior**	**2-hr**	**prior**	**2-hr**
Head shaking	0/0	0/0	0/0	0/0	27/2	5/1	127/4	5/3
Clear material around mouth	30/3	21/3	90/4	108/4	183/4	213/4	426/4	259/4
Excessive drooling	0/0	0/0	3/1	2/1	53/3	34/3	301/4	39/4
Sclera, marked injection - left eye	24/3	23/2	11/2	17/2	7/3	7/2	6/2	4/2
- right eye	21/3	16/3	14/3	17/2	6/2	4/3	5/2	3/2
Hematology and serum chemistry								
Platelet (10^3/µL) - week 25	280±30.4		270±26.9		342±33.7		387±80.5*	
- week 52	312±38.7		330±30.7		374±96.2		478±99.3*	
Albumin (g/dL) - week 25	3.6±0.19		3.6±0.10		3.2±0.24		3.0±0.19**	
- week 52	3.5±0.05		3.5±0.17		3.4±0.06		3.3±0.44	
Total protein (g/dL) - week 25	6.0±0.08		6.1±0.35		5.9±0.24		5.5±0.60	
- week 52	6.0±0.38		6.4±0.48		5.9±0.17		6.0±1.24	
Cholesterol (mg/dL) - week 25	148±29.5		168±12.4		182±30.0		232±52.8*	
- week 52	132±28.3		149±13.4		197±29.4		283±144.2	
Mean absolute (g) and relative organ weights (g/100 g body weight)								
Liver -absolute	342.0±72.7		382.8±31.0		378.6±36.6		432.4±65.6	
-relative	2.52±0.47		2.80±0.09		2.85±0.18		3.44±0.58*	
Thyroid/Parathyroid - absolute	1.21±0.10		1.03±0.14		1.21±0.06		0.87±0.33	
- relative	0.009±0.0008		0.008±0.002		0.009±0.0006		0.007±0.003	
Thyroid Function								
TSH ng/mL- week 25	0.1±0.05		0.2±0.08		0.1±0.08		2.0±3.92	
- week 52	0.1±0.00		0.2±0.10		0.1±0.06		4.2±8.12	
T3 (ng/dL) - week 52	92.2±9.01		113.2±19.84		104.7±4.73		93.3±47.97	
T4 (µg/dL)- week 52	1.5±0.36		2.5±0.74		2.2±0.95		2.2±1.16	
rT3 (mg/mL)- week 52	0.40±0.074		0.46±0.095		0.53±0.185		0.31±0.110	
Histopathology (no. animals affected/no. animals examined)								
Thyroid Colloid depletion -mild	0/4		0/4		0/3		0/4	
- moderate	0/4		0/4		0/3		0/4	
- severe	0/4		0/4		0/3		1/4	
Follicular cell hypertrophy								
- moderate	0/4		0/4		0/3		1/4	
Testes, seminiferous tubules								
degeneration - minimal	0/4		1/4		1/3		1/4	
- mild	0/4		0/4		0/3		1/4	

a/ Data from Harriman (2004). *, ** for statistical significance at $p<0.05$ and <0.01, respectively.
b/ Clinical observations were made prior to dosing for the day, and two hours after the dosing.

Table 29. Chronic toxicity in female dogs exposed to MeI capsules via the oral route in a one-year study.[a]

Effects	Doses (mg/kg/day)							
	0		1.5		6.0		12.0	
Clinical signs (No. of events/no. of animals affected, prior to and 2 hours post each dosing)[b]								
	prior	**2-hr**	**prior**	**2-hr**	**prior**	**2-hr**	**prior**	**2-hr**
Head shaking	0/0	0/0	0/0	0/0	10/4	0/0	332/4	29/4
Clear material around mouth	2/2	3/3	44/4	31/4	113/4	81/4	225/4	77/4
Excessive drooling	0/0	0/0	0/0	0/0	19/3	12/3	228/4	15/4
Sclera, marked injection- left eye	0/0	0/0	18/2	0/0	44/2	45/3	27/2	20/3
- right eye	0/0	0/0	9/2	0/0	40/2	37/3	34/2	32/3
Hematology and serum chemistry								
Platelet (10^3/µl) -week 25	281±34.6		307±39.9		349±97.5		411±32.2*	
-week 52	314±61.7		347±22.6		422±14.8*		480±88.9**	
Albumin (g/dL) -week 25	3.6±0.10		3.6±0.10		3.3±0.08		2.9±0.34**	
- week 52	3.7±0.10		3.6±0.13		3.3±0.14**		2.7±0.21**	
Total protein (g/dL) -week 25	5.8±0.15		5.9±0.32		6.1±1.05		5.2±0.55	
-week 52	6.2±0.21		6.0±0.22		5.7±0.44		5.0±0.20**	
Cholesterol (mg/dL) -week 25	142±18.9		156±23.4		239±126.2		225±34.3	
-week 52	153±20.5		193±44.0		206±67.9		227±40.1	
Mean absolute (g) and relative organ weights (g/100 g body weight)								
Liver - Absolute	316.3±45.2		302.8±19.7		345.7±35.1		375.4±55.2	
- Relative	2.84±0.33		2.50±0.23		2.90±0.11		3.18±0.13	
Thyroid/Parathyroid -absolute	1.19±0.38		0.80±0.09		1.05±0.25		0.64±0.13	
-relative	0.011±0.003		0.007±0.0006		0.009±0.0024		0.005±0.002*	
Thyroid Function								
TSH ng/mL- week 25	0.1±0.08		0.3±0.13		0.2±0.10		0.5±0.47	
- week 52	0.1±0.00		0.3±0.10		0.2±0.06		2.7±3.93	
T3 (ng/dL) - week 52	111.9±26.63		97.7±14.46		90.9±8.92		82.3±6.05	
T4 (µg/dL)- week 52	3.0±0.29		2.6±0.68		3.0±0.67		2.4±1.47	
rT3 (ng/mL)- week 52	0.62±0.049		0.56±0.149		0.53±0.053		0.42±0.243	
Histopathology (no. animals affected/no. animals examined)								
Thyroid								
Colloid depletion -mild	0/4		0/4		0/4		1/3	
-moderate	0/4		0/4		0/4		0/3	
-severe	0/4		0/4		0/4		0/3	
Follicular cell hypertrophy								
- moderate	0/4		0/4		0/4		0/3	

a/ Data from Harriman (2004). *, ** for statistical significance at $p<0.05$ and <0.01, respectively.
b/ Observations were made prior to dosing for the day, and two hours after the dosing.

III.D.4. Other Studies

In a screening assay of chemicals for the induction of lung tumors, A/He mice (10/sex/ treated group; 30/control, 160/vehicle control) were injected intraperitoneally with MeI (0, 0.06, 0.15, or 0.31 mmoles/kg) three times a week for 24 weeks (Poirier *et al*., 1975). The survival incidences were: 29/30 for control (no injection), 154/160 for vehicle control (tricaprylin); and 19/20 for low dose, 20/20 for mid dose, and 11/20 for high dose of MeI. The lung tumor incidences expressed as average number of lung adenomas/mouse were: 0.21±0.03 (control), 0.22±0.03 (vehicle control), 0.21±0.05 (low dose), 0.30±0.07 (mid dose), and 0.55±0.19 (high dose, $p<0.05$). However, there was little difference when the incidence was expressed as the number affected/total number in group: 6/30 (control), 35/160 (vehicle control), 4/20 (low), 6/20 (mid), and 5/20 (high). The authors compared the tumor incidences for MeI with other alkyl halides tested and concluded that alkyl halides were "weakly" carcinogenic with MeI as the most potent with the highest tumor incidence on a molar basis for the class of compounds. This was a published study, and detailed data on these tumors, such as time to tumor and severity, were not provided.

In a study of the oncogenicity of 12 alkylating compounds, BD rats were given subcutaneous injections of MeI in oil, either weekly for 1 year (10 mg/kg or 20 mg/kg) or as a single dose of MeI (50 mg/kg), and observed for more than 1 year (Druckrey *et al*., 1970). Some animals in the treated groups died of pneumonia: 4/16 in 10 mg/kg group, 2/8 in 20 mg/kg group, and none in 50 mg/kg group. The subcutaneous sarcoma incidences were 9/16 (10 mg/kg) and 6/8 (20 mg/kg) for the weekly injection groups, and 4/14 (50 mg/kg) for the single injection group. The tumors were described as fibrosarcomas, and spindle cell and round-cell sarcomas. They were developed 500 to 700 days after exposure. Pulmonary and lymph node metastases (no incidences given) were reported in some of the treated animals at 10 mg/kg, but no mention of these effects for the other dose groups. This was a published report, which did not include details of the method or results. The authors concluded that MeI is a weak inducer, but has high local reactivity and long delay in tumor induction. According to another report, no tumors were reported in the control group, although the number of animals in this group was unknown (IARC, 1977).

III.E. Genotoxicity

Summary: Methyl iodide can be considered a point mutagen because of positive results from *in vitro* gene mutation assays, in particular those conducted in closed systems. However, in some of those studies, the positive response occurred at cytotoxic doses. The results were negative for mutagenicity studies conducted under FIFRA guidelines. Methyl iodide is a clastogen because of increased chromosomal aberrations in Chinese hamster ovary ($CHO\text{-}K_1$) cells, and formation of small colonies in the mouse lymphoma cells. In an *in vivo* experiment, MeI did not induce effects on the chromosome or mitotic spindle of micronucleated polychromatic erythrocytes from bone marrow of mice given MeI by intraperitoneal injection. Morphological transformation assays using mouse or hamster embryo cells showed mixed results. There was some indication of MeI as an alkylating agent based on alkylation of guanines from DNA of human lymphocytes incubated with MeI. Adducts detected in DNA from tissues (lungs, liver, stomach, and forestomach) of rats exposed to ^{14}C-MeI by either gavage or inhalation is also evidence of direct methylation as well as *de novo* synthesis. A summary of the genotoxicity studies is presented in Table 30.

III.E.1. FIFRA Guideline Studies

III.E.1.a. Gene Mutation

Salmonella typhimurium strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 *uvr*A were preincubated with MeI (purity 99.7%; 0 to 5,000 µg per tube) in the presence or absence of rat liver S9 preparation for 1 hour, and then plated on agar for 48 to 72 hours (Wagner and Dakoulas, 2001). Toxicity, noted as slight to moderate, was reported only for the 5000 µg per plate dose. None of the MeI doses increased reversion frequency. Positive controls (2-nitrofluorene, NF; sodium azide, NAZ; 9-aminoacridine, AAC; methyl methanesulfonate, MMS; and 2-aminoanthracene, AAN) were positive as expected. The USEPA considered this study as a "No Test" because the registrant claim of no volatilization could not be verified (MRID 45593813; McCarroll, 2005). DPR Data Reviewer concurred with the concern, considering that other studies were positive when MeI vapors had been contained by enclosure in desiccators, or where test article was applied in saturated disks (see **III.E.2.a. Gene Mutation**).

Chinese hamster ovary cells ($CHO\text{-}K_1\text{-}BH_4$) were treated with MeI (purity 99.7%; 0 to 200 µg/mL) for 5 hours in the presence or absence of rat liver S9 fraction (San and Clarke, 2001). For cloning efficiency, cells were cultured for 7 to 10 days and number of colonies counted. Methyl iodide reduced cloning efficiency to about 70% of control at 100 µg/mL to 19% at 150 µg/mL (higher doses not tested for -S9 samples) and 41% at 200 µg/mL (with S9 samples). For the expression of the mutant phenotype, cells were subcultured at 2-3 day intervals during the 7-10 day expression period. Methyl iodide did not cause any increase in mutation at the HGPRT (hypoxanthine guanine phosphoribosyl transferase) locus. Adequate positive controls (ethyl methanesulfonate, EMS; benzo(a)pyrene, B(a)P) were included. This study was considered unacceptable to DPR because there was no confirmation of the negative mutation results. The USEPA determined that MeI tested negative in this assay and the study was acceptable (MRID 45593815; McCarroll, 2005).

III.E.1.b. Structural Chromosomal Aberrations

Chinese hamster ovary (CHO-K_1) cells (approximately 5 x 10^5 cells/25 cm^2 flask) were treated with MeI (purity 99.7%; 0 to 350 µg/mL) in the absence (4 and 20 hours) and presence (4 hours) of rat liver S9 fraction (Gudi and Brown, 2001). MeI at >150 µg/mL was toxic to the cells with growth inhibition at about 20% for 150 µg/mL and increased to 100% for 350 µg/mL. Metaphase cells (200 cells per treatment, up to 250 µg/mL for no S9 and to 200 µg/mL for +S9 fraction) were harvested and evaluated 20 hours after treatment initiation. Methyl iodide induced a significant increase of structural chromosomal aberrations (chromatid breaks and exchanges) at MeI ≥150 µg/mL (in the absence of S9), and MeI ≥100 µg/mL (+S9). It did not induce numerical chromosomal aberrations. Positive controls (cyclophosphamide, CP; mitomycin, MMC) functioned as expected. This study was considered acceptable to DPR. The USEPA also found the study to be acceptable (MRID 45593814; McCarroll, 2005).

III.E.1.c. Other Genotoxic Effects

ICR mice (5 or 10/sex/group) received a single intraperitoneal injection of MeI (purity 99.7%) (Gudi and Krsmanovic, 2001). A toxicity study conducted with 50, 100, 200, and 280 mg/kg showed that 100 mg/kg was the maximally tolerated dose. At 200 and 280 mg/kg, there were high mortality (≥ 60% died) and clinical signs (lethargy, piloerection, crusty eyes, crusty nose, and tremors). In the bone marrow assay, mice were injected with 25, 50, or 100 mg/kg MeI and micronucleated polychromatic erythrocytes were examined to determine if there was chromosomal damage or damage to the mitotic apparatus. MeI did not cause any damage or increase in the number of micronucleated polychromatic erythrocytes. The positive control (CP) functioned as expected. This study was considered acceptable to DPR. The USEPA also found the study acceptable and that MeI was not clastogenic or aneugenic (MRID 45593816; McCarroll, 2005).

III.E.2. Published Studies

III.E.2.a. Gene Mutation

Methyl iodide was evaluated as one of 14 “alkylating agents” among a total of 99 test compounds (Rosenkranz and Poirier, 1979). *Salmonella typhimurium* strains TA1535 and TA1538 were tested by colony counts. The disk diffusion, rather than plate incorporation exposure, was used for both systems, in recognition of the volatility of the test article. There were significant increases (about 3- to 12-fold with or without S-9, respectively, over a 5-fold dose range) in revertants with TA 1535 (base-pair mutagen), but no response with frameshift mutant TA 1538. USEPA considered this study to provide valid qualitative data indicative of mutagenic potential (McCarroll, 2005).

There was a difference between conducting the Ames’ assays under standard assay conditions and those in a sealed container. Simmon *et al.* (1977) found MeI to be negative when the test strains (TA 1535, 1537, 1538, 98, or 100) were preincubated with MeI in capped test tubes, and then plated onto petri dishes. However, when MeI was added to a desiccator containing uncovered culture dishes with TA 100 (without rat liver S-9 fraction) and sealed during incubation time, there was about a 2.5-fold increase of revertants. This result was repeated in another report by the same investigator in a screening of 101 chemicals using the

Ames assay (Simmon, 1979a). MeI did not increase revertants in standard petri dish assays with TA 1535, TA 1536, TA 1537, TA 1538, TA 98 and TA 100. It was positive in the desiccator system, with the increase of revertants about 2-fold with S-9, and about 3-fold without S-9 preparation.

The alkylation and mutagenicity of MeI and other test compounds were compared using epichlorohydrin as the reference (Hemminki *et al*., 1980). Only summary results were provided in this report. Alkylation rates were measured using two substrates: a synthetic electrophile, 4-(p-nitrobenzyl)-pyridine, and deoxyguanosine. With both substrates, MeI alkylation rate was 27% of epichlorohydrin rate. These investigators also examined the mutagenicity of MeI using the *E. coli* WP2 uvrA assay. Methyl iodide was found to be mutagenic, 90% as active as epichlorohydrin in a test system without liver S9 activation preparation.

Methyl iodide was mutagenic at cytotoxic levels, assayed by *E. coli* WP2 revertant cell counts (Takahashi and Kawazoe, 1987). It was considered a "chemoselective methylating agent," as it effectively activated the *alkA* gene, but had only weak activation of the *umuC'* gene, in contrast to more reactive chemicals such as MMS. The investigators proposed that MeI stimulated the bacterial "adaptive response" (which increases cell repair activity in the presence of methylating agents) by direct methylation of a key methyltransferase. The USEPA noted this study provided a possible mechanism for MeI induction of the adaptive response in bacteria (McCarroll, 2005). In addition, these assays measured cellular release of β-galactosidase (a marker of both adaptive and SOS responses) at much lower MeI dose levels than the concentration determined to be cytotoxic in the Ames test submitted to fill FIFRA guideline requirements.

In a screening study, MeI was one of 101 chemicals tested in *Saccharomyces cerevisiae* D3 heterozygous for mutation *ade2* (Simmon, 1979b). Recombinants, which are homozygous for *ade2*, have a red pigment, which serves as the test endpoint. Methyl iodide was positive for recombinants, when incubated with and without rat liver S9 preparation.

Methyl iodide increased the mutation rates in CHO cells at the HGPRT locus (Amacher and Zelljadt, 1984). From 0.5 µg/mL to 3.0 µg/mL, the revertant rates were 3-fold, 8.5-fold, and 5.7-fold higher than that for the control, with the lower number at 3.0 µg/mL likely due to cytotoxicity (60% survival for this dose). The investigators concluded that MeI at the dose range tested, was positive for point gene mutations.

Methyl iodide was tested in mouse lymphoma mutation assay (with or without rat liver S-9 preparation) at two loci: the rapidly-expressing TK locus and the slowly expressing HGPRT locus (Clive *et al*., 1979). Clive *et al.* indicated that some carcinogens positive at the TK locus could be non- or very weakly mutagenic at the HGPRT locus, because the latter change could be diluted during a long expression time. At the $TK^{+/-}$ locus for MeI, the greatest sensitivity was following short exposure intervals and shorter expression periods (mutagenic at 48 or 72 hour expression, but not after 144 hour expression). At less than 90% lethality, the only positive finding with MeI treatment was a marginal increase in total mutant ($TK^{-/-}$) colony counts after incubation in the presence of S-9 for 4 hours, and 48-hour expression time. The colonies were classified as small, which the investigators indicated as a result of chromosomal aberration (large colonies would be the result of gene or point mutation). Severe toxicity (≤ 40% survival) was noted at ≥ 60 µg/mL. At these test concentrations, results were negative at the HGPRT locus.

Methyl iodide, at a cytotoxic level, was one of the chemicals in a method development, which used increased mutation frequencies in L5178Y/TK$^{+/-}$ mouse lymphoma cells to illustrate the utility of the "SES" [sequester, express, and select] technique (Moore and Clive, 1982). Genotoxicity, due to chromosomal aberrations, was noted as the prevalence of small colonies elicited by MeI. There was some apparent mutagenicity response at various dose levels including one, which allowed 58% survival. Only reduced data (plots) were presented.

In other experiments using the L5178Y/TK$^{+/-}$ mouse lymphoma cells, MeI (without rat liver S-9 preparation) increased the frequencies of colonies in the dose range associated with 20% to 60% survival, with small colonies being prevalent (Moore *et al*., 1985a and b). A figure in the report (Moore *et al.*, 1985a) identified the bimodal distribution of large and small colonies at less-toxic dose levels. A prevalence of small colonies was an indication of clastogenic activity.

L5178Y/TK$^{+/-}$ mouse lymphoma cells incubated with MeI showed elevated mutant frequency over controls at about 3.75 and 5 μg/mL, corresponding to 40% to 60% reductions in relative growth in the ouabain-resistant locus gene mutation assay (Amacher and Dunn, 1985). Maximum increase at about 3.75 μg/mL was approximately 5-fold over concurrent controls. Both large and small ouabain-resistant colonies were observed, suggesting to investigators that at least some of the mutants reflected point mutations.

III.E.2.b. Other Genotoxic Effects

In a test for the morphological transformation of mouse embryo cell line (C3H/10T1/2 CL8 cells) by alkylating agents, MeI was negative (Oshiro *et al.*, 1981). Other compounds, including MNNG and β-propiolactone, were positive in this test system.

Methyl iodide was one of many test chemicals in a carcinogen screening assay based on the morphological transformation of Golden Syrian Hamster embryo cells derived from cryopreserved primary cultures (Pienta *et al*., 1977). Tests included several hundreds of control group dishes, and tens of thousands of control colonies, all of which were negative. For MeI, the ratios of transformed colonies/surviving colonies were 0/400 (control), 0/624 (0.1 μg/mL), 2/609 (1 μg/mL), 1/673 (10 μg/mL), and 0/207 (100 μg/mL). DPR Data Reviewer considered the study to be positive for MeI considering the extreme rarity of transformed colonies in the control.

Human lymphoblast cells or DNA extracted from lymphocytes of male donors were incubated with MeI at 80 mM or 160 mM, and compared with iodoethane (Cloutier *et al*., 2001). Alkylation was measured along the sequences of the promoter and exon 1 of the Fragile-X mental retardation 1 (FMR1) gene, and was detected using ligation-mediated polymerase chain reaction. Both MeI and iodoethane, as representatives of S_N2 alkylating agents, caused the formation of hyper-reactive sites at two guanine positions of the gene. The methylating frequency at one of the guanine positions for MeI was 2-fold higher than that for iodoethane. The distribution patterns of alkylated guanines were similar for the *in vivo* and *in vitro* studies. The authors considered these hyper-reactive sites as hotspots for damage, which if left unrepaired, could lead to mutation.

F344 rats were exposed to 54 μmol/animal of ^{14}C-MeI by inhalation for 6 hours or to a single oral gavage dose of 7.2 μmol/animal of ^{14}C-MeI (Gansewendt *et al*., 1991). The animals were sacrificed immediately after inhalation exposure, or 24 hours after oral exposure. DNA was isolated from liver, lung, stomach, and forestomach, and subjected to nucleotide analysis. Detectable radioactivity was found in the isolated DNA of all tissues. The highest tissue uptake (dpm/mg DNA) was in stomach, followed by forestomach, with less in liver and lung for both routes of exposure. High pressure liquid chromatography analyses of the hydrolyzed DNA showed the presence of N7-methylguanine, O^6-methylguanine, and N3-methyladenine as DNA adducts. After oral exposure, label incorporation, as N7-methylguanine, was 2 to 10 times higher than of O^6-methylguanine. Relative tissue distribution of radioactivity following inhalation exposure to ^{14}C-MeI was comparable to that for the oral route. However, N7-methylguanine levels were only 1 to 2-fold higher than for O^6-methylguanine. The location of the ^{14}C in the DNA samples was determined by high pressure liquid chromatography analysis. The co-elution of radioactivity with naturally occurring nucleosides led the authors to state that a "major part" of the ^{14}C found in the macromolecular DNA had been incorporated via the C1-pool in the *de novo* synthesis of nucleotides. The presence of methylated guanines was further identified by gas chromatography/mass spectrometry. O^6-methylguanine level in the samples was too low to be studied. The presence of the DNA adducts after MeI exposure also led the authors to conclude that MeI has a systemic genotoxic effect in rats. The USEPA considered the presence of N7-methylguanine, O^6-methylguanine, and 3-methyladenine as evidence of MeI direct methylation of DNA (McCarroll, 2005).

Table 30. Genotoxicity of MeI.

Test type/System	Results	References
Gene mutation		
Salmonella typhimurium strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 *uvr*A	No increase in reversion frequency (there is concern about volatility)	*Wagner and Dakoulas, 2001
Chinese hamster ovary cells	No increase in mutation at the HGPRT locus (study lacks confirmation of the negative mutation results)	San and Clarke, 2001
Salmonella strains	TA 1535: positive TA 1538: negative	Rosenkranz and Poirier, 1979
	Standard petri dish system: negative Closed system: positive	Simmon *et al*., 1977; Simmon, 1979a
Escherichia coli strain WP2 *uvr*A	Positive	Hemminki *et al*., 1980
	Positive	Takahashi and Kawazoe, 1987
Saccharomyces cerevisiae	Positive	Simmon, 1979b
Chinese hamster ovary cells	Increased mutant colonies (point mutation) at the HGPRT locus for all doses	Amacher and Zelljadt, 1984
Structural chromosomal aberrations		
Chinese hamster ovary cells	Induction of structural chromosomal aberrations. No induction of numerical chromosomal aberrations	*Gudi and Brown, 2001
Mouse lymphoma cell mutation assay	Increased mutant colonies (chromosomal aberration) at the $TK^{+/-}$ locus	Clive *et al*., 1979; Moore and Clive, 1982; Moore *et al*., 1985a
Mouse lymphoma cell mutation assay	No mutation at the HGPRT locus	Clive *et al*., 1979
Mouse lymphoma cell mutation	Increased mutant colonies (chromosomal aberration and point mutation) at ouabain-resistant locus	Amacher and Dunn, 1985
Other effects		
ICR mice intraperitoneal injection	No damage to micronucleated polychromatic erythrocytes from bone marrow	*Gudi and Krsmanovic, 2001
Mouse embryo cell line (C3H/10T1/2 CL8 cells)	Negative for morphological transformation	Oshiro *et al*., 1981
Golden Syrian hamster embryo cells	Positive for morphological transformation	Pienta *et al.*, 1977
Human lymphoblasts and DNA from lymphocytes	Alkylation of guanines	Cloutier *et al*., 2001
Rats gavage or inhalation	Alkylation of guanines and adenine in tissue DNA	Gansewendt *et al.*, 1991

a/ These studies were submitted to DPR as mandated by SB 950, with * indicating the study was acceptable to DPR.

III.F. Reproductive Toxicity

Summary: In the definitive 2-generation study with rats exposed to MeI via inhalation, the parental effects included organ weight changes (liver, adrenal, and thymus), reduced body weights, and degeneration of the olfactory epithelium for the parents. The reproductive effects included increased primordial follicles, reduced corpora lutea, as well as decreased implantation sites and live litter size. The developmental effects reported were decreased pup body weights and viability, and delayed development as measured by vaginal patency and balanopreputial separation.

III.F.1. Rat - Inhalation

A range-finding study on 3 phrases of a 2-generation reproductive toxicity study was conducted with Crl:CD(SD)IGS-BR rats to determine the appropriate doses for the definitive study (Nemec, 2004).

In the pre-mating exposure phase study, rats (10/sex/group) were exposed to MeI (purity 99.7%; analytical concentrations of 0, 25, 73, or 148 ppm, with the high dose reduced to 99 ppm on day 8) by whole-body inhalation for 6 hours per day for 28 days prior to mating (Nemec, 2004). Pregnant rats continued their exposures to gestation day (GD) 11. The high dose was lethal with 11 rats (6 males, 5 females) that died or were killed moribund (often preceded by clinical signs) during the first week. Following reduction of MeI to 99 ppm for this group, an additional 7 rats died.

During premating, 73 ppm exposure resulted in reduced mean body weights of both genders (significant at $p<0.05$) starting on days 11 and 18 for males (92 to 83% of control), and females (91% to 90% of control), respectively, for the entire study. Over the premating period (52 days), the male mean body weights (n=10) were 498±38.8 g (control), 491±33.9 g (25 ppm), and 392±43.9 g (73 ppm, 79% of control, $p<0.01$). For the females over the premating period (27 days), the body weights (n=10) were 242±16.3 g (control), 243±21.2 g (25 ppm), and 217±15.9 g (73 ppm, 90% of control, $p<0.05$). These reductions were reflected in the lower mean body weight gain and food consumption, with values for some time intervals at statistical significance ($p<0.05$). During gestation, the pregnant rats showed significantly reduced body weight for all intervals (89% to 87% of control for day 0 to day 13), as well as decreased body weight gain and food consumption. The mean absolute brain, liver, and kidney organ weights were significantly ($p<0.05$ or 0.01) reduced (about 10%, except 20% for female kidneys), while the thyroid weight was significantly increased (by 40%, $p<0.05$) in the males in this group. Laparohysterectomy on GD 13 showed effects only for the 73 ppm group, but the values were not statistically significant different than the controls. They included: reduced mean number of implantation sites (15.2/litter control *vs.* 13.0/litter treated), viable embryos (97.9%/litter control *vs.* 89.5%/litter treated), as well as increased early resorption (2.1%/litter control *vs.* 10.5%/litter treated), pre-implantation loss (6.2%/litter control *vs.* 16.8%/litter treated), and post-implantation loss (2.1%/litter control *vs.* 10.5%/litter treated). For comparison between studies, the 25 ppm (34 mg/kg/day) dose could be considered a NOEL.

In the reproductive toxicity phase study, pregnant rats (15/group) were exposed to MeI (purity 99.7%; analytical concentrations of 0, 25, 72, or 99 ppm) by whole-body inhalation for 6 hours per day during GD 0 to 20, and on lactation day (LD) 5 to 20 (total exposure of 37 days)

(Nemec, 2004). One F1 pup of each gender from the control and 25-ppm group were further exposed to MeI during postnatal day 22 through 26. At 99 ppm, 12/15 dams died or were killed moribund. One 72-ppm dam died. These deaths were attributed to treatment. The 72-ppm dams had significantly reduced body weight, body weight gain, and food consumption. The mean body weights (n=10) were 416±27.3 g (control), 406±47 g (25 ppm), and 369±26.6 g (72 ppm, 89% of control, $p<0.01$). While the mean number of pups born, implantation sites and unaccounted sites were not affected by any dose, reduced mean live litter size, postnatal survival, pup weight gain, and increased pup death were reported for the 72-ppm group. No significant treatment-related effects were observed at 25 ppm. For comparison between studies in risk assessment, the 25 ppm (34 mg/kg/day) dose could be considered a NOEL.

In the subchronic toxicity phase study, rats (10/sex/group) were exposed to MeI (purity 99.7%; analytical concentrations of 0, 25, 72, or 99 ppm) by whole-body inhalation 6 hours per day, 5 days per week, for 4 weeks (Nemec, 2004). At 72 and 99 ppm, there were significant reductions in body weight gains (both genders) and food consumption (males only). Several hematology and clinical chemistry changes were statistically significant ($p<0.01$), possibly due to treatment; they included: increased mean albumin (99 ppm), A/G ratio (99 ppm, females only), globulin (99 ppm), total protein (99 ppm), and cholesterol (75 and 99 ppm); and reduced phosphorus (75 and 99 ppm) levels.

Histopathology was assessed only in controls and high dose rats. Histopathology effects at 99 ppm included: hypertrophy of the pituitary pars distalis, degeneration of nasal epithelium, and thyroid hyperplasia and degeneration. For comparison between studies in risk assessment, the 25 ppm (24 mg/kg/day) dose could be considered a NOEL.

Benchmark dose analysis was conducted for the body weight as the endpoint in the hazard identification for subchronic exposure. These 3 datasets were selected because they showed higher body weight changes than those measured during other times. The results, using the continuous linear model, are summarized below.

Exposure duration/gender	**MeI ppm**					
	ED_{05}	**LED_{05}**	**ED_{10}**	**LED_{10}**	**$ED_{0.61\sigma}$**	**$LED_{0.61\sigma}$**
Body weight reduction in rats						
52 days/Males Premating	17.1	13.9	34.1	27.8	16.1	16.1
27 days/Females Premating	34.2	23.6	68.3	47.2	29.8	19.6
20 days/Females Gestation	32.1	23.6	64.2	47.1	34.5	22.7

In the definitive study, Sprague-Dawley Crl:CD(SD)IGS-BR rats (30/sex/group) received daily 6-hour (7 days/week) whole-body inhalation exposure to MeI (purity 99.7%; 0, 5, 20, and 50 ppm) through 2 generations (Nemec, 2001- interim report, 2002a-final report, 2002b-amendment). The mean analytical concentrations for both generations were 5, 20 and 50 ppm (F0-parental: 5, 20, and 50 ppm; F1: 5, 21, and 49 ppm). The exposure concentrations were 0.03, 0.11, and 0.28 mg/L at 5, 20, and 50 ppm, respectively with equivalent dosages at 7, 27, and 68 mg/kg/day.

Parental animals were exposed for at least 10 weeks prior to mating, and daily during mating through GD 20. There was no exposure between GD 21 and LD 4, resuming on LD 5 to weaning. During lactation, the dams were removed from their litters for the 6-hour exposure period. The F1 parental animals were not exposed between postnatal days 22 and 28 due to excessive mortality in all study groups, with exposure resumed on day 28. The offspring (F1 pups from F0 males/females, F2 pups from F1 males/females) were thus exposed *in utero* to GD 20, and via nursing during LD 5 to 21.

For the adults, clinical observations and physical examinations showed no treatment-related effects. Mean body weights were lower for the 50 ppm groups with statistical significance noted for the F0 females during premating and gestation periods, the 50 ppm F1 males during premating, and the 50 ppm F1 females during gestation period (Table 31 and 32). The organ weights for liver, adrenal gland, and thymus were significantly affected by treatment (Table 31 and 32). The mean and/or relative weights were increased for liver (50 ppm) and thymus (20 ppm males, 50 ppm both genders), and decreased for adrenal gland (50 ppm). However, there were no correlating microscopic changes in these organs. Thyroid organ weight was not measured.

Histopathological examination of the adult tissues showed increased incidences of olfactory epithelium degeneration for both generations at 50 ppm (Table 31 and 32). For the males, the incidences for the F0 were higher than those for F1, which had much longer exposures (during *in utero* as F0 offspring, and as F1) (Table 31). On the other hand, the total incidences for all sites were similar for the F0 and F1 females (Table 32). The degeneration was graded minimal to mild with one incident at moderate for a 50 ppm F0 male. It was described as loss of sustentacular cells, vacuolation and desquamation of neuroepithelial cells. "Attempted" regeneration was noted by the presence of ciliated columnar epithelium. No treatment-related effects were noted in other organs (including the thyroid) by macroscopic examination.

The effect of MeI on reproductive parameters is shown in Table 33. The mean numbers of primordial follicles and corpora lutea in the ovaries of the 50 ppm F1 females were significantly increased (20%) and decreased (20%), respectively, from those of the controls. At 50 ppm, the mean number of implantations per dam was the same as the control for the F0 generation, but was fewer (11.7) than that of the control (15.2) for the F1 generation. The mean litter sizes for the 50-ppm group of both generations were reduced with statistical significance for the F1 generation.

The F2 pups, from the F1 parents, showed reduced body weight, viability, and delayed development (Table 33). While the mean body weights of the F1 pups were not affected, those for the 20 and 50-ppm F2 pups were significantly less than those of the control on post-natal days 14 and 21. The mean body weight for 5 ppm females was significantly reduced on day 1

and day 14, but the reduction was less than 10%. The viability index for the 50 ppm pups of both generations was lower than that of the controls with most of the pup deaths occurring within the first 24 hours as indicated by the reduction of the first day survival index. For F1 pups, there was also significant reduction in fetal viability from day 1 to day 4. Developmental landmark was measured only for F1 pups, not F2 pups, and showed delayed development. Of the 50-ppm F1 male pups, the mean body weight when balanopreputial separation occurred was less than that of the controls. For the F1 20 and 50-ppm female pups, the mean number of days required to achieve vaginal patency was significantly increased over that of the controls.

The parental NOEL was 20 ppm (27 mg/kg/day) based upon lower mean body weights and degeneration of olfactory epithelium at 50 ppm (68 mg/kg/day). The reproductive NOEL was also 20 ppm based upon reduced live litter size for both generations of the 50 ppm group. The developmental NOEL was 5 ppm (7 mg/kg/day) based upon lower mean body weights and delayed development (females) of the 20-ppm pups. This study was considered acceptable to DPR according to FIFRA guidelines.

The USEPA established a systemic parental NOAEL of 20 ppm for decreases in body weight, body weight gain, changes in organ weights, as well as gross pathology and histopathological findings at 50 ppm (MRID 45710301; USEPA, 2006a). The port of entry NOAEL was 20 ppm based on degeneration of the olfactory epithelium. The offspring NOAEL was 5 ppm based on decreases in body weight, body weight gain, and thymus weight. The reproductive NOAEL was 5 ppm for the delay in attainment of vaginal patency.

Benchmark dose analysis was performed on two reproductive effects as well as adult body weight to be used in the selection of point of departure for subchronic exposure in hazard identification. The results are listed in the following summary:

Exposure duration/gender	**MeI ppm**							
	ED_{05}	**LED_{05}**	**ED_{10}**	**LED_{10}**	**$ED_{0.61\sigma}$**	**$LED_{0.61\sigma}$**	**$ED_{0.36}$**	**$LED_{0.36\sigma}$**
Body weight 22 weeks/ Males, Premating (continuous linear model)	23.2	17.6	46.3	35.2	25.4	18.9	Not determined	
Body weight 22 weeks/ Females, Premating (continuous linear model)	33.9	23.8	67.7	47.6	34.5	23.8	Not determined	
F2 pup weight/Males (polynomial model)	5.7	4.1	Not determined		7.5	5.2	4.3	3.0
F2 pup weight/Females (polynomial model)	6.3	4.4	Not determined		8.1	5.4	4.6	3.1
Vaginal patency/ Females (polynomial model)	22.0	10.7	Not determined		20.4	10.1	10.8	5.6

Table 31. Effects in male parental rats exposed to MeI by inhalation in a two-generation reproductive toxicity study.[a]

Effects	Doses			
ppm	0	5	20	50
mg/kg/day	0	7	27	68
Mean body weight (g)				
F0 (parental) Males				
Week 10 premating	503	502	508	485
F1 Males				
Week 10 premating	503	512	501	466**
Week 17-Week 38	570±46.2 (n=29)	581±45.3 (n=29, 102%)	564±64.4 (n=30, 99%)	514±51.6** (n=30, 90%)
Mean absolute (g) and relative organ (%) weights				
F0 (parental) Males				
Liver -absolute	19.0	19.5	19.9	20.7
-relative	3.39	3.41	3.47	3.78**
Adrenal glands-absolute	0.066	0.067	0.062	0.056**
-relative	0.012	0.012	0.011	0.010**
Thymus-absolute	0.226	0.241	0.284**	0.267
-relative	0.041	0.043	0.050*	0.049*
F1 Males				
Liver -absolute	19.7	19.9	20.7	19.6
-relative	3.43	3.40	3.59	3.73**
Adrenal glands-absolute	0.062	0.062	0.058	0.049**
-relative	0.011	0.011	0.010	0.009**
Thymus-absolute	0.238	0.261	0.286*	0.281*
-relative	0.042	0.045	0.050*	0.054**
Degeneration of the olfactory epithelium (total for all severity/no. examined)[b]				
F0 (parental) Males				
All levels	1/30**	0/30	0/30	15/30**
Level II	0/30**	0/30	0/30	14/30**
Level III	1/30**	0/30	0/30	11/30**
Level IV	0/30**	0/30	0/30	10/30**
F1 Males				
All levels	0/29**	0/29	0/29	9/28**
Level II	0/29**	0/29	0/29	5/28*
Level III	0/29**	0/29	0/29	4/28
Level IV	0/29*	0/29	0/29	2/28

a/ Data from Nemec (2002a and b). *, ** for statistical significance at $p<0.05$ and <0.01, respectively. Significance in trend by the Cochran-Armitage Trend test is denoted at the control value.

b/ All degeneration was graded as minimal or mild, except one was moderate at Level III of 50 ppm.

Table 32. Effects in female parental rats exposed to MeI by inhalation in a two-generation reproductive toxicity study.[a]

Effects	Doses			
ppm	0	5	20	50
mg/kg/day	0	7	27	68
Mean body weight (g)				
F0 (parental) Females				
Week 10 premating	303	303	298	285**
Day 20 gestation	430	429	419	399**
F1 Females				
Week 17-38 premating	324±27.9 (n=29)	340±30.8 (n=30, 105%)	330±29 (n=30, 102%)	307±21.2 (n=30, 95%)
Day 20 gestation	419±27.1 (n=24)	439±41.0 (n=26, 105%)	424±27.0 (n=23, 101%)	385±33.4** (n=24, 92%)
Mean absolute (g) and relative organ (%) weights				
F0 (parental) Females				
Liver -absolute	12.6	13.1	12.8	13.6
-relative	3.75	3.94	3.95	4.33**
Adrenal glands-absolute	0.080	0.079	0.079	0.068**
-relative	0.024	0.024	0.024	0.022*
Thymus-absolute	0.262	0.267	0.261	0.276
-relative	0.078	0.080	0.081	0.088
F1 Female				
Liver -absolute	12.5	13.2	13.4	13.0
-relative	3.84	3.86	4.04	4.22**
Adrenal glands-absolute	0.080	0.080	0.074	0.063**
-relative	0.025	0.024	0.022*	0.021**
Thymus-absolute	0.285	0.304	0.277	0.274
-relative	0.088	0.090	0.084	0.089
Degeneration of the olfactory epithelium (total for all severity/no. examined)[b]				
F0 (parental) Females				
All levels	0/30**	0/30	0/30	20/30**
Level II	0/30**	0/30	0/30	11/30**
Level III	0/30**	0/30	0/30	10/30**
Level IV	0/30**	0/30	0/30	6/29*
F1 Females				
All levels	0/29**	0/29	2/30	12/30**
Level II	0/29**	0/29	2/30	7/30**
Level III	0/29**	0/29	0/30	7/30**
Level IV	0/29**	0/29	0/30	3/30

a/ Data from Nemec (2002a and b). *, ** for statistical significance at $p<0.05$ and <0.01, respectively. Significance in trend by the Cochran-Armitage Trend test is denoted at the control value. NA=data not available because they were not collected.
b/ All degeneration was graded as minimal or mild.

Table 33. Reproductive effects and effects in rat pups exposed to MeI *in utero* in a two-generation reproductive toxicity study.[a]

Effects	Parental Doses			
ppm	0	5	20	50
mg/kg/day	0	7	27	68
Reproductive Effects				
F1 Females				
Primordial follicles[c] (mean)	132.0±42.7	NA	NA	158.4±52.8*
Corpora lutea[c] (mean)	172.1±52.5	NA	NA	138.4±61.2*
F0 and F1 parents	F0 F1	F0 F1	F0 F1	F0 F1
Mean number of implantations	15.6 15.2	16.0 16.2	15.6 14.9	15.4 11.7**
F1[b] pup/litter born	14.4±2.57	15.0±1.75	14.4±3.04	13.8±2.91**
F1[b] live pup/litter born	14.2±2.87	14.8±1.79	14.1±3.08	12.5±3.61**
F2[c] pup/litter born	14.3±1.43	15.3±3.40	13.8±2.79	11.0±4.59**
F2[c] live pup/litter born	13.9±1.85	14.9±3.50	13.6±2.74	10.5±4.19**
Mean pup weight in grams (% control)				
F2 pups n=	25	25	23	23
Day 1-males	7.2±0.5	6.9±0.6	7.1±0.6	7.2±0.8
-females	6.9±0.6	6.4±0.6*(93%)	6.6±0.6	6.8±0.8
Day 7-males	15.0±1.8	14.8±1.3	14.5±1.6	13.6±2.2* (91%)
-females	14.3±1.8	13.4±1.4	13.4±1.6 (94%)	13.0±2.0 (91%)
Day 14-males	29.7±3.1	28.7±2.8 (97%)	26.8±2.0** (90%)	24.3±3.2** (82%)
-females	28.3±3.0	26.4±3.1*(93%)	25.3±2.2** (89%)	23.3±2.7** (82%)
Day 21-males	45.1±5.2	44.4±4.2 (98%)	38.7±4.7** (86%)	36.2±5.4** (80%)
-females	42.9±4.6	40.6±4.1 (95%)	37.2±5.1** (87%)	35.0±4.1** (82%)
Pup viability (%/litter)				
F1 pups				
Survival index (day 0 to day 1)	98.0±4.49	99.0±3.08	98.2±3.54	82.6±23.09**
Survival index (day 1 to day 4)	99.4±1.62	96.5±6.86*	98.1±5.18	87.2±31.58**
F2 pups				
Survival index (day 0 to day 1)	99.5±1.86	99.3±1.99	99.4±2.78	92.2±13.41**
Survival index (day 1 to day 4)	98.8±5.09	98.6±2.82	99.7±1.49	95.8±12.37
Balanopreputial Separation, F1 pups (n=30, except n=29 for 50 ppm)				
Mean number of days to separation	46.5±2.58	45.1±2.97	46.4±2.82	47.0±2.82
Mean body weight (g) at separation	219.5±20.62	218.5±16.13	213.6±20.40	203.4±14.66**
Vaginal patency, F1 pups (n=30, except n=31 for 5 ppm number of days, and n=29 for 50 ppm body weight)				
Mean number of days to patency	37.0±2.34	37.9±2.68	38.8±3.38*	40.0±3.17**
Mean body weight (g) at patency	119.8±14.11	125.4±12.78	130.2±18.52	128.3±18.05

a/ Data from Nemec (2002a and b). % of control in parenthesis. *, ** for statistical significance at $p<0.05$ and <0.01, respectively. The number of litter was 27-29 for the F1 generation, and 23-25 for the F2 generation.

b/ Survival= $\frac{\Sigma \text{ (viable pups per litter at the end of interval/viable pups per litter at the start of interval)}}{\text{No. litter per group}} \times 100$

III.G. Developmental Toxicity

Summary: Pregnant rats and rabbits exposed to MeI by inhalation during gestation showed reduced body weight gain. In treated pregnant rabbits, changes in some parameters of hematology and clinical chemistry, and thyroid hormone levels were reported. No developmental toxicity was observed in rats under the experimental conditions used. With rabbits, there was reduced litter size, fetal weight, and viability, with increased incidences of late resorption and fetal death. The critical time of exposure was between GD 23 and 26 for the induction of late resorption. Histopathology of the thyroid (decreased colloid, and follicular cell hypertrophy) was observed for both maternal and fetal rabbits.

III.G.1. Rat - Inhalation

Mated Crl:CD(SD)IGS-BR female rats (24/group) were exposed to MeI (purity 99.7%; analytical concentrations: 0, 5, 20, and 60 ppm) by whole-body inhalation daily for 6 hours, 7 days per week on GD 6 through 19 (Nemec, 2002c). All animals were sacrificed on GD 20. Calculated exposure concentrations were 0.03, 0.11, and 0.34 mg/L, respectively, with the equivalent dosages at 7, 27, and 81 mg/kg/day, respectively. No treatment-related clinical signs were reported. Statistically significant reductions (19% and 14.5%) in maternal body weight gains for GD 6 through 20 and days 0 through 20, respectively, were recorded for the 60-ppm group. The body weight effects occurred on two occasions. On the first three days of exposure (GD 6 to 9), the 60 ppm rats did not have any weight gain compared to 7 to 9 grams for other groups. For this high dose group, the weight gain was similar to the other groups from GD 10 to 18, but was lower (12 grams compared to 14 to 17 grams for the other groups) for GD 19 to 20. The maternal NOEL was 20 ppm (27 mg/kg/day) for reduced body weight gain. No developmental effects were observed, with a NOEL of 60 ppm (81 mg/kg/day), the highest dose tested. This study was considered acceptable to DPR according to FIFRA guidelines. The USEPA also established the maternal and developmental NOAELs at the same levels (MRID 45593812; USEPA, 2006a). Note that Mileson *et al.* (2009) and USEPA (2007) reported the exposure ended on GD 17 instead of GD 19. When exposure was terminated is an issue for fetal death (see discussion in **Appendix A** of **Volume I**).

III.G.2. Rabbit - Inhalation

Inseminated New Zealand white female rabbits (24/group) were exposed to MeI (purity 99.7%; 0, 2, 10, and 20 ppm) for 6 hours per day, 7 days per week by whole-body inhalation exposure from GD 6 through 28, and sacrificed on day 29 (Nemec, 2002d; Nemec *et al.*, 2009). The calculated exposure concentrations were 0.011, 0.057, and 0.113 mg/L, respectively. The equivalent dosages were 1.5, 8, and 15 mg/kg/day. The report stated that a mid-coronal section of the brain from each fetus (not specified as to whether dead or live fetuses) was examined. The report, however, did not provide any details on the methodology or results for this examination.

A statistically significant reduction (47%) in body weight gain was recorded for GD 6 through 29 at 20 ppm (Table 34a). This was started with a body weight loss of 12 grams on GD 24 to 25. These does continued to lose weight with a loss of 71 grams from GD 24 to 29. Body weight loss was lower for the 2-ppm and 10-ppm groups. The mean gravid uterine weight was also reduced at 10 ppm and 20 ppm ($p<0.05$). The decreases in the number of implantations per dam for the treated groups were not statistically significant. The only treatment-related clinical sign

was wet clear matting around the nose at higher incidences for the treated groups when compared to the control (Table 34a). This finding was described as "slight", and was observed primarily during the last week of exposure.

Table 34a shows the fetal data expressed for all litters for the following discussion, as well as those with the exclusion of litters with 100% early resorption. The values for the latter category will be discussed in **Appendix A** of **Volume I** in the comparison of studies, and are presented here for completeness. While no significant teratogenic effects were observed with treatment, adverse effects included reduced viability and fetal weight, as well as increased late resorption and post-implantation loss at 10 and 20 ppm. The mean fetal body weight was reduced for all dosed groups with statistical significance at 10 ppm (females, 88% of control), and 20 ppm (both genders, 84% and 70% of control).

There was a dose-related decrease in the number of viable fetuses. Compared to 6.1 fetuses/litter in the control group, the mean of 3.6 fetus/litter at 20 ppm was statistically significant. The reduction in viable fetuses was associated with post-implantation loss due to dose-related increase in late resorption and fetal death, and not early resorption. For late resorption, both the numbers of fetuses resorbed and affected litters were increased with treatment. When expressed as % fetuses/litter, the mean incidences were 11.1% at 10 ppm and 21.5% at 20 ppm ($p<0.01$). While statistical significance was reported only for the 20-ppm group, the result for the 10-ppm group was considered toxicologically significant because of an almost 7-fold increase from the control (1.7%). The lack of statistical significance due to variability in the data is shown in Table 34b for late resorption. In addition, dead fetuses were found in both the 10-ppm and 20 ppm groups. From 36 studies conducted from 1999 to 2004, the historical control data (% fetus/litter) showed the following values (mean and range): post-implantation loss (9.0±4.67%, range 0.6-23.4%), early resorption (7.8±4.55%, range 0.6-22.7), late resorption (1.1±1.21%, range 0-6.2%), and fetal death (0±0.14, range 0-0.6%) (WIL Research Laboratories, 2006). For the same duration, the mean number of implantations/dam was 6.9±0.7 with a range of 5.3 to 8.1. While the thyroid and its function were not evaluated in this study, Sloter (2005b) showed that 20-ppm MeI caused thyroid follicular cell hypertrophy in rabbit fetuses.

The developmental NOEL was 2 ppm (1.5 mg/kg/day) for the effects on reduced fetal weight and viability; and increased late resorption and fetal death at 10 ppm and 20 ppm. The maternal NOEL was 10 ppm (8 mg/kg/day) for body weight loss at 20 ppm (15 mg/kg/day). This study was considered acceptable to DPR according to FIFRA guidelines. DPR analysis of fetal death data using nested logistic model (USEPA Benchmark Dose software, BMDS 2.0) showed extra risk response at 10 ppm is 18-20%, higher than the default of 10% for a no-effect level. Moreover, the study authors stated that "the prenatal developmental toxicity was expressed at...10 and 20 ppm by increases in postimplantation losses (primarily late resorptions), reduced mean numbers of viable fetuses and/or reduced mean fetal body weights...the NOAEL...for ...prenatal developmental toxicity was considered to be 2 ppm." Thus both the BMD analysis and the study authors' conclusions supported DPR's NOEL at 2 ppm. The USEPA established a higher developmental NOEL of 10 ppm based on statistically significant increased fetal losses and decreased fetal weight (↓20%) at 20 ppm (MRID 45593811; USEPA, 2007). The maternal NOEL was 20 ppm for lack of effects observed at this dose, the highest dose tested.

Concerns were raised by the SRC regarding the apparent residual effects of both fetal body weight and fetal death at 2 ppm (**Volume IV Part 1-A**). For fetal death endpoint, using nested

logistic model (USEPA BMDS version 2.0) and excluding litters without any surviving fetus at risk for late resorption, DPR scientists' initial BMD analysis showed that the 2 ppm NOEL is approximately at $LED_{04,}$ the lower 95th bound of dose for a 4% increased fetal death (DPR August 2009 draft; DPR response to OEHHA comments in mei_vol4_oehha.pdf). DPR's risk assessment practice is to consider the seriousness of response in setting the benchmark response (BMR), *e.g.*, quantal 1% extra risk for death (DPR MT-1, 2004). However, the initial reluctance to apply 1% BMR to this data set was due to the sizable data variability, *i.e.*, 1.8±6.4% death per litter in the control group (the mean value is at approximately 75th quartile of historical data from WIL laboratory). Nevertheless, at the advice of the SRC to establish the BMD at 1% BMR regardless of the data characteristics, this risk assessment derived the ED_{01} and LED_{01} as below, allowing the model to estimate the intralitter correlations and using the overall mean litter-specific covariate (5.88889) which is slightly lower than the mean of the control group:

	MeI (ppm)					
BMD model	**ED_{05}**	**LED_{05}**	**ED_{01}**	**LED_{01}**	**P**	**AIC**
Nested Logistic	5.3	2.5	1.5	0.5	0.2465	269.931
NCTR	4.7	2.3	1.2	0.6	0.4326	268.436
Rai & Van Ryzin	4.8	2.4	1.2	0.6	0.1513	277.606

Although the AIC (Akaike's Information Criterion) indicated that the NCTR model may have a slightly better overall fit, 0.5 ppm at LED_{01} from the Nested Logistic model was chosen as the POD for this endpoint because visual inspection and χ^2 residuals showed that this model has a slightly better fit at the dose region of interest. The ED_{01} is slightly lower than the 2 ppm NOEL and the LED_{01} is 4-fold lower.

For the fetal body weight endpoint, the weight data are first normalized based on the correlation between fetal weight and litter size. The mean number of fetus per litter in the control group is 6.36 (the WIL laboratory historical mean of viable fetus per dam is 6.5±0.84). These transformed data are then used in the BMD analysis within USEPA BMDS version 2.0. The normalization raises the slope of dose-response by increasing the average weight of the control group by 5% and lowering the high dose group weight by 4%. However, caution is needed to interpret the following BMD results for the normalized data. First, the variances of the normalized data are not homogeneous among the dose groups but cannot be modeled within the provision of the BMDS version 2.0. In addition, no continuous models available within the BMDS can provide a fit within the p at 0.1 criterion. The following results are from polynomial model (p at 0.048).

Data	**ED_{10}**	**LED_{10}**	**ED_{05}**	**LED_{05}**	**$ED_{0.61\sigma}$**	**$LED_{0.61\sigma}$**	**$ED_{0.36\sigma}$**	**$LED_{0.36\sigma}$**
un-normalized	11.5	8.4	6.2	3.9	11	7.5	6.7	4.2
normalized	8.1	6.2	4.1	3.0	6.6	4.9	3.9	2.8

DPR's risk assessment practice is to consider the seriousness of response in setting the BMR for the hybrid model, *e.g.*, applying a multiplier of standard deviation at 0.36 (at $P_0 = 0.05$, $\pi = 0.05$) instead of 0.61 (at $P_0 = 0.05$, $\pi = 0.1$) (DPR MT-2, 2004). Thus, the threshold based on this endpoint would be 3.9 - 6.7 ppm at $ED_{0.36\sigma}$ and 2.8 - 4.2 ppm at $LED_{0.36\sigma}$.

Alternatively, based on the correlation of human birth weight and infant mortality from data on cigarette smoking and criteria air pollutants, the SRC advised to consider a BMR at 0.07σ as a LOAEL (**Volume IV Part 1-A**). The cut off at a 0.07 multiplier of the standard deviation at 5.34 g for the normalized control group is a 0.37 g reduction of rabbit fetal body weight. The BMD analysis showed the $ED_{0.07\sigma}$ and $LED_{0.07\sigma}$ at 0.8 and 0.5 ppm, respectively, for the normalized data and 1.4 and 0.8 ppm, respectively for the un-normalized data.

DPR scientists agree with the SRC on the important implications of decreased fetal body weight to post-natal survival and development. However, DPR scientists disagree with the recommendation to directly apply the 0.07 multiplier of standard deviation developed from human data with predominantly single birth to rabbit data with multiple fetuses per litter. Applying BMR criterion of 0.07σ as the threshold LOAEL response to the rabbit data from this study would mean an average of 61% fetus per litter in the control group having body weight at least 0.37 g below the group mean, or an incidence of 15/22 (86%) litters in the control group having ≥50% of fetuses exhibiting the "LOAEL" effect. Thus, the SRC's BMR criterion is not used for this dataset.

In conclusion, the BMD analyses show that fetal death remains the most sensitive endpoint from this rabbit pre-natal developmental study. The LED_{01} as recommended by the SRC for this endpoint is used for assessing the risk of acute exposure to MeI.

Table 34a. Maternal and fetal effects in rabbits exposed to MeI by inhalation during gestation days 6 to 28.[a]

Effects	Doses			
ppm	0	2	10	20
mg/kg/day	0	1.5	8	15
Maternal Data				
Mean maternal body weight changes (g) during gestation				
GD 6-29	262	305	219	138*
GD 24-25	7	-5	3	-12
GD 24-29	27	-5	-4	-71*
Mean gravid uterine weight (g)	390.6	353.0	319.8	269.1*
Number implantation/dam	6.8±2.2	6.1±2.9	5.9±2.7	5.6±2.9
Clinical observations (total occurrences/ number of animals) during gestation				
Wet clear matting around nose	35/10	83/18	92/17	117/20
Fetal Data				
Total Litters with implantation	23	20	20	21
Fetal body weight (g, % control)				
Mean male	46.8±5.70	45.6±6.7 (97%)	44.3±7.4 (95%)	39.5±7.1** (84%)
Mean female	46.9±5.48	44.6±7.1 (95%)	41.3±7.4* (88%)	37.0±7.5** (79%)
Viable fetuses				
-live fetus/total litter	140/23	109/20	91/20	76/21
-mean fetus/litter	6.1±2.6	5.5±2.6	4.6±2.6	3.6±2.2**
-% fetus/litter	86.2±26.47%	87.9±24.50%	82.1±26.28%	67.7±29.96%**
Post implantation loss				
-affected litter/total litter	10/23*	8/20	9/20	16/21**
-affected fetus/total litter	17/23	13/20	26/20	42/21
-% fetus/litter	13.8±26.5%	12.1±24.5%	17.9±26.3%	32.3±30.0%**
Early resorptions				
-affected fetus/total litter	14/23	7/20	8/20	8/21
-% fetus/litter	12.1±26.5%	9.0±22.4%	6.2±10.3%	10.1±22.7%
Late resorptions				
-affected litter/total litter	2/23*	2/20	6/20	11/21**
-affected fetus/total litter	3/23	6/20	17/20	33/21
-mean fetus/litter	0.1±0.46	0.3±1.13	0.9±1.60	1.6±2.11
-% fetus/litter	1.7±6.2%	3.1±10.7%	11.1±21.2%	21.5±26.9%**
Dead fetus				
-dead fetus/total litter	0/23	0/20	1/20	1/20
-affected litter/total litter	0/23	0/20	1/20	1/21
-% fetus/litter	0	0	0.6±2.80%	0.8±3.64%
Exclusion of litters with 100% fetal loss due to early resorption[b]				
Litters with 100% early resorption	1	1	0	1
Late resorption and dead fetus[c]				
-affected litter/total litter	2/22*	2/19	6/20[c]	11/20[c,] **
-affected fetus/total fetus	3/143*(2%)	6/115(5%)	18/109**(17%)	34/110**(31%)
-% fetus/litter	1.8±6.4%	3.3±10.9%	11.1±21.2%	22.5±27.2%**

a/ Data from Nemec (2002d). *, ** for statistical significance at p<0.05 and 0.01, respectively. Notation at the control indicates significant in trend. Mean fetus/litter= the quotient of affected fetus/total litter, % fetus/litter=group mean for % affected fetus in each litter, with % affected fetus = # fetuses affected/# total implantation sites x 100%.

b/ Total litter= all, except litter with 100% resorption. Total fetuses=viable+dead+late resorption.

c/ 1 litter had both dead fetuses and late resorption.

Table 34b. Variability in late resorption data for rabbits exposed to MeI by inhalation during gestation days 6 to 28.[a]

Late Resorption	Dose (ppm)			
	0	**2**	**10**	**20**
Number of litters	23	20	20	21
Number of implantation sites in each litter	2 to 11	1 to 11	2 to 10	1 to 10
Affected litter	2	2	6	11
Range of % fetus affected in affected litter	10.0% 28.6%	16.7% 45.5%	12.5% to 71.4%	10.1% to 87.5%
Range of % fetus affected for all litters	0 to 28.6%	0 to 45.5%	0 to 71.4%	0 to 87.5%
Mean % fetus affected/litter	1.7±6.2%	3.1±10.7%	11.1±21.2%	21.5±26.9%

a/ Data from Nemec (2002d). % fetus/litter=group mean for % affected fetus in each litter

In a follow up study, the critical time of exposure for the induction of late resorption, window of vulnerability, was examined (Nemec, 2003; Nemec *et al*., 2009). Artificially inseminated female New Zealand white rabbits (24/group) were exposed to MeI (purity 99.7%; analytical concentrations of 0 or 20 ppm; 0.11 mg/L or 15 mg/kg/day) by whole-body inhalation on various days during gestation:

Group 1: Control
Group 2: 20 ppm on GD 6 to 28
Group 3: 20 ppm on GD 6 to 14
Group 4: 20 ppm on GD 15 to 22
Group 5: 20 ppm on GD 23 to 24
Group 6: 20 ppm on GD 25 to 26
Group 7: 20 ppm on GD 27 to 28

All pregnant rabbits were sacrificed on GD 29. Mean maternal body weight gains were significantly lower than that of the control only during the exposure period for each respective group. The weight gain of Group 4 was only 71 grams ($p<0.05$) compared to 148 grams for the control. Both Groups 5 and 6 showed weight loss (35 g and 48 g, respectively; $p<0.01$) during the treatment periods. However, weight gain recorded after the treatment period was not significantly different than the control. The weight loss of these groups was not associated with food consumption, which was not different than the control during the exposure days.

Table 35 shows the fetal data expressed for all litters for the following discussion, as well as those with the exclusion of litters with 100% early resorption. The values for the latter category are discussed in Hazard identification (under **IV.A.2.a.)** to compare the number of fetuses or litters at risk between this study and the other Nemec study (2002d). The critical time of exposure was between GD 23 and 26. For the "all litters" data set, the fetal body weight for Groups 2 and 6 were lower than the other groups. The mean number of live fetuses per litter for Group 2 was significantly lower than that of the controls. There was no difference in the total litters with implantations.

Post-implantation loss considers loss due to early resorption, late resorption, and born dead. After MeI exposure, the mean litter proportions of implantation loss for Group 2 (26.8% per litter) and Group 6 (20.6% per litter) were higher than the control (10.7%) (Table 35). While this value for Group 2 was not statistically significant from the concurrent control, the report noted that it exceeded the maximum historical control value (23.1% per litter) for the conducting laboratory. Early resorption was not affected by MeI exposure. The late resorption incidence for Group 2 (16.3% per litter) was significantly higher than the control and other groups. The report noted that this value and that (8.7% per litter) for Group 6 were higher than the maximum mean value in the laboratory's historical control data (6.2% per litter). Furthermore, the value for Group 5 (5.7% per litter) was also considered treatment related because the number of litters with late resorption in the group were similar to that for Group 6. There was no increase in malformation due to treatment. These results were consistent with the previous study with fetal effects noted at 10 and 20 ppm (Nemec, 2002d). Thus, the developmental NOEL was <20 ppm for late resorption and decreased viable fetuses with the vulnerable period for fetal death between GD 23 and 26. This study was considered supplemental information to DPR.

Table 35. Fetal data for rabbits exposed to MeI by inhalation during selected days of gestation.[a]

Effects	0 ppm	20 ppm (15 mg/kg/day)					
		GD 6-28	GD 6-14	GD 15-22	GD 23-24	GD 25-26	GD 27- 28
Groups	**1**	**2**	**3**	**4**	**5**	**6**	**7**
All litters							
Fetal weight -mean in grams (% of Control)	45.5	**41.4** **(90%)**	48.3	46.2	**45.9**	**43.0** **(95%)**	47.0
Total Litters with implantation	19	21	23	20	17	23	21
Viable fetuses -total live fetus/total litter -mean fetus/litter -% fetus/litter	 127/19 6.7 89.3%	 **89/21** **4.2*** **73.2%**	 119/23 5.2 92.9%	 131/20 6.6 93.8%	 **108/17** **6.4** **88.6%**	 **127/23** **5.5** **79.4%**	 131/21 6.2 90.7%
Post implantation loss -affected fetus/total litter -mean fetus/litter -% fetus/litter	 8/19 0.4 10.7%	 **30/21** **1.4** **26.8%**	 13/23 0.6 7.1%	 9/20 0.5 6.2%	 **19/17** **1.1** **11.4%**	 **13/23** **1.0** **20.6%**	 9/21 0.4 9.3%
Early resorption -affected fetus/total litter -mean fetus/litter -% fetus/litter	 6/19 0.3 9.6%	 **5/21** **0.2** **10.5%**	 11/23 0.5 6.0%	 9/20 0.5 6.2%	 **8/17** **0.5** **5.7%**	 **7/23** **0.3** **11.8%**	 9/21 0.4 9.3%
Late resorption -affected litter/total litter -affected fetus/total litter -mean fetus/litter -% fetus/litter	 2/19 2/19 0.1 1.1%	 **10/21** **25/21** **1.2** **16.3%****	 2/23 2/23 0.1 1.1%	 0/20 0/20 0 0.0%	 **5/17** **11/17** **0.6** **5.7%**	 **6/23** **16/23** **0.7** **8.7%**	 0/21 0/21 0 0.0%
Dead fetus -dead fetus/total litter	 0/19	 0/21	 0/23	 0/20	 0/17	 0/23	 0/21
Exclusion of litters with 100% fetal loss due to early resorption[b]							
Litters with 100% early resorption	1	2	0	0	0	2	1
Late resorption and dead fetus -affected litter/Total' litter -affected fetus/Total' fetus -% fetus/litter	 2/18 2/129 1.1%	 **10/19**** **25/114**** **18.3****	 2/23 2/121 1.1	 0/20 0/131 0.0	 **5/17** **11/119**** **6.3**	 **6/21** **16/143**** **9.6**	 0/20 0/131 0.0

a/ Data from Nemec (2003). Does were sacrificed on day 29. *, ** Statistical significance at $p<0.05$ and 0.01, respectively. Bolded values are those reported during the critical time GD 23 to 26. Mean fetus/litter= the quotient of affected fetus/total litter, % fetus/litter=group mean for % affected fetus in each litter, with % affected fetus = # fetuses affected/# total implantation sites x 100%.

b/ Total'= # for viable, dead, and late resorption.

Additional studies were conducted to generate data to establish the MOA for fetal toxicity and PBPK modeling (Sloter, 2005a and b; Sloter *et al.*, 2009). In the first study (Sloter, 2005a), pregnant New Zealand white rabbits (10 does/group) were divided into 9 groups. Groups 1-7 were untreated, and one group was sacrificed each day between GD 21 through 27. Treated does were exposed to MeI (25 ppm, 0.14 mg/L, or 19 mg/kg/day) by inhalation for 6 hr per day for 2 days (GD 23-24: Group 8) or for 4 days (GD 23-26: Group 9); they were sacrificed after the last daily exposure. For comparisons, the controls were Groups 4 and 6, for Groups 8 and 9, respectively. Blood samples were collected "immediately prior to scheduled euthanasia as soon as following exposure as practicable for Groups 8 and 9." Fetal blood was collected at scheduled laparohysterectomy from the umbilical vessels of each fetus; analysis was performed on pooled samples.

No apparent treatment-related clinical signs were observed in the pregnant rabbits. Body weight gain decrements were reported in treated does; these were statistically significant during GD 23-24 for Group 8 and GD 24-25 and GD 25-26 for Group 9 (Table 36). The net body weight change over the course of pregnancy was significantly reduced in Group 9 does, and was associated with a significant reduction in gravid uterine weight (Table 36). During the treatment period (GD 23-26), Group 9 also had significantly reduced food consumption: 74 g/doe/day versus control Group 6 mean of 140 g/doe/day ($p<0.01$).

Hematology and clinical chemistry data showed statistically significant changes in Groups 8 and 9 (Table 36 and 37). Values for red cells, hemoglobin, and hematocrit were increased (significantly for almost all measurements) for both does and fetuses. In addition, the prothrombin time and activated partial thromboplastin time were reduced in the does. Clinical chemistry showed increased protein (albumin, globulin, and total protein) levels only for the fetuses. Variable changes were reported for other parameters (calcium, phosphorus, potassium, creatinine, and chloride). Lipid levels (cholesterols and triglycerides) for both does and fetuses were increased, with statistical significance only for the fetal values.

Significant GSH depletion was reported in the blood (Group 8 does, Groups 8 and 9 fetuses) (Table 38). GSH levels in the liver, kidney, and nasal tissues of Groups 8 and 9 were not affected. Increased methylation by MeI was evident by increased S-methylcysteine adduct formation in Groups 8 and 9 does and fetuses (Table 38).

After MeI exposure, iodide was highly elevated in treated does and fetuses (Table 39 and 40). While there was a large range of levels within each group, in general, serum iodide levels of untreated fetuses were several-fold higher than the does, and levels of iodide in treated fetuses were more than two-fold higher than corresponding does. There were treatment effects on thyroid hormones in does (Table 39). For Groups 8 and 9, maternal serum TSH increased to 136% of respective controls and serum T3 decreased to 76% to 79% of respective controls, with significance only for Group 8. There was no significant change with T4.

Thyroid hormones T3, T4, and TSH levels in the fetal blood were measured as pooled samples from multiple fetuses per litter in order to obtain sufficient material for assay (Table 40). T3 was not detected in fetal serum until GD 22 (Group 2), suggesting that conversion from T4 to T3 occurred around GD 22. In Group 8, following two days of MeI exposure on GD 23-24, fetal serum T3 was significantly reduced to 47% of Group 4 control, but serum TSH and T4 were unaffected. Following 4 days of exposure on GD 23-26, Group 9 fetal serum TSH was

significantly increased to 711% of control and T4 decreased ($p<0.05$) to 21% of control. Serum T3 on GD 26 for this group was similar to the control.

Gross examination of the maternal tissues showed dark red areas in the lungs in 5 treated does (two in Group 8, and three in Group 9), but not in any other groups, thus indicating a treatment-related effect. There were no apparent effects on weights of maternal brain, kidneys, or liver. Maternal thyroid was not examined. While there was no significant fetal malformation or variations from MeI, late resorption was increased in the two treated groups (5 does per group each in Groups 8 and 9) compared to the controls (3 or fewer per group) (Table 41). While the incidences were not statistically significant, it was considered a treatment-related effect.

Microscopic examination of the fetal thyroids showed dose- and duration-related effects in Groups 8 and 9 (Table 41). These included follicular cell epithelial vacuolation and hypertrophy, as well as decreased colloid. The incidences of these responses increased with exposure duration (Group 8 compared to Group 9). Overall, the results showed a NOEL of <25 ppm for fetal late resorption and thyroid effects. This study was considered supplemental information to DPR.

Table 36. Body weight, clinical chemistry and hematology data for pregnant rabbits exposed to MeI (25 ppm) by inhalation.[a]

Effects	Groups								
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Sacrifice on Gestation Day	21	22	23	24	25	26	27	24	26
Maternal Treatment Days	-	-	-	-	-	-	-	23-24	23-26
Body weight change (g)									
GD 23-24	NA	NA	NA	20	3	2	27	-42‡‡	-20
GD 24-25	NA	NA	NA	NA	16	32	28	NA	-30††
GD 25-26	NA	NA	NA	NA	NA	9	31	NA	-36††
Gravid uterine weight (g)	183.9	255.0	261.0	316.4	353.2	464.8	471.1	310.3	348.3††
Hematology									
Red cell (million/µL)	2.1	2.73	2.96	3.18	3.19	3.39	3.59	3.34	3.72†
Hematocrit (%)	30.4	39.6	41.4	42.7	41.6	43.2	45.3	46.0	47.4†
Hemoglobin (g/dL)	7.8	10.1	10.3	10.8	10.8	11.4	11.7	11.6	12.2††
Prothrombin Time (sec)	10.0	9.0	8.6	9.0	9.1	8.7	9.1	9.4‡	9.5††
Activated partial thromboplastin time (sec)	12.9	12.5	13.2	12.6	13.1	13.8	13.1	11.7	11.4††
Clinical Chemistry									
Calcium (mg/dL)	14.6	14.1	14.1	13.9	13.5	13.0	12.8	13.1 ‡	12.0††
Phosphorus (mg/dL)	4.9	4.5	4.1	4.0	4.2	4.5	4.2	4.0	3.7 †
Potassium (mEq/L)	4.49	4.29	4.71	4.83	4.76	4.56	4.22	4.25	3.90†
Cholesterol (mg/dL)	18	15	12	10	9	8	9	13	8
Triglycerides (mg/dL)	181	114	85	53	54	43	46	63	63
HDL cholesterol (mg/dL)	10.5	9.7	10.5	9.5	9.5	10.3	10.7	12.8	9.4
LDL+VLDL cholesterol (mg/dL)	2	3	1	1	1	2	2	2	2

a/ Data from Sloter (2005a). †, †† for statistical significance at $p < 0.05$ and < 0.01, respectively in comparison with Group 6. ‡, ‡‡ for statistical significance at $p < 0.05$ and < 0.01, respectively, in comparison with Group 4. NA=not applicable. VLDL=very low density lipoprotein. n=10.

Table 37. Clinical chemistry and hematology data for rabbit fetuses exposed to MeI (25 ppm) *in utero*.[a]

Effects	Groups								
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Sacrifice on Gestation Day	21	22	23	24	25	26	27	24	26
Maternal Treatment Days	-	-	-	-	-	-	-	23-24	23-26
Hematology									
Red cell (million/µL)	2.10	2.73	2.96	3.18	3.19	3.39	3.59	3.34	3.72†
Hemoglobin (g/dL)	7.8	10.1	10.3	10.8	10.8	11.4	11.7	11.6	12.2
Hematocrit (%)	30.4	39.6	41.4	42.7	41.6	43.2	45.3	46.0	47.4†
Clinical Chemistry									
Albumin (g/dL)	0.8	1.1	1.3	1.5	1.8	1.9	2.1	1.6	2.2 ††
Globulin (g/dL)	0.5	0.6	0.6	0.7	0.8	0.9	0.9	0.8	1.0 †
Total protein (g/dL)	1.4	1.6	1.9	2.3	2.6	2.8	3.0	2.4	1.0††
Creatinine (mg/dL)	0.3	0.4	0.4	0.7	0.8	0.7	0.7	0.8 ‡	0.9 †
Calcium (mg/dL)	7.6	7.5	8.7	12.1	12.9	13.2	13.1	13.1	15.0†
Chloride (mEq/L)	91	87	91	97	100	100	101	100	96†
Cholesterol (mg/dL)	161	170	175	176	167	150	140	205 ‡	209††
Triglyceride (mg/dL)	340	304	200	154	154	137	132	215‡‡	202††
HDL Cholesterol (mg/dL)	15.9	19.7	27.6	28.1	30.1	27.9	31.8	33.3‡‡	34.5 ††
LDL+VLDL Cholesterol (mg/dL)	64	77	104	121	121	111	95	144‡	157††

a/ Data from Sloter (2005a). †, †† for statistical significance at $p < 0.05$ and < 0.01, respectively, in comparison with Group 6. ‡, ‡‡ for statistical significance at $p < 0.05$ and $p < 0.01$, respectively, in comparison with Group 4. n=10.

Table 38. Glutathione levels and hemoglobin adducts in pregnant and fetal rabbits exposed to MeI (25 ppm) by inhalation.[a]

Tissue Source	Groups								
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Sacrifice on Gestation Day	21	22	23	24	25	26	27	24	26
Maternal Treatment Days	-	-	-	-	-	-	-	23-24	23-26
Maternal Data									
Liver GSH (mM)	5.92 ±1.9	8.41 ±1.0	8.45 ±0.99	5.91 ±2.3	6.36 ±1.5	7.34 ±0.70	7.41 ±0.78	8.06 ±0.78 (136%)	6.77 ±1.6 (92%)
Kidney GSH (mM)	1.75 ±0.37	1.65 ±0.17	1.76 ±0.18	1.59 ±0.29	1.43 ±0.36	1.81 ±0.24	1.73 ±0.13	1.59 ±0.09 (100%)	1.86 ±0.36 (103%)
Blood GSH (mM)	0.61 ±0.15	0.626 ±0.10	0.541 ±0.12	0.599 ±0.12	0.526 ±0.15	0.387 ±0.15	0.645 ±0.06	0.469 ±0.06* (78%)	0.460 ±0.15 (119%)
Naso-olfactory epithelium GSH (mM)	2.03 ±0.44	1.75 ±0.47	1.97 ±0.60	1.85 ±0.33	1.63 ±0.37	1.41 ±0.46	1.64 ±0.19	1.82 ±0.24 (98%)	1.75 ±0.35 (124%)
Naso-respiratory epithelium GSH (mM)	1.00 ±0.68	0.73 ±0.11	0.84 ±0.23	0.77 ±0.35	1.26 ±0.95	1.01 ±0.45	0.76 ±0.13	0.80 ±0.17 (104%)	0.65 ±0.10 (64%)
S-methylcysteine concentration (nmol/g hemoglobin)	ND	ND	ND	70.2 ±33.1	ND	48.4 ±6.3	ND	101.5 ±22.1 (145%)	103.4 ±27.8 (214%)
Fetal Data									
Blood GSH (mM)	0.429 ±0.08	0.424 ±0.11	0.465 ±0.11	0.473 ±0.08	0.436 ±0.05	0.382 ±0.09	0.310 ±0.05	0.338 ±0.12* (72%)	0.216 ±0.09* (57%)
Liver GSH (mM)	1.88 ±0.40	1.65 ±0.57	1.56 ±0.14	2.16 ±0.53	2.29 ±0.28	2.22 ±0.29	2.60 ±0.18	2.37 ±0.13 (110%)	2.23 ±0.18 (100%)
S-methylcysteine concentration (nmol/g hemoglobin)	ND	ND	ND	81.2 ±20.4	ND	60.1 ±9.2	ND	116.3 ±34.3 (143%)	98.7 ±17.5 (164%)

a/ Data from Sloter (2005a).* for statistical significance at $p<0.05$ compared with corresponding baseline group using Dunnett's test. ND=not determined. % of Control, in parenthesis, for Group 8 was based on Group 4 as the control. % of Control for Group 9 was based on Group 6 as the control. n=10.

Table 39. Mean serum iodide and thyroid hormone concentrations in pregnant rabbits exposed to MeI (25 ppm) by inhalation.[a]

Group	Exposure days Dosage (ppm)	Iodide (ng/mL)[b]	TSH (ng/mL)	T3 (ng/dL)	T4 (µg/dL)
1	GD 21	ND	0.66 ± 0.10	227.1 ± 24.9	1.9 ± 0.5
2	GD 22	ND	0.74 ± 0.13	199.8 ± 50.3	1.8 ± 0.7
3	GD 23	ND	0.70 ± 0.09	215.3 ± 32.5	2.0 ± 0.6
4	GD 24	20.6 (27 to <100)	0.73 ± 0.13	189.8 ± 21.3	1.9 ± 0.5
5	GD 25	ND	0.71 ± 0.12	172.8 ± 24.9	1.9 ± 0.7
6	GD 26	15.4 (<20 to 110)	0.77 ± 0.11	154.0 ± 24.9	1.8 ± 0.5
7	GD 27	ND	0.80 ± 0.11	153.0 ± 20.4	1.7 ± 0.5
8	GD 23-24 25 ppm	16,700 (9,800 to 22,700)	0.99 ± 0.32* (136 ± 51%)[c]	143.9 ± 29.6* (75.8 ± 17.7%)[c]	1.4 ± 0.5 (77.9 ± 33.6%)[c]
9	GD 23-26 25 ppm	31,100 (10,200 to 78,000)	1.05 ± 0.30* (136 ± 43%)[d]	121.7 ± 26.1* (79.1 ±21.2%)[d]	1.6 ± 0.6 (89.3 ± 39.1%)[d]

a/ Data from Sloter (2005a). Groups 1 to 7 are not treated; Group 8 and 9 were sacrificed after the last daily exposure. n=10/group. ND=not determined. * for statistical significance at p<0.05 by Dunn's test, or t-test.

b/ Mean values for maternal iodide levels in Groups 4 and 6 were based on estimated values using the method of standard additions (MSA) described in the report. They included values from duplicate samples. Without the duplicate being counted, the iodide concentrations were 17,200 ng/mL and 26400 ng/mL for Groups 8 and 9, respectively.

c/ % of control based on Group 4 values.

d/ % of control based on Group 6 values.

Table 40. Mean serum iodide and thyroid hormone concentrations in fetal rabbits exposed to MeI (25 ppm) during gestation.[a]

Group (n)	Exposure days Dose (ppm)	Iodide (ng/mL)[b]	TSH (ng/mL)	T3 (ng/dL)	T4 (µg/dL)
1 (n=10)	GD 21	ND	1.43 ± 0.36	0.0 ± 0.0	0.09 ± 0.08
2 (n=6)	GD 22	ND	1.43 ± 0.30	4.7 ± 4.1	0.08 ± 0.08
3 (n=8)	GD 23	ND	1.31 ± 0.18	2.9 ± 2.7	0.01 ± 0.01
4 (n=9)	GD 24	181 (119 to 262)	1.70 ± 0.23	7.0 ± 2.8	0.09 ±0.07
5 (n=13)	GD 25	ND	1.59 ± 0.28	10.7 ± 3.7	0.21 ± 0.09
6 (n=9)	GD 26	131 (<100 to 165)	1.37 ± 0.27	11.2 ± 5.3	0.26 ± 0.13
7 (n=13)	GD 27	ND	1.66 ± 0.45	14.3 ± 6.3	0.33± 0.17
8 (n=8)	GD 23-24 25 ppm	37,100 (21,600 to 55,900)	1.47 ± 0.42 (87 ± 27%)[c]	3.3 ± 3.3* (47.1 ± 50.4%)[c]	0.05 ± 0.10 (63.6 ±119.7%)
9 (n=8)	GD 23-26 25 ppm	67,600 (33,500 to 128,000)	9.71 ± 8.94* (711 ± 669%)[d]	11.7 ± 6.1 (104.5±73.9%)[d]	0.06 ± 0.07* (21.4 ± 29.5%)[d]

a/ Data from Sloter (2005a). Groups 1 to 7 are not treated; Group 8 and 9 does were sacrificed after the last exposure. ND=not determined. * for statistical significance at p<0.05 by the Dunn's test or t-test. n=10, except for 9 in Group 8, and 8 in Group 9.

b/ Mean values for this group excluded values below 100 ng/mL (the lower limit of quantitation by injection method described in the report). The range is presented within parentheses.

c/ % of control based on Group 4 values.

d/ % of control based on Group 6 values.

Table 41. Late resorption data and microscopic findings in fetal rabbit thyroids after exposure to MeI (25 ppm) by inhalation during gestation.[a]

Effects	Groups								
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8** 25 ppm	**9** 25 ppm
Sacrifice on Gestation Day	21	22	23	24	25	26	27	24	26
Maternal Treatment Days	-	-	-	-	-	-	-	23-24	23-26
All Fetuses									
Late resorption affected litter mean fetus/litter % fetus/litter	0 0 0%	0 0 0%	1/10 0.1±0.3 0.8%	2/10 0.2±0.4 1.8%	1/10 0.1±0.3 0.9%	2/10 0.2±0.4 1.7%	3/10 0.3±0.5 3.0%	3/9 0.6± 0.9 5.7%	4/10 0.5±0.7 5.2%
Thyroid-Male Fetuses (# fetuses affected/total fetuses)									
Epithelial vacuolation Minimal to mild	0/39	0/37	0/35	0/38	0/38	0/60	0/48	12/37	43/45
Decreased colloid Mild to severe	0/39	0/37	0/35	0/38	0/38	0/60	0/48	2/37	43/45
Hypertrophy, follicular cell Minimal to moderate	0/39	0/37	0/35	0/38	0/38	0/60	0/48	11/37	42/45
Thyroid-Female Fetuses (# fetuses affected/total fetuses)									
Epithelial vacuolation Minimal	0/46	0/60	0/49	0/41	0/44	2/39	0/43	26/36	25/36
Decreased colloid Minimal to severe	0/46	0/60	0/49	0/41	0/44	0/39	0/43	8/36	29/36
Hypertrophy, follicular cell Minimal to mild	0/46	0/60	0/49	0/41	0/44	0/39	0/43	16/36	34/36

a/ Data from Sloter (2005a).

b/ Mean number of fetuses/litter with % fetuses per litter indicated in parenthesis.

Three groups of mated New Zealand white female rabbits (40/group; 5/sacrifice time point) were exposed by whole-body inhalation to filtered air or MeI (99.7% purity, 20 ppm equivalent to 0.11 mg/L or 15 mg/kg/day) for 6 hours/day, or intravenous infusion to NaI (20.3 µM as four 15 minute infusion over a 6 hour period; equivalent to 81.2 µmole/doe/day or 2.58 mg iodide/kg/day) for up to 4 consecutive days, beginning on GD 23 (Sloter, 2005b). Samples collected and sacrifice times are outlined in Table 42. Liver and nasal epithelium tissues were not collected from the NaI group. There were neither treatment-related clinical signs nor body weight effects on the does for any group.

Methyl iodide and NaI exposures increased circulating iodide to at least several hundred-fold higher than controls (Table 43 and 44). Methyl iodide groups had about twice the serum iodide concentration as the concurrent NaI groups. Fetal iodide levels at a particular sacrifice interval were commonly 2- to over 10-fold higher than corresponding maternal levels, whether the does were given NaI or MeI.

Results from MeI groups after a non-dosing period (a recovery period) showed that the does clear excess iodide more rapidly than did the fetuses (Table 43). For example with GD 23_{T6} and GD 24_{T6+R18} groups with the same total exposure hours, the maternal serum iodide level decreased about 80%, when measured 18 hours after the last exposure. In the fetuses, the decrease after recovery was about 70%. A comparison of maternal and fetal iodide levels measured after various recovery time after 3 doses, GD $25_{2(T6+R18)+T6+R6}$, GD $25_{2(T6+R18)+T6+R12}$, and GD $26_{3(T6+R18)}$, showed a slow clearance rate (20-30% loss) between 12 hours and 18 hours of recovery. These results indicated that most of the loss seen in the first comparison likely occurred during the first 6 hours. For NaI, there appeared to be a slower clearance because 18 hours of recovery resulted in a decrease of about 50% of maternal and fetal iodide level of the GD 23_{T6} and 24_{T6+R18} groups (Table 44).

Maternal thyroid hormone data showed some changes associated with MeI or NaI treatment (Table 45). They included increased TSH, decreased T3, and variable change in T4. The fetal control data for the MeI group showed T3 increased two fold from 10.1 ng/dL on GD 23 to 23.9 ng/dL on GD 29. Neither TSH nor T4 showed any time-related changes in levels. With treatment, there was a dose-related increase in TSH, from GD 25 (2.7 ng/mL) to GD 29 (4.4 ng/mL), usually statistically significant for both MeI and NaI fetuses (Table 45). A higher increase might be expected if there were no recovery period, as shown by results from the GD $26_{3(T6+R18)+T6}$ and GD $29_{4(T6+R18)+R48}$ groups. T4, in general, was reduced from GD 25 and onward, with statistical significance for one of the GD 25 MeI groups, possibly due to a high control value (0.20 µg/dL) compared to other controls (range from 0.05 to 0.14 µg/dL).

S-methylcysteine levels showed a 34% increase in MeI treated does and a 56% increase for fetuses after exposure to MeI for 4 days (Table 46). Maternal and fetal blood GSH levels were reduced for GD 23_{T6} and GD $24_{T6+R18+T6}$, with a statistically significant difference reported for some durations (Table 46). There were no consistent GSH changes in maternal nasal respiratory epithelium, or fetal or maternal liver of MeI treated rabbits after one or two days of treatment.

While fetal viability was not affected by NaI exposure, it was most affected in the GD 29 MeI group, with the mean % of viable fetuses/litter of 46.8% with MeI exposure versus 93.1% in controls (Table 47). The post-implantation loss after MeI treatment was primarily due to increased (50.4 %/litter) late resorption, which was significantly different than the control of

4.7%/litter. In comparison, the post-implantation loss from NaI treatment was due to both early and late resorption. External examination of the fetuses showed no MeI or NaI treatment-related malformations.

Histopathology of thyroids (the only organ evaluated) showed hypertrophy of the follicular cells and colloid depletion in the does and fetuses after at least 2 exposures with either MeI or NaI (Table 48). Does, evaluated only on GD $26_{3(T6+R18)+T6}$, showed higher incidences of hypertrophy and colloid depletion from MeI exposure than from NaI treatment. This could be explained by the higher internal maternal serum iodide level in the MeI treated does, compared to that for the NaI does. However, MeI and NaI fetuses responded at similar degrees. The majority of fetuses had minimal hypertrophy after 2 exposures (GD $24_{T6+R18+T6}$). Increased severity and incidences of hypertrophy and colloid depletion were observed with additional exposures. These effects were more apparent on GD $26_{3(T6+R18)+T6}$, with some indication of recovery because of lower incidences in the GD 29 group, which was examined 48 hours after the last treatment on GD 26. It is not known if the change is associated with iodide levels since neither maternal nor fetal iodide levels were measured for this group. The only measured difference between these two periods was a decrease in TSH in the NaI group, while the TSH remained elevated in the MeI group.

These results were consistent with previous studies in showing a NOEL of <20 ppm for increased late resorption, decreased fetal viability, and fetal thyroid effects after a few days of exposure during late gestation.

Table 42. Schedule of laparohysterectomy and sample collection from rabbits exposed to MeI or sodium iodide during gestation.[a]

Groups	Study Report notation	Doses	Tests Before Last dose	Time after completion of last dose for sample collection or sacrifice				
				Immed-iately after	6 hours later	12 hours later	18 hours later	3 days (GD 29)
GD 23_{T3}	GD 23-3	GD 23 (3 hours)	F TSH	FM iodide FM GSH F histo				
GD 23_{T6}	GD 23-6	GD 23		FM iodide FM GSH FM TH F histo				
GD 24 T6+R18	GD 24-0	GD 23					FM iod FM GSH F TH F histo	
GD 24 T6+R18+T6	GD 24-6	GD 23, GD 24		FM iodide FM TH FM GSH F histo				
GD 25 2(T6+R18)+ T6+R6	GD 25-12	GD 23, 24, 25			FM iod FM TH F histo			
GD 25 2(T6+R18)+ T6+R12	GD 25-18	GD 23, 24, 25				FM iod F TH no histo		
GD 26 3(T6+R18)	GD 26-0	GD 23, 24, and 25					M iod	
GD 26 3(T6+R18)+ T6	GD 26-6	GD 23, 24, 25, 26		FM iodide FM TH FM histo				
GD 29 4(T6+R18)+ R48	GD 29	GD 23, 24, 25, 26						FM TH F histo

a/ Protocol from Sloter (2005b). Except for Group 1 with 3 hours of exposure, all exposures were 6 hours of duration. Abbreviations: F=fetal; GSH= glutathione in maternal and fetal liver, maternal nasal respiratory epithelium; histo=histology; M=maternal; TH=TSH, T3 and T4; T=treatment hours, R=Recovery hours before sampling or sacrifice. For iodide measurements, maternal blood was collected from 5 does per group per time point. Fetal blood collected for each litter may be pooled. n=5 for each group, except $GD26_{3(T6+R18)}$ and GD $26_{3(T6+R18)+T6}$ used the same animals.

Table 43. Maternal and fetal serum iodide levels in rabbits exposed to MeI (20 ppm) by inhalation.[a]

Groups	Maternal serum iodide range (ng/mL)	Maternal serum iodide (ng/mL) in doe with late resorption	Fetal serum iodide range (ng/mL)
Controls GD 23 to 26	5.18±0.09-48.6±56.6[b]	NA	124±2.5-217±55.3[c]
Treated Groups (MeI 20 ppm)			
GD 23_{T3}	7,500 ± 488 (6,940-8,070)	7,660 (1 doe)	15,100 ± 4,620 (10,600-22,700)
GD 23_{T6}	9,570 ± 4,750 (135-13,500)	No resorption	27,800 ± 9,250 (16,000-42,100)
GD 24_{T6+R18}	1,740 ± 1,340 (720-4,020)	4,020 (1 doe)	8,960 ± 4,830 (4,390-16,500)
GD $24_{T6+R18+T6}$	14,300 ± 2,360 (12,850-18,700)	No resorption	33,200 ±11,900 (14,800-46,400)
GD $25_{2(T6+R18)+T6+R6}$	5,110 ± 1,760 (2,960-7,370)	7,370 (1 doe)	40,100 ± 15,700 (20,300-62,200)
GD $25_{2(T6+R18)+T6+R12}$	4,470 ± 3,250 (2,100-10,800)	No resorption	32,000 ± 12,800 (18,000-56,900)
GD $26_{3(T6+R18)}$	3,610 ± 1,200 (1,750-4,830)	ND	ND
GD $26_{3(R6+R18)+T6}$	16,600 ± 6,800 (11,100-29,600)	3,180 (1 doe)	72,600 ± 23,200 (53,850-110,000)
GD $29_{4(T6+R18)+R48}$	ND, 4/4 does had resorption (% fetus/litter=50.4±28.1%)		

a/ Data from Sloter (2005b). The does in the MeI group were exposed for 3 or 6 hours each day (T3 or T6). Samples were taken at the end of the last exposure or after a recovery period (for example R18 means 18 hours after the end of last dose). The Day 29 group was sacrificed on GD 29, but had its last exposure on Day 26. Fetal serum iodide levels were those from live fetuses. ND=not determined

b/ Range from mean value for each sampling period with n=2 using the method of standard additions (MSA), excluding the other 3 samples with iodide levels indicated as <100 ng/mL. The MSA is validated down to 20 ng/ml; values less than that are considered estimates. The high value of 48.6 ng/mL for does was measured on GD 23_{T6}. Without this point, the range was 5.18 to 19.7 ng/mL.

c/ The highest control mean fetal iodide level was 217 ng/mL in the GD $25_{2(T6+R18)+T6+R12}$ group, measured by MSA.

Table 44. Maternal and fetal serum iodide levels in rabbits exposed to sodium iodide by intravenous injection.[a]

Groups	Maternal serum iodide range (ng/mL)	Maternal serum iodide (ng/mL) of does with late resorption	Fetal serum iodide range (ng/mL)
Controls GD 23 to 26	5.18±0.09- 48.6±56.6[b]	NA	124±2.5- 217±55.3[c]
Treated Groups (sodium iodide 81.2 μmol/daily)			
GD 23_{T3}	3,400 ± 346 2,830-3,740	No resorption	7,420 ± 1,330 5,580-9,080
GD 23_{T6}	5,830 ± 611 4,870-6,780	5740 in one doe	14,900 ± 8,120 7,880-31,500
GD 24_{T6+R18}	2,290 ± 294 1,810-2,550	No resorption	7,610 ± 4,860 613-13,200
GD $24_{T6+R18+T6}$	6,290 ± 528 5,750-6,750	No resorption	23,000 ± 6,320 15,400-30,250
GD $25_{2(T6+R18)+T6+R6}$	4,330 ± 1,610 2,290-6,360	4070, 3480 in 2 does	25,000 ± 8,530 10,600-32,400
GD $25_{2(T6+R18)+T6+R12}$	1,740 ± 563 681-2,020	1620, 1830 in 2 does	18,600 ± 4,900 13,200-24,700
GD $26_{3(T6+R18)}$	4,870 ± 8,480 634-20,000	ND	ND
GD $26_{3(T6+R18)+T6}$	9,630 ± 11,000 3,330-29,200	No resorption	35,900 ± 17,200 14,400-55,300
GD $29_{4(T6+R18)+R48}$	Serum iodide not measured. 2/5 does had resorption (% fetus/litter=6.8±10.9%)		

a/ Data from Sloter, 2005b. The does in the MeI group were exposed for 3 or 6 hours each day (T3 or T6). Samples were taken at the end of the last exposure or after a recovery period (for example R18 means 18 hours after the end of last dose). The Day 29 group was sacrificed on GD 29, but had its last exposure on Day 26. Fetal serum iodide levels were those from live fetuses. ND=not determined.

b/ Range from mean value for each sampling period with n=2 using the method of standard additions (MSA), excluding the other 3 samples with iodide levels indicated as <100 ng/mL. The MSA is validated down to 20 ng/ml; values less than that are considered estimates. The high value of 48.6 ng/mL for does was measured on GD 23_{T6}. Without this point, the range was 5.18 to 19.7 ng/mL.

c/ The highest control mean fetal iodide level was 217 ng/mL in the GD $25_{2(T6+R18)+T6+R12}$ group, measured by MSA.

Table 45. Maternal and fetal TSH, T3, and T4 in rabbits exposed to MeI (20 ppm) by inhalation or sodium iodide by intravenous injection.[a]

Groups	TSH (ng/mL)			T3 (ng/dL)			T4 (µg/dL)		
	Control	MeI	NaI	Control	MeI	NaI	Control	MeI	NaI
Does									
GD 23_{T6}	0.50 ±0.10	0.52 ±0.19	0.78 ±0.58	180 ±24	173 ±12	139 ±5*	1.76 ±0.27	1.75 ±0.40	1.26 ±0.38
GD 24 $_{T6+R18+T6}$	0.46 ±0.11	0.62 ±0.04*	0.62 ±0.08*	173 ±16	158 ±20	133 ±22*	1.43 ±0.42	1.44 ±0.46	1.15 ±0.71
GD 25 $_{2(T6+R18)+T6+R6}$	0.56 ±0.05	0.68 ±0.20	0.72 ±0.04	160 ±36	136 ±34	127 ±31	1.33 ±0.24	0.95 ±0.85	0.38 ±0.39
GD 26 $_{3(T6+R18)+T6}$	0.58 ±0.24	0.58 ±0.15	0.60 ±0.07	122 ±24	114 ±25	123 ±16	0.60 ±0.38	0.84 ±0.89	0.61 ±0.66
GD 29 $_{4(T6+R18)+R48}$	0.56 ±0.11	1.05 ±0.65	0.74 ±0.33	168 ±30	150 ±18	149 ±44	0.77 ±0.35	0.40 ±0.36	1.03 ±0.67
Fetuses									
GD 23_{T3}	1.2 ±0.1	1.1 ±0.2	1.2 ±0.1	10.1 ±5.2	8.9 ±5.4	7.2 ±3.2	0.12 ±0.12	0.07 ±0.02	0.10 ±0.04
GD 23_{T6}	1.2 ±0.4	1.1 ±0.2	1.1 ±0.3	4.5 ±2.6	6.5 ±4.8	9.0 ±4.6	0.07 ±0.03	0.10 ±0.05	0.13 ±0.09
GD 24_{T6+R18}	1.5 ±0.2	1.0 ±0.2*	1.5 ±0.2	11.3 ±4.3	10.1 ±6.3	9.2 ±5.5	0.09 ±0.05	0.03 ±0.03	0.07 ±0.09
GD $24_{T6+R18+T6}$	1.9 ±0.5	1.7 ±0.4	2.0 ±0.6	10.4 ±2.0	13.6 ±4.6	7.6 ±2.0	0.05 ±0.04	0.08 ±0.05	0.03 ±0.03
GD 25 $_{2(T6+R18)+T6+R6}$	1.7 ±0.4	2.7 ±0.6	3.5 ±1.5*	13.1 ±6.5	13.3 ±5.8	10.8 ±6.0	0.20 ±0.11	0.06 ±0.09*	0.01 ±0.01*
GD 25 $_{2(T6+R18)+T6+R12}$	1.5 ±0.2	4.2 ±1.1*	3.8 ±1.1*	12.0 ±2.4	13.2 ±5.6	14.5 ±4.2	0.08 ±0.07	0.00 ±0.00	0.01 ±0.02
GD 26 $_{3(T6+R18)+T6}$	1.9 ±0.9	5.1 ±1.5*	5.2 ±2.9*	15.4 ±3.1	26.6 ±12.6	15.7 ±2.4	0.06 ±0.04	0.03 ±0.05	0.01 ±0.01
GD 29 $_{4(T6+R18)+R48}$	1.1 ±0.2	4.4 ±3.4*	1.7 ±0.5	23.9 ±4.8	49.4 ±30.2	31.8 ±9.1	0.14 ±0.04	0.10 ±0.15	0.09 ±0.05

a/ Data from Sloter (2005b). The does in the MeI group were exposed for 3 or 6 hours each day (T3 or T6). Samples were taken at the end of the last exposure or after a recovery period (for example R18 means 18 hours after the end of last dose). The Day 29 group was sacrificed on GD 29, but had its last exposure on Day 26. *for statistical significance at $p<0.05$.

Table 46. Maternal and fetal S-methylcysteine and glutathione levels in rabbits exposed to MeI (20 ppm) by inhalation.[a]

Groups	Does		Fetuses	
	Control	MeI	Control	MeI
S-methylcysteine adduct (nmole/g globulin)				
GD $26_{3(T6+R18)+T6}$	69.7 ± 9.3	93.4 ± 5.0 (134%)	86.9 ± 20.1	131.1 ± 11.0 (151%)
GSH (mM)				
Blood				
GD 23_{T3}	0.512±0.150	0.469±0.074 (92%)	0.314±0.081	0.258±0.149 (82%)
GD 23_{T6}	0.565±0.097	0.451±0.100 (80%)	0.410±0.104	0.253±0.098* (62%)
GD 24_{T6+R18}	0.652±0.082	0.584±0.063 (90%)	0.437±0.025	0.408±0.077 (93%)
GD $24_{T6+R18+T6}$	0.642±0.045	0.413±0.051** (64%)	0.411±0.115	0.227±0.056* (55%)
Liver				
GD 23_{T3}	6.55±1.33	6.32±2.73 (96%)	1.86±0.71	2.14±0.05
GD 23_{T6}	8.00±0.89	6.54±0.29** (82%)	2.01±0.14	2.05±0.16
GD 24_{T6+R18}	6.91±0.63	7.25±0.59 (105%)	2.45±0.19	2.37±0.19
GD $24_{T6+R18+T6}$	7.23±0.66	7.31±0.87 (101%)	2.27±0.18	2.01±0.46
Nasal respiratory epithelium				
GD 23_{T3}	0.619±0.117	0.588±0.146	ND	ND
GD 23_{T6}	0.792±0.124	0.754±0.093		
GD 24_{T6+R18}	0.723±0.112	0.753±0.213		
GD $24_{T6+R18+T6}$	0.770±0.275	0.702±0.187		

a/ Data from Sloter (2005b). The does in the MeI group were exposed for 3 or 6 hours each day (T3 or T6). Samples were taken at the end of the last exposure or after a recovery period (for example R18 means 18 hours after the end of last dose). The Day 29 group was sacrificed on GD 29, but had its last exposure on Day 26. hr=hours, ND=not determined. *, ** for statistical significance at $p<0.05$ and <0.01, respectively. % of control is in parenthesis.

Table 47. Fetal viability for pregnant rabbits exposed to MeI (20 ppm) by inhalation.[a]

Groups	Control	Methyl Iodide	Sodium Iodide
GD 23$_{T3}$, GD 23$_{T6}$, and GD 24$_{T6+R18}$			
Viable fetuses			
-mean fetus/litter	9.5 ± 1.29 (14)	9.0 ± 1.41 (15)	9.5 ± 1.13 (15)
-% fetus/litter	94.1 ± 9.88	94.6 ± 9.64	96.0 ± 6.58
Late resorption			
-% fetus/litter	3.4 ± 7.77	3.4 ± 9.50	0.7 ± 2.58
GD 24$_{T6+R18+T6}$			
Viable fetuses			
-mean fetus/litter	9.0 ± 3.16 (5)	9.2 ± 2.17 (5)	9.0 ± 2.12 (5)
-% fetus/litter	92.2 ± 7.55	98.2 ± 4.07	89.3 ± 11.46
Late resorption			
-% fetus/litter	2.0 ± 4.47	0	0
GD 25$_{2(T6+R18)+T6+R6}$ and **GD 25$_{2(T6+R18)+T6+R12}$**			
Viable fetuses			
-mean fetus/litter	8.5 ± 2.27 (10)	9.4 ± 2.32 (10)	9.5 ± 2.32 (10)
-% fetus/litter	96.0 ± 6.79	94.5 ± 10.06	91.4 ± 10.39
Late resorption			
-% fetus/litter	1.1 ± 3.51	1.0 ± 3.16	4.4 ± 6.09
GD 26$_{3(T6+R18)+T6}$			
Viable fetuses			
-mean fetuses/litter	8.6 ± 1.52 (5)	8.6 ± 2.30 (5)	9.8 ± 1.79 (5)
-% fetus/litter	90.0 ± 22.36	96.0 ± 8.94	100.0
Late resorption			
-% fetus/litter	0	4.0 ± 8.94	0
GD 29$_{4(T6+R18)+R48}$			
Viable fetuses			
-mean fetus/litter	7.2 ± 0.84 (5)	4.0 ± 2.71 (4)*	9.6 ± 1.14 (5)
-% fetus/litter	93.1 ± 10.1	46.8 ± 29.3*	87.5 ± 7.05
Post-implantation loss			
-% fetus/litter	6.9 ± 10.10	53.2 ± 29.3	12.5 ± 7.05
Late resorption			
affected litter	2/5	4/4	2/5
mean fetus/litter	0.4 ± 0.55	4.3 ± 2.50	0.8 ± 1.30
-% fetus/litter	4.7 ± 6.48	50.4 ± 28.09*,[b]	6.8 ± 10.9

a/ Data from Sloter (2005b). For mean viable fetuses/litter, the number of litter is indicated in the parentheses. The does in the MeI group were exposed for 3 or 6 hours each day (T3 or T6). Samples were taken at the end of the last exposure or after a recovery period (for example R18 means 18 hours after the end of last dose). The Day 29 group was sacrificed on GD 29, but had its last exposure on Day 26. Statistical significance was based on Dunn's test (% data), or Dunnett's test with * for $p<0.05$. ND=not determined. Mean fetus/litter= group mean for # of fetuses affected in each litter. % fetus/litter= group mean for # fetuses affected/total implantation sites for each litter x 100%.

b/ Three of four does accounted for most of the late resorptions with % ranging from 55.6 to 77.8 for all animals.

Table 48. Microscopic findings in the thyroid of pregnant rabbit and fetuses after exposure to MeI (20 ppm) by inhalation.[a]

Effects	Control	Methyl iodide (20 ppm)	Sodium iodide
Does at GD $26_{3(T6+R18)+T6}$			
Hypertrophy, follicular cell, minimal	0/5	2/5	0/5
Depletion, colloid, minimal	0/5	3/5	1/5
Fetuses[b]			
GD 23_{T6}			
Hypertrophy, follicular cell, minimal	0/20	0/20	0/20
Depletion, colloid, minimal	0/20	0/20	0/20
GD $24_{T6+R18+T6}$			
Hypertrophy, follicular cell, minimal	0/20	16/20	12/20
Depletion, colloid, minimal	0/20	1/20	0/20
GD $25_{2(T6+R18)+T6+R6}$ Hypertrophy, follicular cell, minimal	0/20	20/20	18/20
Depletion, colloid, total	0/20	5/20	9/20
minimal	0/20	4/20	5/20
mild	0/20	1/20	4/20
GD $26_{3(T6+R18)+T6}$			
Hypertrophy, follicular cell, total	0/20	16/20	18/20
minimal	0/20	9/20	8/20
mild	0/20	7/20	10/20
Depletion, colloid, total	0/20	13/20	17/20
minimal	0/20	6/20	7/20
mild	0/20	1/20	4/20
moderate	0/20	6/20	6/20
GD $29_{4(T6+R18)+R48}$			
Hypertrophy, follicular cell, total	0/20	6/16	5/20
minimal	0/20	2/16	5/20
mild	0/20	4/16	0/20
Depletion, colloid, total	0/20	6/16	6/20
minimal	0/20	1/16	6/20
mild	0/20	2/16	0/20
moderate	0/20	3/16	0/20

a/ Data from Sloter (2005b). The does in the MeI group were exposed for 3 or 6 hours each day (T 3 or T6). Samples were taken at the end of the last exposure or after a recovery period (for example R18 means 18 hours after the end of last dose). The Day 29 group was sacrificed on GD 29, but had its last exposure on Day 26.

b/ In the published report of this study (Sloter *et al*., 2009), it indicated different number of fetuses examined for the following groups: 16 (control and MeI groups, GD 23_{T6}), 17 (NaI group, GD 23_{T6}), 24 (control, MeI and NaI groups, GD $24_{T6+R18+T6}$), 19 (control, GD 23_{T6}), and 13 (MeI group, GD $29_{4(T6+R18)+R48}$). Also, the incidence for follicular cell hypertrophy was 17/19 instead of 18/20 shown on this table.

III.H. Neurotoxicity

The acute neurotoxicity study (Schaefer, 2002) after MeI inhalation exposure is already presented in Section **III.B.2. Rat - Inhalation**. At the LOEL of 93 ppm, rats showed reduced body temperature and motor activity, and clonic convulsion. Neurotoxicity observed in humans after accidental exposure or ingestion of MeI is discussed in the following section.

A developmental neurotoxicity study in laboratory animals has not been conducted; and this study is not required for the registration by the USEPA (USEPA, 2006a and 2007). The importance for examination of potential for pre- and post-natal developmental neurotoxicity from MeI exposure is discussed under Section **V.C. Risk Characterization**.

III.I. Human Toxicity Case Reports

One of the early reports was on a worker who complained of giddiness, sleepiness, diarrhea, and mental irritability accentuated by noise (Garland and Camps, 1945). Air concentrations in the worker's MeI manufacturing factory were not provided. His symptoms disappeared after he stopped working. When he resumed work 3 months later, he vomited and was drowsy after his first day of work. In the hospital, he showed drowsiness, inability to walk, slurred and incoherent speech, abnormal eye movement, twitching upper limbs, splastic lower limbs, absence of abdominal reflexes, and oliguria. Iodine was detected in the urine at 9 mg/100 mL, but not in the cerebral spinal fluid. Two days later, vomiting, restlessness, and incontinence were reported. The patient became comatose and died several days later. At autopsy, all organs showed congestion with broncho-pneumonia and hemorrhage in the lungs. Analysis of the brain tissue (unknown amount) yielded 6 mg of "combined iodine."

Appel *et al.* (1975) described a white male chemist, who experienced blurred vision and unsteady gait after inhalation exposure to MeI while synthesizing this compound. He had been doing the synthesis on the weekends for 3 weeks. His symptoms progressed to include double vision, lethargy, confusion with dysarthric speech, and gross dysmetria of the upper extremities. After he was admitted to the hospital, test results (including clinical chemistry, cranial nerve function, motor, and sensory tests) were normal. He continued to complain of diplopia, and showed ataxic gait, dysmetria, and slurred hypophonic, but fluent speech. Serum iodide was 31 µg/100 mL, and cerebrospinal fluid iodine was 5.3 µg/100 mL. Over the next 3 weeks, the eye and gait effects slowly resolved but mental impairment (paranoia with delusions, and auditory and visual hallucinations) developed. At this time, the serum iodide was 6.4 µg/100 mL. He was discharged on the 6^{th} week. Follow-up examination performed 5 months later showed normal neurological function but residual paranoia and confusion.

Two workers were exposed to excess MeI during the production due to inadequate exposure protection (Hermouet *et al.*, 1996). The reported average MeI concentration was 124 mg/m^3, exceeding the TLV and STEL of 10 and 30 mg/m^3, respectively, measured after the second worker was admitted. The first worker (59-year old male) complained of headache and double vision, a "few" hours after the exposure. It was not known if he had previous exposure. Clinical examination revealed tremor, ataxia, dysmetria, and incomplete left third cranial nerve palsy resulting in strabismus without ptosis or mydriasis. Tests for cranial nerve, motor, and sensory functions, and electro-encephalogram were normal. The neurological symptoms gradually subsided over 3 weeks, but the patient developed depressive ideation. Symptoms of

dysarthria, hypermetria, ataxia, and tremor returned when he was re-exposed to MeI again several months later. The patient's health was not followed up further.

The second worker (42-year old male) of the report complained of drowsiness and vertigo, and was ataxic. He had been working with MeI for three years. The symptoms resolved after two days of non-exposure, but the worker was reported to be depressed. The worker returned to work and continued to experience neurological symptoms. Over the next 9 months, ataxia, painful paresthesia in the feet, double vision and slurred speech, and tingling of the lower extremities were reported to occur for about 1 month and then resolved spontaneously. About 9 months later, the worker was readmitted with similar symptoms. Clinical examination reported pyramidal syndrome, a cerebellar syndrome, and incomplete bilateral third nerve palsy. An electronystagmogram showed bilateral vestibular hypoexcitability. The electro-encephalogram was described as diffusely abnormal with irregular rhythms. Computerized tomography of the brain showed a small low-density lesion of the right caudate nucleus. All symptoms gradually resolved over 3 months, but the depression recurred. After he returned to work for 1 year, he developed symptoms similar to the last episode with the additional problems of bladder dysfunction, increased latency of lower limb somatosensory-evoked responses, decreased peripheral conduction velocity, lesions of the right internal frontal white matter and pigmented nuclei, and impaired memory. After mitigation measures were instituted in the facility, this worker recovered with almost all clinical manifestation resolved. Four years after the last episode, clinical tests showed a small right paraventricular lesion, slight deficit of short-term visual memory, and increased left central conduction time in the lower limb somatosensory-evoked response test. He reported difficulty in running and slight urinary hesitancy.

Additionally, Hermouet *et al* (1996) summarized the results of several reports of overexposure by 2 chemists and 3 workers. The common symptoms were vertigo, drowsiness, headache, ataxia, diplopia, dysarthris, and/or weakness.

Direct skin exposure to MeI resulted in contact dermatitis in a worker (Knudsen and Nielsen, 1999). The worker reportedly wore "nitril" (latex) gloves when he accidentally spilled MeI on his fingers and hands. Vesicles and bullae developed at the site on the next day, but the skin healed without scarring in a few weeks.

In a more severe accident, a worker suffered severe burns and systemic effects after loading newly manufactured MeI onto a truck (Schwartz *et al*., 2005). The exposure might have occurred via damaged soles of his chemical protective shoes. The burns initially involved the groin area, but later to include the torso, back, and lower extremities. The patient was hospitalized as he experienced episodic syncope and was in hypovolemic shock. Delirium was noted on the 4^{th} day of the hospital stay. After discharge from the hospital, his skin healed but his mental status continued to be affected. He experienced problems with memory, concentration, and performance of tasks, and changes in behavior and personality shown by prolonged staring, decreased activity, "flat emotion", and lassitude. A Magnetic Resonance Imaging study of the brain showed mild cerebral atrophy and prominence of the cortical sulci greater than expected for his age. Other tests of his neurological status showed deficits in attention, memory, information processing, and task performance, 4 months after his initial exposure. At follow-up 2 months after, there was improvement of his ability to concentrate and mental acuity.

In an intentional poisoning case, a 19-year old male gave himself an intravenous injection of MeI (about 14 g, or 165 mg/kg for 85 kg body weight) (Robertz-Vaupel *et al*., 1991). He showed somnolence, agitation, convulsion, and severe hypotension. Three hours after exposure, serum iodide concentrations in three samples ranged from 52.44 µg/mL to 75.24 µg/mL (average 60 µg/mL). He was given acetylcysteine and hemoperfusion. After hemoperfusion, serum iodide concentration was about 0.2 µg/mL and the patient survived. Note that data from this study is used to test the human model in PBPK modeling of acute exposure by Arysta (Sweeney *et al*., 2009; **Appendix A** of **Volume I**).

In these case reports, there is sufficient evidence that MeI causes acute neurotoxicity in humans. Of greater concern is neurotoxicity in form of psychiatric problems developed well after cessation of exposure. In Appel *et al*. (1975), the chemist developed paranoia with delusions, auditory and visual hallucinations 3 weeks later, and had residual paranoia and confusion 5 months after the initial hospitalization. Hermouet *et al*. 1996 reported depression in two male workers 2 or 3 weeks after exposure. Delayed effects (deficits in attention, memory, information processing, and task performance) and permanent brain damage (mild cerebral atrophy and prominence of the cortical sulci) were found in the worker, who was exposed to MeI likely by dermal exposure (Schwartz *et al*., 2005). The SRC recommended giving "greater attention in terms of the implications of the findings even given the lack of exposure data. There are clearly brain regions and cell types that are especially vulnerable, based on symptomatology and direct assessments of in neuronal cells" (**Volume IV Part 1-A**). In this document, the concern is addressed by including an evaluation of neurotoxicity after subchronic and chronic exposures, as presented in the Hazard Identification section (**IV.A.2.**).

III.J. PBPK and Mode of Action Studies

This section describes additional studies which had been conducted for PBPK modeling and toxicity of MeI.

III.J.1. PBPK Parameters

To describe the MeI uptake into body tissues and fluids, the partition of MeI (10,000 ppm) between air and minced tissues from Sprague-Dawley rat and New Zealand white rabbit, human blood, and saline was studied in septum-sealed vials (Table 49; Gannon, 2004). Partition coefficients for fat (88 in rat, and 87 in rabbit) were relatively higher than other tissues. Some tissues (brain, kidney, muscle) showed a similar extent of partitioning between tissues, and between the rat and rabbit. However, the coefficient for blood in the rat was 2 to 3-fold higher than those for rabbit or human. The thyroid coefficient for the rabbit was 3-fold higher than that for the rat. Methyl iodide also partitioned into the rabbit placenta, the only species studied. This study was considered supplemental to DPR.

Table 49. Partition coefficients for MeI in rat and rabbit tissues and human blood.[a]

Tissues	Tissue/blood: Air Partition Coefficients		
	Rat	Rabbit	Human
Blood	39.3 ± 5.5	Fetal 12.0 ± 2.2 Maternal 16.0 ± 0.8	Male blood 18.0 ± 0.6 Female blood 17.1 ± 0.9
Brain	9.5 ± 1.2	6.7 ± 0.5	ND
Fat	88.8 ± 2.3	87.3 ± 3.9	
Kidney	8.4 ± 1.1	9.0 ± 2.0	
Liver	24.1 ± 2.8	13.3 ± 3.0	
Muscle	7.5 ± 2.3	6.4 ± 0.5	
Nasal	5.7 ± 0.9	8.3 ± 0.7	
Thyroid	11.4 ± 1.8	38.9 ± 3.6	
Placenta	ND	6.8 ± 1.1	

a/ Data from Gannon (2004). Value represent regression analysis intercept at time = 0 hours ± regression standard error. Partition of MeI in saline = 3.9 ± 0.7. ND=not determined.

Three studies were conducted to characterize the MeI uptake by rat and rabbit nasal cavities (Thrall *et al*., 2004a, b, and c; Thrall *et al.*, 2009a). Anesthetized female New Zealand white rabbits (12 to 17 weeks old, 9 animals) were placed in sealed glass chambers and exposed by whole-body inhalation to MeI concentrations ranging from 1 to 46 ppm (measured) for 30 minutes (Thrall *et al*., 2004a). A plethysmograph assessed breathing frequency, tidal volume, and allowed calculation of minute volume. Results showed the minute volumes ranged from approximately 300 to 1700 mL/min. Breathing frequencies ranged from 38 to 52 breaths per minute (bpm). Tidal volumes ranged from 2.8 to 12.9 mL/kg. The amount of MeI absorbed (also referred to as scrubbed) in the nasal cavity was the fraction of MeI concentration detected in the rabbit's nose (samples from a tube which extended into the nasopharynx) for the exposure duration (as area under the curve) over the chamber MeI concentration for the same duration. An estimate was that 72% of MeI was absorbed, irrespective of initial chamber MeI concentration. MeI did not affect the tidal volume, breathing frequency, or minute volume. This study was considered supplemental information to DPR.

Anesthetized male Sprague-Dawley rats (9-11 weeks of age, 6 animals) were placed in a sealed glass chamber and exposed (whole-body) to MeI at 0.7 to 1 ppm (measured) for 40 minutes (Thrall *et al*., 2004b). The minute volumes ranged from 23 to 95 mL/min with an average of 71 ± 9 mL/min over the 40-minute exposure period. Breathing frequencies ranged from 54 to 808[15] breaths per minute (bpm). Tidal volumes ranged from 0.08 to 2.8 mL/kg. The calculated breathing rates (0.09 to 0.36 m^3/kg/day) for these anesthetized rats were much lower than those (1.51 to 1.89 m^3/kg/day) for unanesthetized rats (Himmelstein, 2004). For rats, an estimated 63 % of MeI was absorbed, using an initial chamber MeI concentration of about 1.1 ppm. MeI did not affect tidal volume, breathing frequency, or minute volume. This study was considered supplemental information to DPR.

[15] The report noted that two animals had very high breathing frequencies (657 and 808 bpm), while the other 4 animals ranged from 54 to 95 bpm. It cited a literature published range of 47 to 136 bpm.

Non-anesthetized and unrestrained female New Zealand white rabbits (12 to 15 weeks of age, 3/group) were exposed to MeI (1, 2, 10, or 50 ppm) by whole-body inhalation for 4 hours (Thrall *et al*., 2004c). The remaining MeI air concentrations after 4 hours averaged less than 10% of initial concentrations, regardless of exposure level. Non-specific loss of MeI in the chamber was estimated to be less than 5% per hour. Additional non-specific loss to the body of a single deceased rabbit was estimated to be 9% over 4 hours. An effort to use some rabbits pre-treated with diethyl maleate (to retard metabolism of MeI) was unsuccessful due to death or distress of rabbits. This study was considered supplemental information to DPR.

Respiratory parameters were measured in New Zealand white rabbits (4 females/dose) exposed to MeI (0 or 18.5 ppm; 99.7% purity) for 6 hours while housed in a whole-body plethysmograph (DeLorme, 2004; DeLorme *et al*., 2009). Treated rabbits showed similar breathing frequency of 126.6 ± 12.3 breathes per minute as the control (130.6 ± 6.5 breathes per minute). The minute volume of 524.1±46.2 mL/min for the treated rabbits, compared to 403.9±74.4 mL/min for the control, was significantly ($p<0.05$) increased by 30%. The tidal volume for the treated rabbits was also significantly increased at 5.1±1.2 mL, compared to 3.6±1.3 mL for the control. Based on a 2 kg body weight (as stated by Sweeney *et al.,* 2009 for this study), on a per kg basis, they (1.8 or 2.6 mL/kg) are much lower than those (2.8 to 12.9 mL/kg) obtained by Thrall *et al*. (2004a). In addition, blood samples were collected for serum inorganic iodide and hemoglobin adduct analyses. There was increased S-methylcysteine concentration in hemoglobin of treated rabbits (89 ± 20 nmol/g globin, not statistically significant), compared to the control (70 ± 3 nmol/g globin). Rabbits exposed to MeI demonstrated over a 1000-fold increase in inorganic serum iodide levels (mean of 11800 ± 2040 ng/mL) compared to control (9 ± 3 ng/mL). This study was considered supplemental information to DPR.

Computational fluid dynamics simulation was used to predict the percentages of inhaled air expected to pass through dorsal and ventral regions of the nose, and to characterize inter-individual differences in flow patterns in rabbits (Corley *et al.*, 2004). Three untreated female New Zealand white rabbits were anesthetized for imaging of the head by Magnetic Resonance Imaging to reveal the three-dimensional structures of the nasal passages. The average percentages of airflow were 27.6% (dorsal respiratory), 19.84 (dorsal olfactory), 72.36 (ventral respiratory slice a), and 80.11% (ventral respiratory slice b). The report stated that the 20% for the ethmoid turbinate region was consistent with previous published estimates for the male F344 rat. This study was considered supplemental information to DPR. The published study reported values for 5, instead of 4, compartments resulting in significantly different values: 91.6% (dorsal respiratory), 47.4 (dorsal olfactory), 8.4 (ventral respiratory slice a), and 52.6% (ventral respiratory slice b) (Corley *et al*., 2009). The conclusion was that the 50% airflow to the ethmoid turbinate region was higher than those for the male F344 rat (19%) and human (7%).

III.J.2. Iodide and Fetotoxicity

This section describes studies on iodide disposition in rabbits, in addition to those already discussed under Section **III.G.2. Rabbit - Inhalation**, for PBPK modeling.

Timed-pregnant New Zealand white rabbits (21/dose) received ^{131}I-NaI by intravenous injection (ear vein, single bolus dose) at 0.75 and 10 mg/kg on GD 25 (Morris *et al*., 2004). Three rabbits per group were sacrificed at 0.5 to 24 hours post-dosing. The distribution of ^{131}I was quantified in several tissues from the does and fetuses. The amniotic fluid sample was a combined sample of 3 fetuses per litter. Whole blood was withdrawn from the fetal hearts of 3 litters (3 fetuses/litter) per group, except the 4-hour 10 mg/kg group which had only 2 fetuses in one of the 3 litters. The thyroid sample was a section of the trachea containing the thyroid (thyroid+trachea), which was too small to collect by itself. A trachea sample posterior to the thyroid was also collected as a reference. The iodide level in the thyroid+trachea sample represents that in the thyroid alone (Thrall *et al.*, 2009b).

In the maternal tissues, thyroid iodide levels increased with time and dose (Table 50). They were many-fold higher than those for the blood and plasma, which peaked after 1 hour of exposure and continued to decline over the 24 hours. The relative concentration of label in maternal thyroid compared to the other tissues in 10 mg/kg does increased over time to about 20-fold over other tissues by 24 hours. In the low-dose rabbits, the relative concentration in maternal thyroid by 24 hours was over 100-fold higher than any other maternal tissues evaluated. In does, the skin also had high ^{131}I-radioactivity content with the level diminished over time. In comparison, fetal stomach had the highest tissue iodide levels, with lower levels in other sites (thyroid+trachea, trachea only, blood, and amniotic fluid). For the blood, peak levels were measured about 4 hours after exposure, and were higher than that for the does. At 0.75 mg/kg, the combined thyroid and trachea iodide levels were higher than those for trachea alone. This effect was not evident for the 10 mg/kg/ group. The fetal/maternal blood ratios (F/M) showed an increase with time, indicating some concentration of iodide in the fetuses; this was particularly evident in the low dose group. This study was considered supplemental information to DPR. The published study (Thrall *et al*., 2009b) contained generally higher iodide values for both maternal and fetal values. The authors concluded that there was no evidence of preferential accumulation of radioiodide in fetal thyroid tissues because there were no consistent differences in radioactivity detected in thyroid+trachea and trachea alone samples.

Table 50. Radioiodide recovered from pregnant rabbits and fetuses given sodium iodide by intravenous injection.[a]

Hours post dose	Tissue Iodide Levels (µg/g)								F/M Blood ratio
	Maternal[b]			Fetal[c]					
	Thyroid	Blood	Plasma	Thyroid +trachea	Tra-chea	Blood	Stomach content	Amniotic fluid	
Pregnant rabbits at 0.75 mg/kg (2.82 mg to 3.10 mg total dose)									
0.5	0.93 ±0.39	0.09 ±0.02	0.10 ±0.02	1.28 ±0.46	0.62 ±0.62	0.20 ±0.08	0.83 ±0.17	0.04 ±0.02	2.22
1	1.34 ±0.39	0.13 ±0.04	0.14 ±0.05	2.15 ±1.08	1.68 ±1.09	0.35 ±0.11	1.76 ±0.63	0.12 ±0.04	2.69
2	2.34 ±0.29	0.09 ±0.05	0.17 ±0.09	2.23 ±0.94	1.77 ±1.72	0.37 ±0.12	4.38 ±1.48	0.39 ±0.13	4.11
4	4.45 ±2.41	0.14 ±0.09	0.14 ±0.08	3.84 ±2.50	1.73 ±1.36	0.37 ±0.13	6.90 ±5.70	0.59 ±0.19	2.64
6	3.52 ±1.07	0.07 ±0.02	0.08 ±0.02	2.75 ±1.24	1.77 ±1.38	0.40 ±0.14	4.93 ±1.34	0.73 ±0.23	5.71
12	5.80 ±2.57	0.06 ±0.02	0.07 ±0.02	2.93 ±1.56	1.83 ±1.45	0.25 ±0.08	8.55 ±6.19	0.87 ±0.28	4.17
24	13.73 ±12.60	0.05 ±0.01	0.05 ±0.02	2.47 ±0.41	2.04 ±2.61	0.29 ±0.07	8.51 ±5.32	0.84 ±0.36	5.80
Pregnant rabbits at 10 mg/kg (36.91 mg to 40.72 mg total dose)									
0.5	4.64 ±0.81	2.64 ±0.43	2.80 ±0.31	3.83 ±1.45	3.64 ±1.91	1.71 ±0.87	3.74 ±1.56	0.21 ±0.08	0.64
1	9.94 ±7.05	3.07 ±0.82	3.16 ±0.67	6.82 ±2.12	7.46 ±2.70	2.8 2±0.50	13.00 ±3.83	0.81 ±0.38	0.91
2	6.74 ±2.62	2.22 ±0.52	2.51 ±0.57	7.74 ±5.05	5.30 ±1.88	3.44 ±0.60	25.13 ±10.17	2.48 ±0.75	1.55
4	8.50 ±1.55	2.18 ±0.18	2.30 ±0.44	7.54 ±1.83	9.38 ±4.40	5.08 ±1.05	47.65 ±18.37	4.81 ±1.84	2.33
6	7.80 ±4.79	1.77 ±0.11	1.91 ±0.11	7.36 ±1.70	9.29 ±3.98	4.59 ±1.91	56.62 ±26.22	5.37 ±2.01	2.59
12	13.55 ±5.23	1.79 ±0.90	1.91 ±0.99	8.38 ±4.17	10.07 ±4.45	5.07 ±1.79	52.06 ±22.32	9.50 ±3.20	2.83
24	21.11 ±7.71	1.06 ±0.48	0.89 ±0.55	8.96 ±6.22	19.68 ±25.61	2.87 ±1.12	53.79 ±37.56	6.64 ±1.51	2.71

a/ Data from Morris *et al*. (2004). F/M blood ratio=fetal-to-maternal blood ratio.

b/ Mean of 3 rabbits.

c/ Mean of 9 fetuses from 3 litters (3 fetuses/litter), except the 4 hour 10 mg/kg group which had only 2 fetuses in one of the 3 litters.

d/ Since the fetal thyroid is so small, a section of the trachea containing the thyroid was sectioned. The iodide level represents that for the thyroid only.

In a study to determine the fetal and maternal iodide levels and their ratios in humans in PBPK modeling, Rayburn *et al.* (2007, 2008) collected maternal plasma and newborn umbilical cord plasma from live births after caesarean or vaginal delivery. The gestational age ranged from 29 weeks to 41 weeks, with <37 weeks of gestation defined as pre-term. Phase I was the main study. Phase II and III involved collection of amniotic fluid and placental tissue; these studies were stopped due to contamination of amniotic fluid with maternal blood, and difficulty in collecting placental tissues. This study was reviewed and approved by the University of New Mexico Human Research Review Committee. Only results for plasma samples are discussed.

The report provided only a single measurement per sample for iodide (reported as free iodide). The fetal-to-maternal ratios were calculated from values of matched pairs. Two values were excluded. Subject #95 (gestation 33 weeks) fetal iodide level at 460.7 μg/dL was considered too high, was possibly due to sample contamination since the maternal iodide was not elevated. Subject #97 (gestation 33 weeks) showed both high maternal (50.2 μg/dL) and fetal (20.6 μg/dL) levels, possibly due to a drug (unidentified) taken to treat fetal tachycardia.

For plasma iodide, there was no difference in the levels between mothers who gave birth to pre-term or term babies (Table 51). The overall average was 1.5±0.7 μg/dL for the total of 121 deliveries. The iodide in the cord plasma showed a mean value (1.6±0.7 μg/dL), similar to that for the maternal plasma. However, the iodide level for preterm cord plasma was significantly lower (1.4±0.5) than that for term cord plasma (1.7±0.7).

The average cord-to-maternal plasma iodide ratio for preterm was significantly lower (0.9±0.3) than that for all and term only deliveries (Table 51). But there was wide variability with an overlapping range of values: 0.35 to 2.11 for preterm and 0.35 to 5.4 for term deliveries.

Table 51. Iodide levels in human maternal plasma and newborn cord plasma and ratios.[a]

	n	Mean ±sd	Range
Iodide level (μg/dL)			
Maternal Plasma			
All deliveries	121	1.5±0.7	0.3 to 5.6
Pre-Term deliveries	29	1.6±0.4	0.4 to 3.4
Term deliveries	92	1.5±0.5	0.3 to 5.6
Cord Plasma			
All deliveries	121	1.6±0.7	0.3 to 4.5
Pre-Term deliveries	29	1.4±0.5**	0.3 to 2.5
Term deliveries	92	1.7±0.7	0.7 to 4.5
Cord-to-maternal plasma iodide ratios			
All deliveries	121	1.2±0.7	0.35 to 5.4 (n=12 for 2.0 to 5.4)
Pre-Term deliveries	29	0.9±0.4**	0.35 to 2.11
Term deliveries	92	1.3±0.8	0.35 to 5.4

a/ Data from Rayburn *et al*. (2007). ** indicates preterm values as significantly lower than term values.

III.J.3. Glutathione and MeI Toxicity

Metabolism of MeI via reaction with GSH was measured *in vitro* using headspace techniques. MeI and GSH (10 mM) were added to the headspace of sealed vials containing cytosol prepared from liver, kidneys, olfactory epithelium, and respiratory epithelium of pregnant New Zealand white rabbits (GD 25-26), liver and kidneys of pooled rabbit fetuses, liver and kidneys of male SD rats, and liver and kidneys of female human donors (Poet and Wu, 2004; Poet *et al.*, 2009). Samples were taken from the headspace at designed time points between 0 and 45 minutes, for the gas chromatographic analysis of MeI. Heat-inactivated controls were conducted concurrently. Metabolic rate constants were determined using a two-compartment model that described the uptake of MeI from the headspace into the media and the metabolism of MeI within the media (Table 52). The best-fit loss rate (first-order rate; hr^{-1}) was estimated from the slope of the line for the initial loss of MeI by optimization of the least-squares fit of the mathematical model to the concentration data. Maternal rabbit olfactory epithelium was the most efficient at metabolism of MeI (*i.e.*, high K_m and V_{max} values) under test conditions (in the presence of excess GSH). Fetal tissues, in contrast, were inefficient (liver) or apparently incapable of metabolism (kidney), as evidenced by low V_{max} values. Other values were intermediate, with liver consistently more active than kidneys. Human liver cytosol values were highly variable, and one liver sample had an extremely low V_{max} value. It was not clear whether this case represented quality control problems with the samples (which were purchased from an outside source), or whether this represented an individual who is a non-conjugator.

In addition, MeI (3.25 to 250 μM) and GSH (0-10 mM) were incubated with blood from male rats and female rabbits. No difference in the loss of MeI from the headspace was observed between active and heat-inactivated samples. The non-specific (heat-inactivated) loss was described to be greater in the blood than other tissues. The addition of diethyl maleate (750 μM for 15 minutes) to deplete GSH in rabbit blood did not have any effect on the MeI loss from the headspace. The authors concluded that MeI was not metabolized by direct GSH conjugation in the blood under the experimental conditions. The present study did not assess the availability of reduced GSH in the tissues. This study was considered supplemental information to DPR.

Table 52. Metabolic rate constants for MeI in tissues *in vitro*.[a]

Tissues	Human (female)	Rat	Pregnant Rabbit	Fetal Rabbit
Liver Km µM	78.3	25.3	46.7	5.19
Vmax nmol/min·mg	47. 1	40.0	10.0	0.411
Vmax/Km hr^{-1}	36.4	94.6	12.9	4.75
Kidney Km µM	12.9	13.4	73.8	NA
Vmax nmol/min·mg	11.8	15.0	4.38	NA
Vmax/Km hr^{-1}	55.0	67.5	3.56	NA
Olfactory Km µM	NA	NA	24,922	NA
Vmax nmol/min·mg	NA	NA	20,110	NA
Vmax/Km hr^{-1}	NA	NA	48.4	NA
Respiratory Km µM	NA	NA	2,669	NA
Vmax nmol/min·mg	NA	NA	214.1	NA
Vmax/Km hr^{-1}	NA	NA	4.81	NA

a/ Values presented are averages from Poet and Wu (2004). NA= not measured in these tissues. The numbers of samples were: 5 (human liver), 1 (human kidney), 8 (rat liver or kidney), 4 (all pregnant rabbit and fetal rabbit tissues). For simplicity, standard deviations are not indicated in this table.

The relationship between metabolism and MeI toxicity in the nasal cavity was also studied *in vitro* using the headspace technique with vials containing MeI, GSH, and liver and nasal (olfactory and respiratory epithelium) tissues from Wistar rats (Chamberlain *et al*., 1998b). Glutathione depletion was more prominent in the cytosolic fraction compared to the microsomal fraction of the three tissue preparations. With the cytosol, the liver had the highest GSH-S-transferase activity with GSH depletion rate of about 60 nmol/min/mg protein (estimated from Figure 3 from report) with slower rates in the olfactory (40% of liver rate) and respiratory (7% of liver rate) epithelium. The GSH depletion in the liver microsomal fraction was about 1/10 of the cytosol. The authors suggested that this activity was due to cytosolic contamination of the microsomal fraction since no activity was detected in the olfactory or respiratory epithelial microsomes. The non-enzymatic conjugation rate was estimated at 5 nmol/min when no tissue preparation was added. S-methyl-GSH was identified as the conjugation product with 1:1 stoichiometry for substrate used and metabolite formation for both liver and olfactory cytosols. Affinity chromatography with various substrates showed that the theta class of GSH-S-transferase catalyzed the conjugation of MeI with GSH. Methyl iodide was not metabolized by a cytochrome P450-dependent pathway because formation of formaldehyde was not detected in microsomal incubations. Covalent binding studies with ethmoturbinates (mainly olfactory epithelium) and naso- and maxilloturbinates (respiratory and transitional epithelium) showed time- and concentration- dependent binding of MeI to these tissues. After 3 hours of incubation, the extent of covalent binding was similar for olfactory turbinates (2.73±0.62 nmol/mg protein) and respiratory turbinates (3.68±0.47 nmol/mg protein). Thus, the extent of covalent binding was not a factor in the selective toxicity between olfactory epithelium and respiratory epithelium.

The metabolism and MOA for MeI-induced neurotoxicity were studied *in vitro* using fetal and young mouse neuronal cell cultures containing mixed neuronal and glial cells (Bonnefoi *et al*., 1991). Results with cerebrocortical cells showed that MeI depleted GSH in these cultures. This depletion was related to cell death caused by oxidative stress because pretreatment with the antioxidants, BW 755C and NDGA[16], resulted in a 20-fold increase in the LD50 of MeI. Since GSH depletion occurred (maximal after 2 hours exposure to MeI) before lactate dehydrogenase release (16 hours after exposure), the depletion was considered as the starting point for eventual cell death. Methyl iodide also caused an increase in formaldehyde production. However, formaldehyde, as a GSH-mediated metabolite, was apparently not involved in cell death because sulfasalazine, a GSH-s-transferase inhibitor, did not protect the cells against toxicity.

Further studies by Bonnefoi (1992) with mouse fetal cerebrocortical cell cultures examined the mitochondrial GSH pool and functions in MeI toxicity. Methyl iodide was a more effective depleter of cytosolic GSH than mitochondrial GSH; the ED_{50s} were 0.02 mM and 1 mM, respectively. However, the depletion of the cytosolic GSH did not consistently lead to cytotoxicity, while neural cell death occurred whenever mitochondrial GSH was depleted by more than 50% after MeI treatment. Pretreatment of cells with antioxidants, BW 755C and DPPD[17], and the GSH precursor, N-acetylcysteine, reduced the cytotoxicity and GSH depletion in both compartments by MeI. For these effects, the antioxidants were more effective than N-acetylcysteine as they completely blocked the mitochondrial GSH depletion by MeI. Methyl iodide also decreased mitochondrial metabolism, as measured by mitochondrial dehydrogenase reduction of 3-[4,5-dimethylthazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) to formazan. This effect was only partially inhibited by both BW 755C and DPPD under conditions, which had effectively blocked GSH depletion by MeI. This result suggested that MeI might have a direct effect on mitochondrial proteins causing a change in GSH gradient, and not a direct reaction with GSH in the mitochondrial matrix.

Davenport *et al.*, (1992) used mixed neural cultures from mouse embryo cerebral cortex and the cerebellum to show that MeI caused morphological alterations and lactate dehydrogenase leakage. The mechanism was elucidated with inhibitors. The lack of effect by a glutamate antagonist showed that glutamate was not involved in MeI-induced effect. Inhibitors of arachidonic acid metabolism (sodium salicylate, lysine acetyl salicylate, and dexamethasone phosphate) also did not have any protective effects. On the other hand, BW 755C, and NDGA protected the cells against MeI toxicity; this was related to their antioxidant effect.

Instead of mixed cell cultures, Chamberlain *et al.* (1999) investigated the role of GSH in MeI-induced neurotoxicity using rat (8-day old) cerebellar granule cell primary cultures. Methyl iodide extensively depleted GSH and was cytotoxic, but these effects were inhibited by the antioxidants, vitamin E, butylated hydroxytoluene (BHT), and desferrioxamine mesylate (DF). The role of GSH level in cytotoxicity was confirmed when GSH depletion with 1-buthionine sulphoximine (BSO) resulted in enhanced cytotoxicity, while isopropyl ester of GSH (IP-GSH) provided protection. These results are consistent with those by Chamberlain *et al.* (1998a), who noted that GSH depletion was transient and was an early indicator of toxic effects. Since there was little evidence for lipid peroxidation or oxidation of GSH to GSSG by halomethanes from

[16] BW 755C=3-amino-1-[m-(trifluoromethyl)phenyl]-2-pyrazoline and NDGA=nordihydroguaiaretic acid.
[17] DPPD=N,N'-diphenyl-p-phenylenediamine

other studies, the investigators hypothesized that the antioxidants acted to trap MeI, and that cytotoxicity was not caused by oxidative stress. Glutathione was involved in detoxification of MeI.

The potential for MeI-induced GSH depletion in the reproductive tract was studied in male rats given MeI (100 mg/kg) by the oral route (Gandy *et al*., 1990). Liver, testes, and epididymides GSH levels were measured at 1 to 16 hours after dosing. The GSH levels were reduced only at the 1-hour time point. MeI caused significant rapid reduction of GSH in the liver (92% reduction), epididymides (63%), and testes (36%). By 16 hours, the liver and testes GSH increased to control level. The epididymides GSH was also recovered but was only to 64% of control level.

III.J.4. Other Studies

A comparison of exposure routes on adduct formation was conducted with F344 rats (5/group/sex) exposed to ^{14}C-MeI by gavage (9 µmoles/animal) or whole-body inhalation (45 µmoles/animal) (Xu *et al*., 1990). The animals were sacrificed either 6 hours after oral dosing, or immediately after the 24-hours of inhalation exposure. Hemoglobin adducts were detected at similar levels for both genders. Higher level (about 4 times) of adducts were found for the inhalation route than the oral route. The authors hypothesized that the lower adduct levels in the orally treated rats might be due to detoxification in the liver. The report did not provide sufficient information to calculate the dose for this study.

The effects of MeI on deiodinase activity[18] (D1, D2, and D3) were examined in rats and rabbits using *in vitro* and *in vivo* assays (Farwell, 2004; Farwell and Leonard, 2009). The experimental design and results are summarized in Table 53. Some of the tissues used were from other studies (Himmelstein, 2004; Sloter, 2005b). These assays showed that MeI inactivated D1 under some experimental conditions. *In vitro* rat liver and kidney microsomal D1 activities were reduced (50%) at 50 to 100 mM MeI; no effects were detected at lower doses of 100 nM to 10 mM. Both tissues yielded non-linear Dixon plots, indicative of non-competitive inhibition, probably enzyme inactivation. A second study, in which microsomal-MeI incubation was diluted 10-fold first prior to assay, showed much lower D1 activity (about 10% of control) with reason unknown.

In vivo assay of tissues from rats exposed to 25 or 100 ppm MeI (Himmelstein, 2004) showed measurable dose-related inhibition of D1 in kidney and liver homogenates for both dose levels. Kidney D1 activity of pregnant rabbits exposed at 20 ppm (the only treated group; Sloter, 2005b) decreased by about 65% compared to controls. Livers from the same treated does, or those (kidneys and livers) from fetuses, showed no treatment related response.
For D2 *in vitro* assay, the astrocyte cultures from neonatal rat brain were incubated with MeI at 100 nM to 100 mM. D2 activity was inhibited at >100 µM, with 50% and 30% of control activity at 1 mM and 10 mM, respectively. However, the inhibition might be due to cytotoxicity

[18] Deiodinases remove iodine moieties from thyroid hormones, T3 and T4. Type I 5'-deiodinase (D1) removes iodine from the outer ring, and is found in the liver, kidney, thyroid, and brain. Type II 5'deiodinase (D2) also removes iodine from the outer ring, and is found in the brain, pituitary, and rodent brown adipose tissue. Type III 5'-deiodinase (D3) removes iodine from the inner ring, and is found in the placenta and brain. Its function results in the inactivation of T4 and T3 to rT3, and 3,3'-diiodothyronine, respectively. In fetal development, D3 is considered essential in protecting the embryo from excess thyroid hormone.

since 1 mM and possibly even 0.1 mM were cytotoxic under these conditions, based on dye exclusion properties. D2 activity for astrocyte lysates was also inhibited by MeI, at about 5 mM and above. Dixon plot and dilution-recovery studies (similar to D1 tested) were also consistent with enzyme inactivation. Brain homogenates from rats exposed to MeI (Himmelstein, 2004) showed inhibition of D2 activity. At 25 ppm and 100 ppm, there were about 35% and 45-55% reduction, respectively. Brain D2 activities were unchanged in the 20 ppm MeI treated rabbit does or fetuses.

D3 activity in the homogenates of brain from rats (Himmelstein, 2004) and placenta from rabbits (Sloter, 2005b) was not altered by exposure to MeI or NaI.

These results indicated that it was unlikely that deiodinase inhibition was a factor in rabbit developmental toxicity studies. This study was considered a supplementary study. These interpretations should consider the limitations of these studies: no individual data provided in the report, limited doses and exposure duration studied, and different experimental designs between the rat and rabbit *in vivo* studies.

The role of deiodinase inhibition with respect to thyroid tumor formation by MeI is unclear since the thyroid was not examined. Inhibition of 5'-deiodinase can block the conversion of T4 to T3, resulting in thyroid tumors from increased serum TSH stimulation via the thyroid-pituitary axis feedback mechanism responding to the decrease in T3 level.

Table 53. Effects of MeI and NaI on deiodinase activity.[a]

Assays	Tissue Sources	Results			
D1					
in vitro	**Rat**: Adult liver and kidney microsomes	Loss of D1 activity at 50 –100 mM MeI due to enzyme inactivation rather than inhibition.			
in vivo	**Rat**: Liver and kidney homogenate from males exposed to MeI[b]		% Control		
			0	25 ppm	100 ppm
		D1, liver	100%	83.1±3.6*	62.1±7.1*
		D1, kidney	100%	87.0±18.8	59.0±14.3*
	Rabbit: Liver and kidney from pregnant does and fetus exposed to MeI or NaI[c]	Adult or fetal liver- no effect by MeI or NaI Adult kidney-65% decrease by MeI, but not NaI Fetal kidney-No effect by MeI or NaI			
D2					
in vitro	**Rat**: Neonatal rat brains	Astrocyte culture with MeI 1 mM: 50% decrease 10 mM: 70% decrease >1 mM: cytotoxicity Astrocyte lysate with MeI 5 mM: 50% decrease			
in vivo	**Rat**: Brain homogenate from males exposed to MeI[b]		% Control		
			0	25 ppm	100 ppm
		D2, brain	100	64.3±7.6*	44.1±13.0*
	Rabbit: Brain from pregnant does and fetus exposed to MeI or NaI[c]	No effect of NaI or MeI on adult or fetal brain D2			
D3					
in vivo	**Rat**: Brain homogenate from males exposed to MeI[b]	No effect by MeI			
	Rabbit: Placenta from pregnant does[c]	No effect by NaI or MeI			

a/ Data from Farwell (2004).
b/ Tissues were from rats exposed to 25 ppm and 100 ppm MeI in the 2-day inhalation study (Himmelstein, 2004).
c/ Tissues were from rabbits exposed to 20 ppm MeI during GD 23-26 (Sloter, 2005b).

III.K. MeI as an Alkylation Agent

MeI is a common reagent in alkylation reactions and undergoes nucleophilic substitution reaction (S_N2). It has the lowest bond strength compared to other haloalkanes[19]; and would be expected to cause a faster reaction. The alkylation potential of MeI has enhanced capability for covalent bond breakage and binding with macromolecules (**Volume IV Part 1-A**). Reed *et al.* (1995) attributed this property toward MeI being more toxic than methyl bromide for nasal toxicity. In methyl bromide (200 ppm for 6 hours) treated rats, as the positive control, showed similar damage to the olfactory epithelium as the 100-ppm (6 hours) MeI rats. If the carbon and iodide bond can readily be broken in the body, the question is how much free MeI is available for interaction with DNA and other target macromolecules to cause the toxicity reported. As shown in Figure 1, ^{14}C radioactivity found in the tissues in the pharmacokinetic studies may be from the methyl group or the one-carbon pool. At the initial inhalation exposure, higher levels of free MeI would be expected in the circulation. With time, the free MeI level is reduced as MeI metabolizes with the formation of metabolites and methylated adducts. Thus, measured tissue ^{14}C radioactivity after 5.5 hours of exposure in the MeI pharmacokinetic studies conducted with rats (Sved, 2002 and 2003, described under **III.A. Pharmacokinetics**) would likely be methylated products, instead of free MeI. The detection of S-methylcysteine adducts in the blood of rats (Table 9; Himmelstein, 2004) and maternal and fetal rabbits (Table 38; Sloter, 2005a; Table 46; Sloter, 2005b) after MeI inhalation exposure support this possibility.

In addition to alkylation, MeI-induced toxicity likely involves other reactions. For example, these include GSH depletion, oxidative stress, and iodide induced thyroid perturbation. The role of alkylation, and these other reactions in MeI-induced fetal death and thyroid tumor formation, is discussed in the Hazard Identification section (**IV.A**.).

[19] The bond strengths are: C-H (413 kJ/mol), C-F (467 kJ/mol), C-Cl (346 kJ/mol), C-Br (290 kJ/mol), and C-I (228 kJ/mol).

IV. RISK ASSESSMENT

IV.A. Hazard Identification

Hazard identification of MeI is based on the laboratory animal studies and, to the extent possible, human reports. In using laboratory animal data, the assumption is that effects observed will also be observed in humans. This section discusses the relevant toxicity endpoints and the applicable NOELs to characterize the risks of human inhalation exposure to MeI for each duration. The NOELs and effects within each exposure duration are then compared (in terms of mg/kg/day, see calculations in **Appendix B** of **Volume I**) to identify the most appropriate NOEL (critical NOEL) and toxicity endpoint of concern (critical endpoint) for that exposure duration.

IV.A.1. Human Equivalent Concentration Determination

The point of departure (POD) to characterize the toxicity is either the critical NOEL or a benchmark dose, depending on whether the data can be adequately described by the available models. The NOELs and benchmark doses for selected endpoints are in the study summaries (**III.**). Since these values are derived from experimental animal studies, it is converted to a human dose term, human equivalent concentration (HEC).

IV.A.1.a. Use of PBPK Model

In the case of MeI acute exposure, Arysta developed a PBPK model for deriving HECs from critical acute PODs to account for the interspecies pharmacokinetic differences. Chemical-specific data were generated in several pharmacokinetic studies. The model was reviewed and accepted by USEPA and used in their MeI risk assessment (USEPA, 2007). Both the pharmacokinetic data and the model were subsequently published in a designated volume of a peer-review journal (Inhalation Toxicology May 2009).

DPR scientists reviewed the model and agreed with USEPA that it has sufficient merits over the default non-chemical-specific uncertainty factor approach for estimating a single day HECs (DPR August 2009 draft, DPR response to Arysta comments in mei_vol4_arysta.pdf). However, DPR scientists disagreed with some key input parameters used by Arysta and USEPA. A separate set of HECs was established through modifying the input parameters and the choice for HEC dose metrics to reflect our understanding of model applications based on biological and toxicological considerations. An extensive review of the model and its use in deriving DPR HECs were presented in **Appendix A** of **Volume I**. The impact of modification of key parameters was also included. For fetal death endpoint, multiple HECs based on other dose metrics were provided for illustration purposes. The detailed MOA discussion previously included under Hazard Identification in this Volume is now in **Appendix A** for a cohesive presentation of the PBPK model review. Only a summary discussion is provided in this document to illustrate MeI toxicity. It was noted that there was insufficient support for a single MOA of each of these endpoints. Thus, emphasis was made that DPR scientists' use of model and choice of dose metrics were not strictly tied to a specific MOA but focused on markers that reflected the level of exposure (*i.e.*, maternal exposure for fetal death, MeI in brain for neurotoxicity) or the anticipated effects (*i.e.*, threshold GSH depletion in nasal olfactory tissue) and for which some experimental data were available for model output comparisons. DPR

scientists also used the model to account for the additional 16 hours of exposure by workers beyond their 8 hour exposure under occupational settings.

In a subsequent review, the SRC rejected to the use of the PBPK model in favor of the traditional non-chemical-specific default uncertainty factor approach (**Volume IV Part 1-A** and **-B**). The SRC was concerned about model limitations and uncertainties, although detail considerations were not explicitly stated. In one SRC comment regarding the PBPK model application, the panel was unsure about what dose metric was appropriate for the fetal death endpoint but indicated that the MeI parent chemical in maternal or fetal blood was a plausible choice. DPR scientists do not disagree with this general speculation. However, DPR scientists disagree with the use of this dose metric in the context of the current model because it carries substantial model uncertainty for being short-lived (rapidly transformed to iodide) and the lack of data for its direct measurement in the PBPK supporting studies for any model calibration or validation. Instead, DPR scientists opt for the maternal iodide level that was quantified in multiple studies for model output comparison. The SRC agreed with DPR scientists' view that maternal iodide dose metric may reasonably capture the maternal exposure to MeI. DPR scientists' choice of maternal, not fetal, dose metric is because maternal exposure is the very basis for the modeled POD. Details for these and related considerations are presented in **Appendix A** of **Volume I**. Moreover, both the modelers (Sweeney *et al.*, 1009) and DPR scientists' review concluded that there was greater confidence in the maternal than fetal serum iodide dose metric. Nevertheless, the SRC opinion was that the MeI parent chemical profile would be appropriate based on the plausibility of MeI-mediated MOA. The SRC further opined that either experimental studies could be conducted to estimate blood time courses of MeI or that capability exists for calibrating the model to support its use for modeling the HEC.

Due to the aforementioned differences between DPR scientists and the SRC, the model derived HECs in the previous documents are replaced in this revised risk assessment with the default approach with the application of non-chemical specific uncertainty factors. The subsequent discussion demonstrated that the outcome of PBPK modeling based on DPR's choice of dose metric is very close to DPR's current default approach. The DPR default approach had been used for subchronic and chronic endpoints as presented in the August 2008 draft risk assessment. For ease of comparison to USEPA's HECs, DPR's critical NOEL or LED for subchronic, chronic, and lifetime toxicity are also expressed as HECs with interspecies pharmacokinetic difference accounted for by the use of a default PK_{animal} factor of $10^{0.5}$ (see calculations in **Appendix B** of **Volume I**). These calculations do not include the 16-hour non-working hour exposure to MeI that was addressed in the HECs derived from the PBPK model.

IV.A.1.b. Alternatives to PBPK Model and UF Application

An alternative to the PBPK approach was also recommended by the SRC for animal-to-human dose extrapolation based on body weight (BWt) to the 3/4 power while still retaining the full interspecies 10-fold UF (**Volume IV Part 1-A**). Presumably the $BWt^{3/4}$ basis could be an attempt to adjust for interspecies PK differences, however, the retention of a full 10-fold UF would indicate otherwise. If the basis for retaining the 10-fold UF is because the $BWt^{3/4}$ basis might not fully account for the interspecies PK differences, DPR scientists would encourage and have supported the use of PBPK model to fully account for the interspecies PK factors, many of which (*e.g.*, metabolic and physiological parameters) are commonly expressed on a $BWt^{3/4}$ basis. Alternatively, without the PBPK tool, DPR's default approach is to account for interspecies

intake rate based on the breathing rate (BR; tidal volume times breathing frequency). Although the BR is also generally proportional to $BWt^{3/4}$, our rationale for retaining a full 10-fold interspecies UF is because the BR only reflects the different rate of chemical intake across the exposure barrier, not the entire interspecies PK considerations.

The impact of the above conceptual framework in risk assessment can be numerically illustrated below. When the dose is expressed on a per BWt basis, the interspecies extrapolation factor for a $BWt^{3/4}$ basis is $(BWt_{animal}/BWt_{human})^{1/4}$. DPR's intake rate adjustment factor for exposure is (BR_{animal}/BR_{human}).

- Rabbit fetal death endpoint. Since the endpoint is pertinent to females of child-bearing age, the illustration starts with the reference BWt_{rabbit} of 4 kg and $BWt_{h\text{-}adult}$ of 70 kg, and the DPR default BR_{rabbit} of 0.54 m^3/kg/day and $BR_{h\text{-}adult}$ of 0.28 m^3/kg/day. Accordingly, the rabbit-to-human dose extrapolation factor is 0.49 $[=(4/70)^{1/4}]$ for the $BWt^{3/4}$ approach and 1.93 [=0.54/0.28] for DPR's intake rate adjustment. The total interspecies adjustment factor (TIAF) would be 0.16 [=0.49/3] by applying a 3-fold UF for PD in the $BWt^{3/4}$ approach and 0.19 [=1.93/10] by applying a 10-fold UF in the DPR approach.

- Rat nasal and neurotoxicity endpoints. Since these effects are pertinent to humans of all ages, the illustration starts with the reference BWt_{rat} of 0.35 kg and $BWt_{h\text{-}child}$ of 10 kg, and the DPR default BR_{rat} of 0.96 m^3/kg/day and $BR_{h\text{-}child}$ of 0.59 m^3/kg/day. Accordingly, the rat-to-human dose extrapolation factor is 0.43 $[=(0.35/10)^{1/4}]$ for the $BWt^{3/4}$ approach and 1.63 [=0.96/0.59] for intake rate adjustment. The total TIAF would be 0.14 [=0.43/3] by applying a 3-fold UF for PD in the $BWt^{3/4}$ approach and 0.16 [=1.63/10] by applying a 10-fold UF in the DPR approach.

The above illustrations show that the $BWt^{3/4}$ dose extrapolation and DPR's default intake rate adjustment would have resulted in similar TIAFs if the former is indeed to account for the PK factors. However, the SRC's recommendation of retaining the entire 10-fold interspecies UF after dose extrapolation based on $BWt^{3/4}$ would be approximately 3-fold lower (*i.e.*, TIAF of 0.49/10 = 0.05), tending toward more conservative or higher risk estimates at a given exposure level. Because of the significant impact of applying the entire interspecies 10-fold UF to a dose that has already been adjusted based on $BWt^{3/4}$, DPR is unable to implement this recommendation without a clear rationale.

In the previously mentioned comment regarding the choice of dose metric in the PBPK modeling for the fetal death HEC, the SRC speculated that the MeI parent chemical is a plausible dose metric (**Volume IV Part 1-A**). This is to replace maternal serum iodide dose metric chosen by DPR scientists. It is noted that compared to the $BWt^{3/4}$ basis recommendation presented above, this comment would result in an opposite direction, *i.e.*, tending toward a less conservative outcome or lower risk estimate at a given exposure level. The above numeric illustrations can be further extended here to demonstrate the impact of this SRC recommendation. The comparison for the TIAF starts with the model estimated HECs based on a 6 hour exposure at 2 ppm in rabbits but with different dose metrics as presented in **Appendix A** of **Volume I.**

- MeI dose metric recommended by the SRC. As presented in Table A-4, the model estimated 24-hour HECs were 0.73 ppm and 1.0 ppm based on maternal and fetal MeI

AUC, respectively. Compared to the POD of 2 ppm for 6 hr modeled for rabbit, the rabbit-to-human dose difference is 1.5-fold [=(2 x 6/24)/0.73] based on maternal MeI AUC, and 2-fold [=(2 x 6/24)/1.0] based on fetal MeI AUC. Applying DPR's UF of 3 for PD adjustment results in a TIAF 0.5 based on maternal serum MeI AUC and 0.7 based on fetal serum MeI AUC.

- Maternal iodide dose metric chosen by DPR. Using DPR's chosen dose metric, the model estimated 24-hr HEC was 0.24 ppm (Table A-4). Compared to the POD of 2 ppm for 6 hr in rabbits, the rabbit-to-human dose difference is 0.48-fold [=(2 x 6/24)/0.24]. Applying DPR's UF of 3 for PD adjustment results in a TIAF of 0.16.

Accordingly, the final TIAFs based on the SRC suggested dose metric are at least 3-fold higher (or "less conservative") than the DPR's default approach and nearly 10-fold less conservative than the SRC's recommendations for adjustment based on $BWt^{3/4}$ and retaining a 10-fold UF.

It is also noted in the above illustration of DPR's choice dose metric that the TIAF is only slightly lower (or "conservative") than from DPR's default approach (*i.e.*, 0.16 versus 0.19). These outcomes lend some mutual support for both DPR's default approach and the use of PBPK model.

In conclusion, these illustrations demonstrated support for DPR's use of PBPK model. They also show some support for the dose adjustment based on $BWt^{3/4}$ if it presumes to adjust for interspecies PK differences and thus applying only an additional 3-fold UF for interspecies PD adjustment. Finally, these analyses demonstrate that at a given POD for fetal death endpoint, the most sensitive endpoint of MeI, the HEC derived from either DPR default approach or DPR's chosen PBPK application is at the mid point between the two outcomes from the two independent SRC recommendations.

IV.A.2. Acute Inhalation Toxicity

For acute inhalation exposure, toxicity observed after short-term exposure and developmental effects are considered. The critical endpoints are: fetal death in rabbits, olfactory epithelial degeneration in rats, and neurotoxicity in rats (Table 54). The fetal death endpoint is applicable in the risk assessment of women of child-bearing age since it was a result of maternal exposure to MeI. The other endpoints are applicable for the general population exposure.

Table 54. The acute toxicity of MeI.[a]

Studies	ppm (air)		mg/kg/ day	Effects	References
	NOEL	LOEL	NOEL		
Inhalation Studies					
Rat 6 hours/day	27	93	37	↓ Body temperature and motor activity	*Schaefer, 2002[b]
Rat 4 weeks 6 hours/day	21	70	28	Olfactory epithelium degeneration	*Kirkpatrick, 2002b[c]
Rat 6 hours/day x 2 days	<25	25	<67	Nasal GSH depletion; ↑TSH, T3 and T4	Himmelstein, 2004[b]
Rat 6 hours/day GD 6-19	60	>60	81	↓ Maternal weight No developmental toxicity	*Nemec, 2002c[d]
Rabbit 6 hours/day GD 6-28	2	10	1.5	↑ Late resorption, ↓ viable fetuses, ↓ fetal weight	*Nemec, 2002d[d]
Rabbit 6 hours/day GD 23-26	<20	20	<15	↑ Late resorption, ↓ viable fetuses	Nemec, 2003[d]
Rabbit 6 hours/day GD 23-24, or 23-26	<25	25	<19	↑ Late resorption, thyroid effects	Sloter, 2005a[d]
Rabbit 6 hours/day GD 23-26	<20	20	<15	↑ Late resorption, ↓ viable fetuses, thyroid effects	Sloter, 2005b[d]
Oral Studies					
Rat gavage 1 dose	NA	NA	<50	Mortality, clinical signs	*Bonnette, 2001a[b]
Rat gavage, 1 dose	NA	NA	<100	Mortality, clinical signs	Harriman, 2003a[b]
Mouse gavage 1 dose	NA	NA	100	Clinical signs	*Bonnette, 2001b[b]

a/ * indicates the studies were acceptable to DPR according to FIFRA guidelines. Unless specified, the inhalation studies were conducted by whole-body exposure. NA=not applicable.

b/ Studies described in **III.B. Acute Toxicity**.

c/ Study described in **III.C. Subchronic Toxicity**.

d/ Studies described in **III.G. Developmental Toxicity**.

IV.A.2.a. Fetal Death

IV.A.2.a.(1) Critical NOEL and Endpoints

The critical NOEL for acute MeI toxicity established by DPR is 2 ppm based on increased rabbit fetal death (late resorption and dead fetuses) and reduced fetal body weight of females during late gestation period at the LOEL of 10 ppm (Table 34a; Nemec, 2002d). This NOEL of 2 ppm is consistent with that determined by the study investigator as the NOAEL for prenatal developmental toxicity. It was affirmed as the no adverse effect level in the published version of the study (Nemec *et al*., 2009).

Fetal death in rabbits as a consequence of MeI exposure was also reported in a subsequent single-dose study (20 ppm) by Nemec (2003). The most prominent fetal effect of MeI was from exposures during GD 23 to GD 26, the window of vulnerability, with fetal death observed from 2 days of exposure at GD 23-24 or GD 25-26 (Table 35 and 55). Fetal death within this short duration is also important to determine whether the PBPK dose metric for the HEC should be based on single or multiple days of repeated exposure (more discussion in **Appendix A** of **Volume I**). For ease of discussion, the data for this endpoint from both Nemec studies are summarized in Table 55.

Table 55: Rabbit fetal late resorption and death data from MeI treatment.[a]

MeI		Viable fetus	Late Resorption		
ppm	GD		% Fetus/Litter[b]	Litter Affected[b]	Fetus Affected[c]
Study: Nemec 2002d (n=19-22)					
0	NA	6.1±2.6	1.8 ± 6.4	2/22* (9%)	3/143* (2%)
2	6-28	5.5±2.6	3.3 ± 10.9	2/19 (11%)	6/115 (5%)
10	6-28	4.6±2.6	11.1 ± 21.2	6/20 (30%)	18/109** (17%)
20	6-28	3.6±2.2**	22.5 ± 27.2**	11/20** (55%)	34/110** (31%)
Study: Nemec 2003 (n=17-21)					
0	6-28	-	1.1 ± 3.2	2/18 (11%)	2/129 (2%)
20	6-28	-	18.3 ± 24.9**	10/19** (53%)	25/114** (22%)
20	6-14	-	1.1 ± 3.5	2/23 (9%)	2/121 (2%)
20	15-22	-	0.0 ± 0.0	0/20 (0%)	0/131 (0%)
20	23-24	-	6.3 ±11.3	5/17 (29%)	11/119** (9%)
20	25-26	-	9.6 ±21.3	6/21 (29%)	16/143** (11%)
20	27-28	-	0.0 ± 0.0	0/20 (0%)	0/131 (0%)

a/ The estimated dose at 2, 10, and 20 ppm MeI was 1.5, 8, and 15 mg/kg/day MeI. In both studies, fetal observations were made on GD 29. *, ** for statistical significance at $p<0.05$ and <0.01, respectively. Viable fetus = number of viable fetus per litter. % Dead fetus/Litter = average percent of "late resorption" per litter. Litter Affected = number of litter with fetal death/total litter. Fetus Affected = total number of dead fetus/total fetus.

b/ Litters with 100% early resorption were excluded.

c/ Per total fetus at risk (minus early resorption).

One clarification should be made about "late resorption" as an endpoint. This term was used in the submitted toxicity and pharmacokinetic studies of MeI in rabbits. One companion observation in these reports was "dead fetus." As noted in Table 55, one fetus per 10 and 20 ppm dose groups in the Nemec study (2002d) was found dead at sacrifice on GD 29. No dead fetus was found in the subsequent study by Nemec (2003). In this document, fetuses from late resorption are generally referred to as "dead," and the endpoint is collectively referred to as fetal death. When appropriate, "late resorption" is used for cross reference to data presented in Section **III. TOXICOLOGY PROFILE** and in contrast to the post-natal death described in the published literature. Regarding the specific use of rabbit fetal death as an endpoint for human health risk assessment, the default approach of using the critical endpoint from the most sensitive laboratory species is valid since there is no evidence that rabbit is inappropriate as a toxicity model for humans.

Rabbits appear to be more sensitive to MeI induced fetal death than rats within the study protocols, since no excess fetal death was reported in the rat teratology study at as high as 60 ppm (Nemec, 2002c). However, two observations are noted. First, the LOELs for body weight reduction appeared comparable. In the 2-generation rat reproductive toxicity study, the LOEL for 20% body weight reduction in rat pups was 50 ppm (68 mg/kg/day; Table 33; Nemec, 2002a and b). A lower reduction of 12% was reported for rabbit fetal body weight at a LOEL of 10 ppm (8 mg/kg/day) (Nemec, 2002d). Second, the reported MeI endpoints from rat and rabbit studies are only gross observations. The potential for more subtle developmental effects (*e.g.*, neurodevelopmental) in the surviving offspring was not investigated in any toxicity study of MeI, which is shown to markedly affect maternal thyroid functions in both species. In addition, no information on rat fetal thyroid functions or maternal or fetal serum iodide levels associated with MeI exposure is available for interspecies comparison to rabbits. Thus, a complete understanding of species specific sensitivity to developmental toxicity of MeI is not possible.

The acute critical NOEL established by USEPA is 10 ppm, also based on the Nemec study (2002d), 5-fold higher than that by the DPR scientists and the study investigator. The USEPA basis was a lack of statistical significance of fetal death at 10 ppm when data are expressed as percentage of fetal resorption per litter (*i.e.*, group average of 11.1% versus 1.8% in the controls, Table 55). However, DPR scientists' view is that toxicity determination should not rely solely on statistical indications without considering the magnitude of response. The magnitude of greater than 6-fold increase is important, especially when the variability is high for the index. In this case, the large variability is partly due to the varying number of implantation sites per litter, ranging from 1 to 11 for the control and treated groups (Table 34b). It is noteworthy that the increase in late resorption at 10 and 20 ppm is higher than the maximum mean value[20] in the historical control data from the conducting laboratory (Nemec, 2002d; WIL Research Laboratories, 2006). There is also a greater than 3-fold increase in the number of litters with late resorption and dead fetuses at 10 ppm (6/20 versus 2/22 in the controls). The trend of increase is significant ($p<0.05$) over the dose range of the study (Table 55). Furthermore, the ratio of total dead fetuses to the total number of fetuses per treatment group at 10 ppm was 8-fold higher than the controls (17% versus 2% in the controls), and was statistically significant ($p<0.01$). Based on the nested logistic model (USEPA Benchmark Dose software BMDS 2.0),

[20] The average historical data for late resorption per litter from 36 studies by the conducting laboratory (WIL lab) during 1999-2004 is 1.1±1.0%, with the range of 0 to 3.7% (WIL Research Laboratories, 2006).

the extra risk response at 10 ppm is 18 – 20%, a level that cannot be accepted as equivalent to a NOEL.

IV.A.2.a.(2) Mode of Action

DPR scientists explore four respective possible MOAs: fetal thyroid perturbation from excess iodide, GSH depletion, direct alkylation, and altered cholesterol homeostasis (see detailed discussion in **Appendix A** of **Volume I**). No single predominant MOA or its associated key events(s) leading to fetal death can be determined. The delineation of a MOA for fetal death is compromised by the fact that all fetal data are from those that survived the MeI treatment, assuming that they are representative of those that died. The lack of concordance between fetal thyroid status and fetal death after 2 and 4 days of MeI exposure raises doubt about the extent of fetal thyroid status immediate involvement (*e.g.*, 2 exposures within 30 hours) in the MOA for fetal death. In a broader sense, maternal thyroid status appears to correspond better to fetal death, and thus maternal dose metric (MeI or iodide) may be more appropriate than fetal dose metrics. However, no MeI measurements for maternal or fetal tissues are available. The lack of concordance between fetal death from MeI and NaI or KI exposures on equal iodide basis suggests that a different MOA than excess fetal iodide alone is likely involved within the narrow (GD 23-26) window of fetal vulnerability. Data from iodide studies also fail to indicate that rabbit fetuses are more sensitive than rats, as is the case for MeI. Oxidative stress is a possible MOA for rabbit fetal death based on the observation that MeI exposure results in maternal and fetal GSH depletion in the blood or tissues and the correlation between GSH depletion and cytotoxicity. However, data are insufficient to define the extent of its role. S-methylcysteine hemoglobin adduct detected after MeI exposure indicates the presence of MeI in the fetus. However, data are not available to further assess the role of MeI in fetal death. Cholesterol homeostasis appears to be important for fetal survival during the late gestation period in rabbits. Although MeI exposure results in significant changes in these parameters, current data are insufficient to quantitatively assess their contribution to fetal death. Available information did not show a unique sensitivity of rabbit to iodide. Inadequate data are in studies cited to establish the absence of autoregulatory capacity in the rabbit; greater fetal/maternal iodide ratios in the rabbit than other species, including human; or higher postnatal death in rabbits than other species after iodide exposure.

IV.A.2.a.(3) Human Equivalent Concentration

The appropriate critical NOEL is 2 ppm for fetal death in rabbits (Nemec, 2002d). Examination of the fetal death and GSH depletion data supports the conventional default of a single day exposure for developmental toxicity (USEPA, 1991; as discussed in **Appendix A** of **Volume I**).

Using DPR HEC methodology and a POD of 0.5 ppm for 1% extra risk of fetal death (details provided in **III.G.2**.), the HECs are: 0.23 ppm (workers) and 0.08 ppm (women of child-bearing age-24 hours).

IV.A.2.b. Nasal Effects

IV.A.2.b.(1) Critical NOEL and Endpoints

For olfactory epithelial degeneration, the acute critical NOEL is 21 ppm (6 hrs/day, 5 days/week) from a 13-week study in rats by Kirkpatrick (2002b); the same NOEL selected by the USEPA. At the LOEL of 70 ppm, degeneration occurred mainly in the dorsal meatus, dorsal septum, and upper turbinate with some indication of olfactory regeneration and respiratory epithelial metaplasia (Table 11 and 12). Although observations were not conducted before 4 weeks of exposure, DPR scientists consider this NOEL pertinent for assessing the acute exposure to MeI since prolonged repeated exposure from 4 to 13 weeks only slightly increased the severity of nasal effects but did not change the NOEL.

The effect observed at 70 ppm as the LOEL for acute exposure is consistent with the early degenerative changes noted in rats exposed to 100 ppm MeI by nose-only inhalation for 1 hour (Reed *et al*., 1995 and Chamberlain *et al*., 1998a; Table 10). Three-dimensional mapping of the rat nose showed MeI affecting the dorsal-medial aspects of the ethmoturbinates (Robinson *et al*., 2003). The rapid return of GSH level to control level after the end of exposure that often surpasses the initial GSH level (as indicated by values greater than 100% for end of first 24 hours, at first hour after the 2nd MeI dose in rats (Himmelstein, 2004; Table 8) further supports the use of the endpoint for acute exposure.

IV.A.2.b.(2) Mode of Action

The mode of action is unclear for nasal effects at the site of MeI contact. Although MeI is shown to directly alkylate macromolecules (*e.g*., hemoglobin adduct formation), the role of alkylation has not been defined for the nasal effect. The available data indicate that localized GSH depletion from conjugation with MeI is likely an early event associated with nasal epithelial degeneration. Reduction in non-protein sulfhydryl (NP-SH) was reported in both the olfactory and respiratory epithelia of adult male rats within 1 hour of exposure to 100 ppm MeI (Chamberlain *et al*., 1998a). However, lesions occurred in the olfactory but not respiratory epithelium, and severity increased from 2 to 4 hours of exposure. The specific sensitivity of olfactory epithelium to MeI is attributed to a higher conjugation rate of cytosolic glutathione S-transferase (GST) in the olfactory than the respiratory tissue (Chamberlain *et al*., 1998b). The involvement of GSH depletion is further confirmed through modulating the olfactory degeneration by pre-treatment to either replenish GSH (with isopropyl ester of GSH) or deplete GSH (with phorone and buthionine sulphoximine). An *in vitro* study by Chamberlain *et al.* (1998b) showed that the MeI-GSH conjugation was catalyzed by the theta class GST and resulted in the formation of S-methyl GSH. Events subsequent to GSH depletion that result in cell degeneration and cell death are unclear. The possible down stream events leading to cellular degeneration may involve subsequent formation of cytotoxic metabolites such as methanethiol, or oxidative stress caused by extensive GSH depletion (Chamberlain *et al*., 1998a and b). GSH depletion as an acute toxicity endpoint will be discussed under **IV.A.2.d. Glutathione Depletion**.

IV.A.2.b.(3) Human Equivalent Concentration

A BMD analysis to define the point of departure can not be determined because of the poor fit of the data to the available BMD quantal models. This is due to the "hockey stick" dose-response curve with responses at 5 ppm (0/20 affected) and 21 ppm (1/20 affected) close to the control level (2/20 affected after 4 weeks, 0/20 affected after 13 weeks), but a very high response (19/20) at the next dose of 70 ppm (Table 11 and 12). The true NOEL may lie between 21 ppm and 70 ppm. Thus for this endpoint, the NOEL of 21 ppm is the POD.

Using a NOEL of 21 ppm, the HECs are: 17.1 ppm (workers), 5.7 ppm (adult-24 hours), 3.5 ppm (child-24 hours), and 2.7 ppm (infant-24 hours). At the NOEL of 21 ppm, the GSH depletion is 18% from BMD analysis of the GSH depletion data for this tissue 3 hours after MeI exposure (Table 8).

IV.A.2.c. Neurotoxicity

The neurotoxicity of MeI was only studied in the acute neurotoxicity study in rats (Schaefer, 2002 and 2003). This effect on the brain has been demonstrated in accidental inhalation and dermal exposures, and intentional ingestion in humans (**III.I. Human Toxicity Case Reports**).

IV.A.2.c.(1) Critical NOEL and Endpoints

For neurotoxicity, the acute critical NOEL is 27 ppm (6 hrs) from the study by Schaefer (2002 and 2003) in rats, established by both DPR and USEPA. Effects observed 3 hours after the 6-hour exposure at the LOEL of 93 ppm included: decreased mean total motor activity counts, decreased mean total ambulatory motor activity counts, convulsions and clonic (repetitive movement of mouth and jaws), and reduced body temperature (Table 6 and 7). Hypoactivity was observed in another acute inhalation study with rats (Kirkpatrick, 2000 and 2002a), oral study with rats (Bonnette, 2001a), and gavage study with mice (Bonnette, 2001b). With subchronic and chronic exposures at lower doses, clinical signs were observed only in dog studies. Both 13-week and 1 year studies with dogs showed head shaking, excess drooling, and emesis or extrudate around the mouth (Harriman, 2003d and 2004). However, no histopathology was found in the brains of rats, mice, and dogs from long-term studies (Kirkpatrick, 2005; Harriman, 2005a; and Harriman 2004).

IV.A.2.c.(2) Mode of Action

The MOA for MeI neurotoxicity is not known. One possibility is via MeI induced GSH depletion in the brain. In a rat study by Chamberlain *et al.* (1998a), a 20-30% decrease in brain NP-SH was reported at the end of a 6 hour exposure to 100 ppm MeI, with a slightly greater decrease in the forebrain than in cerebellum. The information from *in vitro* investigation showed that GSH depletion by MeI results in cytotoxicity in cultured neural cells. Cell death became more evident long after the recovery of GSH level (Davenport *et al*., 1992; Bonnefoi, 1992; Chamberlain *et al*., 1999). A MOA via direct effect of MeI or excess iodide on the brain is also possible. This possibility assumes the presence of unmetabolized MeI in the brain. The pharmacokinetic study in rats shows the presence of ^{14}C-radioactivity in the brain after single dose gavage and 5.5 hours of inhalation exposure (Table 1 and 2; Sved, 2002 and 2003).

Detectable radioactivity was measured immediately or 1 hour, 6 hour, and 168 hours (7 days) after exposure or dosing. The chemical nature of the radioactivity was, however, not identified.

IV.A.2.c.(3) Human Equivalent Concentration

Based on the benchmark dose $LED_{0.36\sigma}$ of 12.8 ppm for reduction in ambulatory activity in female rats (Schaefer, 2002; Tables 6 and 7), the HECs are: 10.4 ppm (workers), 3.5 ppm (adult-24 hours), 2.2 ppm (child-24 hours), and 1.9 ppm (infant-24 hours).

IV.A.2.d. Glutathione Depletion

In addition to GSH depletion as MOA associated with rabbit fetal death and rat olfactory epithelial degeneration already discussed, GSH depletion itself can be considered a toxicity endpoint after MeI exposure (**III.J.3.**). Glutathione depletion has been measured in the blood and several tissues of rats and is considered the cause of cell death in neural tissues (Chamberlain *et al.*, 1998a; Chamberlain *et al*., 1999; Davenport *et al*., 1992; Bonnefoi *et al*., 1991; Bonnefoi, 1992). While GSH depletion was also detected in the epididymides and testes of rats 1 hour after oral exposure (Gandy *et al*., 1990), the consequence of the depletion is unknown.

The only dataset sufficient for dose-response analysis of GSH depletion is from the 2-day inhalation study in male rats exposed to 25 or 100 ppm MeI by inhalation (Himmelstein, 2004; Table 8). The rabbit studies were conducted with a single dose, with either 20 ppm or 25 ppm MeI (Sloter 2005a and b). In rat study, the NOEL for GSH depletion was <25 ppm with maximal depletion of about 25% at 25 ppm, and 40% depletion at 100 ppm in the blood 3 hours after MeI exposure (Table 8). The magnitude of depletion was similar between the first day dosing and the second day dosing. Benchmark dose analysis of the GSH data in the blood and olfactory epithelium showed ED_{05} of 17.5 ppm and LED_{05} of 14.3 ppm, and ED_{10} of 13.7 ppm and LED_{10} of 11.7 ppm for these two compartments, respectively. This means that a POD of 12.8 ppm for acute exposure represents <5% GSH depletion in the blood and about 10% GSH depletion in the olfactory epithelium. Thus, GSH depletion as an endpoint does not need further evaluation as the use of the lower POD for neurotoxicity will protect against GSH depletion, as a systemic effect. Furthermore, these low levels of GSH depletion at the POD of 12.9 ppm minimize the concern about the recovery of GSH levels in human exposure. As already discussed in **Appendix A** of **Volume I** associated with the dose metric for GSH depletion for olfactory epithelial damage, a 25% GSH depletion represents a level of no effects.

IV.A.3. Subchronic Inhalation Toxicity

For subchronic inhalation exposure, endpoints as a result of less than 1 year continuous exposure from subchronic, developmental, and reproductive toxicity studies are reviewed. They include reproductive and systemic effects in rats (Table 56).

Table 56. The subchronic toxicity of MeI.[a]

Species, Route Duration	ppm (air)		mg/kg/ day	Effects	References
	NOEL	LOEL	NOEL		
Inhalation Studies					
Rat 4 and 13-week, 5 days/week	21	70	20	↑ Relative liver weight, ↓ body weight gain	*Kirkpatrick, 2002b[b]
Rat 28 days prior to mating to GD 11, daily	25	73	34	↓ Mean implantation sites and fetal viability, ↑ pre-implantation loss and prenatal mortality (early resorptions)	Nemec, 2004[c]
Rat GD 0 to 20, and LD 5 to 20; daily	25	72	34	Mortality; ↓ body weight, body weight gain, and food consumption (dams); ↓ mean live litter size, postnatal survival, pup weight gain; and ↑ pup death	Nemec, 2004[c]
Rat 4 weeks, 5 days/week	25	72	24	↓ Body weight gains and food consumption, hematology and clinical chemistry changes	Nemec, 2004[c]
Rat 2-generation, daily	20	50	27	↓ Body weight, nasal degeneration	*Nemec, 2002a[c]
	20	50	27	Reproductive-↓ live litter size	
	5	20	7	Developmental-↓ pup weight, delayed development	
Rat GD 6-29, daily	20	60	27	↓ Maternal body weight	*Nemec, 2002c[d]
Oral Studies					
Rat, gavage 13 weeks	NA	NA	5	Forestomach hyperkeratosis and hyperplasia, submandibular gland ductal squamous metaplasia	*Nishimura, 2002[b]
Mouse, micro-capsules, 3 weeks	NA	NA	11.3	↓ Body weight gain on week 1 (males only)	Harriman, 2003b[b]
Mouse, micro-capsules, 13 weeks	NA	NA	<23.6	↑ weight and colloid of thyroid, hyperkeratosis in the esophagus	*Harriman, 2003c[b]
Dog, capsules, 13 weeks	NA	NA	<1.5	Injected sclera and wet material around the mouth	*Harriman, 2003d[b]

a/ * indicates the studies were acceptable to DPR according to FIFRA guidelines. NA=not applicable.
b/ Studies described in **III.C. Subchronic Toxicity**.
c/ Studies described in **III.F. Reproductive Toxicity**.
d/ Studies described in **III.G. Developmental Toxicity**.

IV.A.3.a. Reproductive Effects

IV.A.3.a.(1) Critical NOEL and Endpoints

For reproductive effects, the critical NOEL is 5 ppm for lowered mean pup body weights, and delayed development (increased number of days to vaginal patency) in rats (Table 33; Nemec, 2002a). In this study, the parental rats were exposed to MeI by inhalation for at least 10 weeks prior to mating, during mating through GD 20, and lactation. The pups were exposed *in utero* during gestation and during LD 5 to 21. The reduction in body weight and delayed development suggest thyroid/pituitary perturbation. While no macroscopic lesions were reported in the thyroid, neither thyroid function nor the organ weight was evaluated in this study. It is unclear whether GSH depletion might also be involved for these effects. Gandy *et al.* (1990) had shown that MeI given by gavage caused significant rapid reduction of GSH in the epididymis and testes of rats (**III.J.3.**). The inhalation toxicity of MeI in male rats by Himmelstein (2004) did not examine the reproductive organ.

IV.A.3.a.(2) Human Equivalent Concentration

Benchmark dose analysis was performed on reduced pup body weight after 21 days and the number of days to vaginal patency since these are the most sensitive reproductive toxicity endpoints (Nemec, 2002a; Table 33). The $LED_{0.36\sigma}$ levels are 3.0 ppm and 3.1 ppm for male and female pup body weight, respectively, and 5.6 ppm for vaginal patency. Thus the POD is 3.0 ppm, the lowest value, with the HECs at 0.51 ppm (child-24 hours) and 0.39 ppm (infant-24 hours).

IV.A.3.b. Systemic Effects

In addition to the endpoints established from the 2-generation reproductive toxicity, systemic effects from subchronic exposure duration were examined to determine critical endpoints to address the adult's subchronic exposure to MeI

IV.A.3.b.(1) Critical NOEL and Endpoints

For systemic effects, which would be applicable for all age groups in the population, the lowest dosage is 20 mg/kg/day based on a NOEL of 21 ppm for increased relative liver weight and decreased body weight gain in rats (Table 11 and 12; Kirkpatrick, 2002b). The effect on the relative liver weight was due to reduced body weight as there was no treatment-related effect in the absolute liver weight. The decreased body weight gain in this study is statistically significant only for the males and only during the first week of study. However, the body weights were reduced on week 6. Examination of other MeI studies showed that decreased body weight is a common finding (Table 56). For the subchronic exposure duration, the body weight datasets with subchronic duration from the reproductive toxicity range finding (Nemec, 2004) and definitive (Nemec, 2002a) studies were subjected to BMD analysis. While many of the body weight measurements were reduced for various durations, the duration with the maximal reduction was selected. These were: adult male rats exposed for 6 weeks (Kirkpatrick, 2002b), F1 parents exposed to MeI during premating (exposed 22 weeks) (Nemec, 2002a), and F0 parents during premating (exposed for 52 weeks for males and 27 days for females) and reproductive phase at gestation (exposed for 20 days) (Nemec, 2004).

Another consistent finding after subchronic exposure to MeI is increased cholesterol levels which may be indicating metabolic alteration that can be biologically significant. The potential relationship between cholesterol levels and fetal effects is already discussed in the sections for fetal death (**IV.A.2.a.**). In rats, cholesterol level was increased (about 50%) at MeI 70 ppm after 4 and 13 weeks of exposure (Table 11 and 12; Kirkpatrick, 2002b). In the chronic study, cholesterol level was significantly increased only at 26 weeks, but not at 52 weeks (Kirkpatrick, 2005).

The increase in cholesterol has also been reported in rabbits exposed to MeI (25 ppm) by inhalation (Sloter 2005a). At 25 ppm given on GD 23-24, the only dose studied, maternal and fetal cholesterol levels increased 30% and 16%, respectively (Table 61). When given on GD 23-26, only fetal cholesterol level was significantly increased, by 39%. Increased cholesterol, as well as other lipids, was reported in rabbits given MeI (57 mg/kg) as a single subcutaneous injection (Hasegawa *et al*. (1971). Matsui *et al*. (1982a) showed that the hyperlipidemia induced by MeI (57 mg/kg by subcutaneous injection for two days) in rabbits were due to an increased lipid synthesis, and not reduced clearance of lipid from the plasma. The increase in triglyceride production was hypothesized to be a consequence of increased insulin resistance and hyperinsulinemia. Another report by Matsui *et al*. (1982b) showed that MeI-treated rabbits (57 mg/kg by subcutaneous injection for two days) were resistant to insulin with elevated serum glucose and glucagon levels.

In addition to these endpoints, the SRC recommended that the potential for neurotoxicity after repeated dosing be considered (**Volume IV Part 1-A**). Severe neurotoxicity after repeated exposure is evident in case reports of workers and chemists (**III.I. Human Toxicity Case Reports**). After exposure has been terminated, these individuals show persistent and additional neurotoxic signs and symptoms. Some developed psychiatric problems weeks after the last exposure. While the exposure levels of these individuals are unknown, it is evident that repeated exposures to MeI have potential profound effect on the nervous system. The acute neurotoxicity in rats is limited to a single day exposure and qualitative neuropathological examination was not conducted until 15 days later (Schaefer, 2002). A repeated dose neurotoxicity study has not been conducted and existing repeated dose experiments do not sufficiently test for neurotoxicity after MeI exposure.

IV.A.3.b.(2) Human Equivalent Concentration

The POD for HEC calculation was derived from the comparison of benchmark dose levels for body weight reduction and cholesterol level increase from several studies.

A comparison of $LED_{0.61\sigma}$ values between studies showed similar levels and indicated consistent effects across studies and duration for exposures less than 1 year. The average $LED_{0.61\sigma}$ are 19.0±4.0 ppm for body weight reduction and 14.2±3.4 ppm for cholesterol elevation in rats. For 1 year or more exposure, the chronic toxicity study in rats showed that body weight reduction continued, but cholesterol levels of the MeI-treated rats after 52 weeks of exposure were similar to those for controls (Table 21; Kirkpatrick, 2005).

For body weight reduction in adult rats, a BMR of 5 % can be considered as the POD since a 10% decrease is an indicator of systemic toxicity as the basis for the MTD in FIFRA guideline toxicity studies. From the MeI data in rats, the average LED_{05} is 20.1±4.2 ppm from 6

datasets (6 weeks males from Kirkpatrick, 2002b; 22 week males and females from Nemec, 2002a; 52 day males and 27 day females in premating phase from Nemec, 2004; and 20 day females in gestation phase from Nemec, 2004).

For increase in cholesterol levels as an endpoint, the toxicological significance of change in a single parameter in the serum is uncertain. There is no normal range for total cholesterol in human as the recommended level is less than 200 mg/dL, as cholesterol is essential for the body function. Evaluation of lipid profile for the potential of cardiovascular diseases considers other parameters in the profile, such as triglycerides and lipoproteins. Thus, a 10% response as a BMR is reasonable to evaluate change in cholesterol levels. From the MeI data in rats, the average LED_{10} is 9.7±2.1 ppm from 6 datasets (4 week and 13 week, male and female data from Kirkpatrick 2002b; 26 week male and female data from Kirkpatrick, 2005). This concentration is lower than the 25 ppm MeI which caused significant increase of fetal cholesterol levels by 16% (when dose from GD 23-24) and 39% (when dosed from GD 23-26) (Table 61, Sloter, 2005a).

For subchronic neurotoxicity, the POD has to be extrapolated from the acute neurotoxicity study (Schaefer, 2002) using a modifying factor. The SRC did not make a recommendation on the magnitude of the factor (**Appendix B** of **Volume IV Part 1-A**). Generally, the default factor is 10-fold for the extrapolation of acute effect to chronic effect. For subchronic toxicity, a modifying 3-fold factor ($10^{0.5}$) seems appropriate. To evaluate the magnitude of this factor, DPR scientists conduct a brief literature search for published studies of subchronic (90-day) neurotoxicity using functional observational battery in laboratory animals after inhalation exposure to relatively low molecular weight chemicals. Neurotoxic chemicals which are cholinesterase inhibitors were excluded from this search since MeI neurotoxicity is not expected to have the same MOA. Most of the studies reported effects for different exposure duration for the given dose levels, or effects only at the end of the study, and thus limit their utilities for dose and duration extrapolation. The one useful study is by Crafton and Zhao (1997) with trichloroethylene where benchmark dose analysis was performed. For ototoxicity in rats, the benchmark concentrations (and exposure durations) which produced a 15-dB increase in threshold were: 5223 ppm (1 day), 2108 ppm (5 days), 1418 ppm (20 days), and 1707 ppm (65 days). The concentration ratio for 1 day to 65 days is 3-fold. Applying a modifying factor of 3-fold to the 12.8 ppm acute $LED_{0.36\sigma}$ (**IV.A.2.c.**) based on the acute neurotoxicity study by Schaefer, 2002, the estimated POD for subchronic neurotoxicity is 4.3 ppm. This value is lower than the average LED_{05} for body weight reduction and LED_{10} for increased cholesterol level. Thus the use of 4.3 ppm as a POD for subchronic exposure of the adult population would be protective against neurotoxicity, body weight reduction, and cholesterol increase after MeI exposure.

With 4.3 ppm as the POD for HEC calculation, the HECs are: 3.5 ppm (workers) and 1.2 ppm (adult-24 hours). The HECs for children (0.7 ppm) and infants (0.5 ppm) are higher than those based on reduced postnatal body weight with a lower POD of 3.0 ppm.

IV.A.4. Chronic Inhalation Toxicity

IV.A.4.a. Critical NOEL and Endpoints

With chronic inhalation exposure, the most sensitive endpoint is mandibular salivary gland metaplasia with a NOEL of 5 ppm in rats after inhalation exposure to MeI for 2 years (Table 22; Kirkpatrick, 2005). Additional effects on the salivary gland included salivation and excess drooling after inhalation (Schaefer, 2002) or oral exposures (Nishimura, 2002) in rats, and oral exposure in dogs (Harriman, 2003d and 2004). These may be due to the effect of iodide, which is known to concentrate in the salivary gland. In a human study with MeI, the iodide level in the saliva was higher than the blood (Morgan *et al*., 1967). Rats exposed to KI in the drinking water (1000 ppm, average daily potassium iodide intake were 53 mg/kg/day and 67 mg/kg/day for males and females, respectively) for 2 years showed squamous cell carcinoma in the salivary gland (Takegawa *et al*., 2000).

Thyroid toxicity is a common finding for laboratory animals (rats, mice, and dogs) exposed repeatedly to MeI by either inhalation or oral exposures, with similar or higher NOELs than that for salivary gland effects (Table 57). Non-cancer effects included altered thyroid hormone levels (increased TSH), increased thyroid organ weight and enlarged gland, and histopathology (increased colloid, vacuolation, and follicular hyperplasia) (Table 19, Harriman, 2003c; Table 21 and 22, Kirkpatrick, 2005; Table 25 and 26, Harriman, 2005a; Table 28 and 29, Harriman, 2004).

Table 57. The chronic toxicity of MeI.[a]

Species Route Duration	ppm (air)		mg/kg/ day	Effects	References
	NOEL	LOEL	NOEL		
Rat inhalation whole-body 2 years	5	20	5	Mandibular salivary gland metaplasia	*Kirk-patrick, 2005
	20	60	19	Nasal epithelial degeneration and thyroid effects (increased organ weight, enlargement, hyperplasia, tumors)	
Mouse microcapsules in the diet, 18 months	<60	60	<8	↓ Body weight; thyroid effects (↑thyroid/ parathyroid weights, ↑increased colloid and cytoplasmic vacuolation, follicular cell hyperplasia), GI tract irritation.	*Harriman, 2005a
Dog capsule oral 1 year	NA	NA	<1.5	Salivation, injected sclera	*Harriman, 2004
			6	Thyroid effects (↑TSH, ↓ relative thyroid weight, colloid depletion, hypertrophy)	

a/ * indicates the study was acceptable to DPR according to FIFRA guidelines. NA=not applicable. Studies described in **III.D. Chronic Toxicity**.

IV.A.4.b. Human Equivalent Concentration

Benchmark dose analyses were conducted for salivary gland metaplasia, enlarged thyroid, and thyroid hyperplasia using quantal models. Comparison of ED_{05} values, showed that salivary gland metaplasia is the most sensitive endpoint with LED_{05} of 3.4 ppm, consistent with the determination based on the NOEL. Therefore, the POD for chronic exposure is 3.4 ppm for the calculation of the HECs. The HECs are 2.0 ppm (workers), 0.66 ppm (adults, 24-hours/day), 0.41 ppm (children, 24-hours/day), and 0.31 ppm (infants, 24-hours/day).

As with subchronic exposure, the potential for MeI-induced neurotoxicity after chronic exposure needs to be considered. Using a modifying factor of 10-fold, an estimated POD of 1.3 ppm can be derived from the acute POD of 12.8 ppm. The HECs are 1.0 ppm (workers), 0.35 ppm (adults, 24-hours/day), 0.22 ppm (children, 24-hours/day), and 0.16 ppm (infants, 24-hours/day).

While the HECs for neurotoxicity are lower than those for salivary gland metaplasia, there is some uncertainty in these values because they are based on an extrapolated value of 1.3 ppm from the 12.8 ppm from a single dose acute study (Schaefer, 2002) and a modifying factor of 10-fold. Thus, the HECs for both salivary gland metaplasia and neurotoxicity will be used in risk characterization.

IV.A.5. Oncogenicity Weight of Evidence

There is a concern for lifetime exposure to MeI because of the weight of evidence showed that MeI is oncogenic causing thyroid tumors and tumors in other tissues from laboratory animal studies.

IV.A.5.a. Evidence in Human and Laboratory Animals

There is no information on MeI exposure and cancer in humans. Case reports for human are those from episodic and accidental exposures to high MeI concentrations (see **III.I.**).

From laboratory animal studies, MeI is an oncogen based on the finding of thyroid tumors in rats (Table 22; Kirkpatrick, 2005) and male mice (Table 26; Harriman, 2005a), and follicular cell hyperplasia/hypertrophy in rats (Table 22; Kirkpatrick, 2005), mice (Table 26 and 27; Harriman, 2005a) and male dogs (Table 28; Harriman, 2004) after long-term repeated exposures. In the rodent studies, the animals were considered adequately challenged because there were reductions in body weight and/or food consumption at the highest dose tested in rats (60 ppm), and in mice (600 ppm). Follicular hypertrophy was also found in rabbits (doe and fetus) after short-term exposures to MeI (Table 41 and 48; Sloter, 2005a and b). There are no long-term studies with rabbits treated with MeI.

There is additional evidence of MeI to induce cellular changes at other tissue sites (salivary gland, brain, cervix/uterus, lungs, and skin). The salivary gland squamous metaplasia in rats (Kirkpatrick, 2005) is a benign change, from columnar or cuboidal cells to squamous cells, in the epithelium. In the chronic toxicity with rats, astrocytoma was found in MeI treated rats (Kirkpatrick, 2005; **III.D.1.**). While the data were incomplete for a dose-response analysis because of incomplete incidence information for the low and mid-doses, it is a rare tumor such

that the increased incidence at the high dose males (6.8%, compared to none in control) should be of concern.

In the 18-month dietary exposure with mice exposed to MeI, DPR scientists consider the finding of fibromas in the cervix/uterus of high dose female mice as a treatment-related effect (Table 27; Harriman, 2005a) and an indication of uncontrolled cell growth. The low incidence and presence in only one species for the fibroma were considered indications that more studies were needed rather than a negative finding. Since the assignment of animals to groups was random, and proper statistical procedures were used, it would be unlikely that the results were due to chance alone. It is not known if similar pathology would also be found in the chronic rat or dog studies, since extensive histological examination was not performed.

In two earlier studies (already described in Section **III.D.4.**), lung tumors were detected in mice injected intraperitoneally with MeI (Poirier *et al*., 1975) while subcutaneous sarcomas were observed in rats given MeI by subcutaneous injection (Druckrey *et al*., 1970). However, there were uncertainties in the results of these older studies because the reports did not provide sufficient details on the methods or results, and the use of a mouse strain known to be sensitive to chemical inducers of lung tumors (Maronpot *et al*., 1986).

IV.A.5.b. Thyroid Tumors Mode of Action

The MOA for thyroid tumors in rats after inhalation exposure to MeI to be considered include: (1) Genotoxicity-MeI induces genetic mutation, and (2) Iodide and thyroid perturbation-excess iodide from MeI affecting the thyroid. The evidence for these MOAs is explored in the following section. The MOA determines the method for the quantitative assessment of potential oncogenicity in human exposure.

IV.A.5.b.(1) Genotoxicity

A genotoxic MOA for MeI-induced thyroid tumor is plausible because antithyroid compounds have also been shown to have genotoxic properties (Hurley *et al*., 1998; Kondo *et al*., 2006). As presented under Section **III.E. Genotoxicity**, MeI causes gene mutation, chromosomal aberration, and DNA alkylation in experimental studies (Table 30). Increased mutation rates were detected in *in vitro* assays using *S. typhimurium* strains under closed systems (Rosenkranz and Poirier, 1979; Simmon *et al*., 1977; Simmon, 1979a), *E. coli* strain WP2 *uvr*A (Hemminki *et al*., 1980; Takahashi and Kawazoe, 1987) and *S. cerevisiae* (Simmon, 1979b). MeI is also positive for gene mutation in mammalian systems as demonstrated by increased mutant colonies in Chinese hamster ovary cells (Amacher and Zelljadt, 1984) and mouse lymphoma cells (Amacher and Dunn, 1985). Structural chromosomal aberration is reported in assays with Chinese hamster ovary cells exposed to MeI causing increase in chromatid breaks and exchanges (Gudi and Brown, 2001). In addition, the formation of small colonies in TK^- lymphoma cells is also an indication of chromosomal aberrations (Clive *et al*., 1979; Moore and Clive, 1982; Moore *et al*., 1985a; Amacher and Dunn, 1985). In addition, MeI is positive in the morphological transformation assay (as a carcinogen screening assay) using Golden Syrian hamster embryo cells (Pienta *et al*., 1977). While there are negative genotoxicity studies in the database (Table 30), the positive findings are relevant in the consideration of MeI oncogenicity potential.

The mutagenic activity of MeI may be attributed to its activity as a S_N2 alkylating agent. With the substrates of 4-(p-nitrobenzyl)-pyridine and deoxyguanosine, its activity was 27% the rate of epichlorohydrin, a potent alkylating agent (Hemminki *et al*., 1980). Takahasi and Kawazoe (1987) proposed that MeI activated the *alkA* and *umuC* genes in *E. coli* by direct methylation of a key methyltransferase. MeI alkylation of DNA has been demonstrated in human lymphoblasts exposed to MeI, as well as isolated DNA extracted from lymphocytes of male donors (Cloutier *et al*., 2001). In an *in vivo* study, DNA adducts (7N-methylguanine, O^6-methylguanine, and 3N-methyladenine) were detected in the liver, lung, stomach, and forestomach tissues (the only tissues examined) of rats exposed to MeI by either oral or inhalation exposures (Gansewendt *et al*., 1991). The ^{14}C detected in the DNA fractions was determined to be on the carbon of guanine and adenine due to *de novo* synthesis, as well as direct methylation of MeI on the bases (Gansewendt *et al*., 1991; Bolt and Gansewendt, 1993). The relative reactivity of MeI to alkylate DNA compared to endogenous agents is unknown since the study (Gansewendt *et al.,* 1991) did not include a control group. Endogenous processes and chemicals (reactive oxygen species and products, aldehydes, and S-adenosylmethionine) have been reported to generate DNA adducts (De Bont and van Larebeke, 2004). The overall outcome of DNA adduct formation also needs to consider the availability of repair mechanisms (Pottenger *et al.,* 2004).

In the consideration of oncogenicity, the direct alkylation of guanine and the formation of O^6-methylguanine adduct, may contribute to the genotoxic MOA for MeI-induced tumors. O^6-methylguanine lesions have been associated with mutation and oncogenic transformations (for example, Loechler *et al.,* 1984; Dosanjh *et al*., 1993; Margison *et al*., 2002; Warren *et al*., 2006). The mechanism for O^6-methylguanine-induced oncogenesis involves not only point mutation, but also initiation of mismatch repair-mediated DNA recombination and cytotoxicity (Margison *et al*., 2002). For example, point mutation can lead to defective genes, such as the tumor suppressor gene. A recombination between homologous chromosomes may result in the inactivation of the tumor suppressor gene. If the cells with the mutations survive, they may undergo hyperplastic growth and tumor formation. In a study with human lymphoblast cells and DNA extracted from lymphocytes of male donors, MeI caused the formation of hyper-reactive sites at two guanine positions of the Fragile-X mental retardation gene (Cloutier *et al*., 2001). These hyper-reactive sites were considered hotspots for damage and mutation, if not repaired.

The presence of unmetabolized MeI is suggested in the pharmacokinetic studies in the rat given ^{14}C-MeI (Sved, 2002 and 2003). ^{14}C-radioactivity was detected in all organs (including the thyroid) analyzed (Tables 1 and 2). After inhalation exposure, the highest levels were measured at the first sample collection time point, immediately following the 5.5-hour of exposure. However, the chemical identity of the ^{14}C was not examined.

Methyl iodide shares structural similarity with halomethanes. A comparison of the toxicity endpoints shows some common as well as differences in effects. When compared with two other halomethanes, the tumors found with MeI exposure are not comparable. Methyl chloride induced kidney tumors in male mice, but not in rats, after inhalation exposure (Bolt and Gansewendt, 1993). On the other hand, methyl bromide, a mutagen and an alkylating agent, has not been found to be oncogenic in laboratory animal studies (DPR, 2002).

A comparison of the chemistry of MeI with other alkylating agents provides support for the genotoxic MOA as MeI behaved analogously to these compounds, in which some are mutagens and carcinogens. MeI reacts with nucleophiles by S_N2 displacement, a reaction common with methylating agents such as methyl methane sulfonate (MMS) and N-methyl-N-nitrosourea (MNU) (Dipple, 1995). The N7 and O^6-guanine adducts found in rats after MeI exposure (Gansewendt *et al*., 1991), would also be expected for MMS and MNU reaction with DNA (Dipple, 1995). Furthermore, MNU, itself, induced thyroid follicular cell adenomas and carcinomas in F344/NCr rats (Ohshima and Ward, 1986). The effect was enhanced in rats under iodide deficiency condition because more carcinomas, relative to adenomas, were found than with MNU treatment alone. The authors considered iodine-deficiency condition as a promoter of thyroid tumors initiated by MNU.

USEPA suggested that mutagenicity may be a contributing factor in MeI-induced thyroid tumorigenesis (USEPA, 2005d). Such a MOA was, however, considered by USEPA unlikely because of the absence of portal-of-entry (respiratory tract) tumors, finding of tumors mainly at terminal sacrifice, and tumors in the thyroid but not at tissue sites where DNA adducts were found (liver, lungs, and forestomach). It is unclear to DPR scientists how these reasons would exclude a genotoxic MOA. The absence of portal-of-entry tumor does not exclude the possibility of a systemic effect. While thyroid tumors were found at terminal sacrifice, the first astrocytoma in rat was detected after less than 1 year (day 218) of treatment. As for DNA adducts, it should be noted that measurements were made only for those 3 tissues and the stomach, and no other tissues.

In summary, a genotoxic MOA for MeI-induced thyroid tumor is plausible because MeI is an alkylating agent with genotoxicity properties in *in vitro* and *in vivo* assays (Table 30). It has been demonstrated form adducts (Gansewendt *et al*., 1991; Cloutier *et al*., 2001), which have been implicated to be important in carcinogenesis.

IV.A.5.b.(2) Iodide and Thyroid Perturbation

MeI-induced thyroid tumor formation involves the perturbation of thyroid function as has been demonstrated for other antithyroid chemicals (USEPA, 1998; Hurley *et al*., 1998). Metabolism of MeI leads to excess iodide, which induces the formation of iodopeptide(s). These peptides inhibit thyroid peroxidase mRNA and protein synthesis, leading to loss of thyroglobulin iodination (or inhibition of the formation of iodothyronines with organic iodine). A reduction in serum thyroid hormones triggers the feedback mechanism to the thyroid-pituitary axis through increased the production and release of TSH. Continuous stimulation of TSH on the thyroid leads to initially to follicular hyperplasia and eventually tumor formation.

The MeI toxicity database in rats provides support for certain aspects of this MOA. Increased serum iodide levels were measured after inhalation exposure of rats in the 2-day study (Table 8; Himmelstein, 2004). There are no such iodide data for repeated exposures. The mean TSH level showed a 12-fold increase ($p<0.01$) when measured on week 26, but was not sustained with lower increase on week 52 (4.1 fold, not statistically significant) and on week 104 (4.7 fold, $p<0.01$) (Table 21; Kirkpatrick, 2005). Analysis of the 60 ppm group TSH levels showed significant gender difference in the response only for the 26 week data (Mann Whitney U-test, $p=0.022$), and not for the 52 and 104 week data. Individual data showed a large range of TSH values for each time point. For the 104 week

60 ppm rats, for example, they were: 1.17 to 4.77 ng/mL (control), 0.92 to 7.95 ng/mL (treated rats without thyroid effects), 6.23 to 32.33 ng/mL (treated rats with non-cancer thyroid effects), and 2.27 to 50.40 ng/mL (treated rats with thyroid cancers) (Table 23). Three male animals had thyroid functions measured at both 26 and 52 weeks and their levels showed mixed results with time (Table 23). It is not known if the higher mean TSH increase in the males after 26 weeks of exposure to MeI is a factor in the higher incidence of thyroid hyperplasia and tumors than that for the females (Table 22; Kirkpatrick, 2005).

The lower incidences of tumors in the female rats, though, could not be attributed to the supposedly higher basal level of TSH in males compared to females as has been suggested by Chen (1984) and USEPA (1998) for antithyroid compounds. The MeI database showed no evidence of a significant gender difference in the basal levels of TSH and hormone levels (Table 21 control groups; Kirkpatrick, 2005). The similarity in incidences for nasal effects and salivary gland metaplasia (Table 22) indicate the gender difference in thyroid response is unlikely to be due to differences in the port-of-entry intake of MeI or systemic iodide level, respectively. Pharmacokinetic studies with rats also showed no gender-specific differences in the disposition of MeI after either inhalation or oral routes of exposure; but note that the study was conducted using ^{14}C-MeI (Sved, 2002 and 2003). Compared to rats, the incidences of thyroid effects were higher in male mice for increased tumor incidences and TSH levels, and in female mice for follicular cell hyperplasia after oral exposure (Harriman, 2003c and 2005a).

With TSH stimulation on the thyroid, increased serum hormone levels are expected. The data, however, showed no significant change in T3, and variable results for T4 (Table 21; Kirkpatrick, 2005). This variability might be due to the comparison of mean values. Individual data with values measured for more than one time point is available for only 3 animals (Table 23). In addition, these levels might be a reflection of the net physiological response, as thyroid hormone levels and TSH are highly regulated by thyroid and extrathyroid processes (Hurley *et al.*, 1998; NRC, 2005). These processes include: (1) increased excretion of excess iodide by down regulation of the sodium iodine symporter, (2) increased release of bound hormones from binding proteins, and (3) inactivation of T4 to rT3 by deiodinase. Existing data with MeI suggest an association between elevated rT3 and lack of thyroid lesions. In the 20 ppm and 60 ppm female rats, significantly higher rT3 levels than those for male rats were measured (Table 21; Kirkpatrick, 2005). While MeI has been shown to inhibit deiodinases D1 and D2 from rat and rabbit tissues (**III.J.4. Other Studies**, Table 53), the role of MeI deiodinase inhibition activity with respect to thyroid tumor formation is unclear since the thyroid deiodinase activity has not been studied. Inhibition of 5'-deiodinase can block the conversion of T4 to T3, resulting in thyroid tumors from increased serum TSH stimulation via the thyroid-pituitary axis feedback mechanism responding to the decrease in T3 level.

The results in the MeI database meet 4 of the 5 requirements to demonstrate that a chemical has antithyroid activity set forth by the USEPA in the guidance document on the assessment of thyroid tumors (USEPA, 1998). The requirements are: (1) increases in thyroid growth, (2) changes in thyroid and pituitary hormones, (3) location of the tumor site(s) associated with antithyroid action, (4) dose correlations on thyroid gland growth and those producing tumors, and (5) reversibility of early stages of disruption of the thyroid-pituitary axis upon cessation of treatment. There are no MeI data which demonstrate reversibility of thyroid effects, concurring with the finding of the USEPA (USEPA, 2005d). This is contrary to the view of Mileson *et al.* (2009) that the decreased serum iodide levels upon cessation of each MeI

exposure in a 2-day (6 hours/day) study with male rats (Table 8; Himmelstein, 2004) provides support for reversibility of thyroid effects. If such data were sufficient, then it is questionable whether thyroid tumor after long term exposure in rats, also 6 hours/day, would involve excess iodide in the MOA.

Published literature on iodide-containing compounds and thyroid effects provides some support for the involvement of iodide in MeI-induced thyroid tumors. Erythrosine (red dye #3, with 58% iodide by weight) caused thyroid effects that showed similar dose-response relationship as for the MeI chronic inhalation study. CD rats were given erythrosine (0% to 4% in the diet; 1.4, 7.3, 14.7, or 71.5 mg iodide/kg/day based on 5% absorption) for 30 months (Borzelleca, *et al.,* 1987; Capen and Martin, 1989). In the 4% group, the thyroid weights were 2 times higher than that for the control. Higher incidences of follicular cell hyperplasia, adenoma and carcinoma were detected males than females. For this group of male rats, incidence for adenomas (15/60) was higher than carcinomas (3/60). The combined thyroid tumor incidences for the control to the highest dose were: 3/181, 3/60, 3/60, 4/60, 18/60. No TSH data was presented. Studies with KI showed effects in the thyroid, but not thyroid tumors. In a study with F344/CuCrj rats given KI in the drinking water (1000 ppm, average daily potassium iodide intake were 53 mg/kg/day and 67 mg/kg/day for males and females, respectively), effect on the thyroid was described as dilatation with increased colloid and flattened epithelia at all dose levels but no tumors were detected (Takegawa *et al*., 2000). The estimated amount of iodide intake (40.5 mg I^-/kg/day) for the males in this study was lower than that (52 mg I^-/kg/day for the 60 ppm group) in the rat inhalation chronic toxicity study (Kirkpatrick, 2005)[21]. However, since these two studies were conducted using different routes of exposure, it may not be appropriate to compare the cancer results using the total doses alone. There are no pharmacokinetic data for rats drinking MeI-containing water intermittenly throughout the day.

Iodinated glycerol is an expectorant and is metabolized to iodide. It was oncogenic in F344/N rats and $B6C3F_1$ mice exposed to this compound (0, 125, or 250 mg/kg for males; 0, 62, or 125 mg/kg for females) by gavage for two years (French, 1990). In rats, there were increased incidences of mononuclear cell leukemia (males only), thyroid follicular cell carcinomas (low dose males only), salivary gland squamous metaplasia (both genders and dose groups, affecting at >90% of the animals), and nasal cavity adenoma (males only). The cause of the thyroid tumors only in the low dose males is unclear. The lack of a dose-response for thyroid tumors, a late-appearing tumor, in the high dose males might be due to the high early deaths in this group. The absence of effect in the female rat group might be due to the lower doses tested (1/2 of the male dose). However, it may not be a dose difference issue because focal thyroid follicular cell hyperplasia, not thyroid tumors, was observed in both genders of mice.

The relationship between iodine intake and thyroid cancer in the human population was studied by the ATSDR (ATSDR, 2004). The review of several epidemiology studies showed no significant association between iodide intake and thyroid cancer for populations with sufficient iodine exposure. Increased iodide intake may be a risk factor for thyroid cancer in certain populations, in particular, populations residing in iodine-deficient areas. Felt-Rasmussen (2001) described two studies where iodine prophylaxis to populations with iodine deficiency resulted in increased ratio of papillary to follicular carcinomas.

[21] Iodide in potassium iodide= 53 mg/kg/day x 126.90 g I^--mole/ 166.0 g KI-mole=40.5 mg I^- /kg/day
Iodide in iodomethane=58 mg/kg/day x 126.90 g I^--mole/ 141.95 MeI-mole=52 mg I^- /kg/day

In summary, MeI-induced thyroid tumors in rodents can be due to thyroid perturbation as the MOA because the increase in serum iodide levels and the pattern of changes in the thyroid function and pathology in rats after MeI exposure are consistent with known effects of iodide on the thyroid. The studies with erythrosine in rats (Borzelleca, *et al.,* 1987) and iodine prophylaxis in human (Felt-Rasmussen, 2001) provide additional support for this MOA.

IV.A.5.b.(3) Evaluation of Thyroid Tumor MOA

In the initial SRC comment on the thyroid perturbation MOA, the SRC stated that low iodide alone is oncogenic in rats, while high iodide is not oncogenic (**Appendix E** of **Volume IV Part 1-A**). Both high iodide and low iodide treatments were said to promote genotoxic-initiated thyroid tumorigenesis. The MeI-induced thyroid effects (enlargement, hyperplasia, vacuolation) and elevated TSH are consistent with the low-iodide type. Since MeI exposure results in elevated iodide, the thyroid findings were considered contradictory to the distinction about low and high iodide effects. Two proposed mechanisms are: spontaneous initiation/TSH-promotion and MeI-initiation/TSH promotion. The first may have a threshold, while the second is probably biphasic with no threshold and an estimated TSH promotion factor of 3-fold to 10-fold. However, this estimated value carried considerable uncertainty.

In the above SRC analysis, the distinction between low and high iodide-induced thyroid effects appears to be based on the two types of nongenotoxic thyroid carcinogens, iodide-deficient and iodide-excess, classified by Kanno *et al.* (1996). In Kanno *et al.* (1996), the key effects for the classification were TSH response and thyroid pathology. Under iodine-deficiency type, Kanno *et al.* described the thyroid effects for iodine-deficient diet, thyroid hormone synthesis inhibitors (thionamides, aminotriazole, sulfonamides, psudohalides), deiodinase inhibitors (3-nitrotyrosine and 3,5-dinitrotyrosine), and thyroid hormone metabolism enhancers (such as phenobarbital). They noted that chemicals in this iodine-deficiency type induced sustained increase in serum TSH and diffuse hyperplasia of the thyroid. On the other hand, Kanno *et al.* (1996) generalized that the chemicals in the iodine excess type promoted thyroid carcinogenesis, with serum TSH neither substantially nor sustained increase in the chronic phase and colloid goiter. They reviewed the studies with KI, Rose Bengal B (red dye #105), erythrosine (red dye #3), iodinated glycerol, all of which contain iodide. In the study described for KI (3 mg/day/rat, or 8 mg/kg/day) given to rats in the drinking water for 24 weeks, there was no increase in TSH and the thyroid was not enlarged but colloid goiter was found (Kanno *et al.*, 1992). In a longer-term study conducted after the Kanno *et al.* review, Takegawa *et al.* (2000) found increased colloid but no thyroid tumors in rats given KI in the drinking water. TSH level was not measured in this study. Kanno *et al.* (1996) attributed excess iodide to be the cause for Rose Bengal R and erythrosine induced thyroid follicular tumors. These results for red dyes and the generalization about TSH by Kanno *et al*. (1996) suggest the pattern of MeI effects (tumor types and incidences, thyroid size, and TSH change; Kirkpatrick, 2005) is consistent with the Kanno *et al.* iodide-excess type rather than low iodide-deficiency type. Clearly, this type of comparison across experiments using different protocols and chemicals with multiple effects provides limited support, rather than definitive, evidence for a certain MOA.

Subsequent comments from the SRC compared the genotoxic MOA and the thyroid tumor promoter MOA. The genotoxic MOA was considered better supported by the weight of the evidence and that the antithyroid MOA was unlikely (**Appendix** in **Volume IV Part 1-B**). Upon evaluation of 26 week TSH data for individual animals in the rat inhalation toxicity (Kirkpatrick, 2005), the SRC modified their conclusion about the thyroid tumor promoter MOA from unlikely to plausible (Errata in **Volume IV Part 1-B**). It should be noted that this risk assessment as well as previous drafts had presented the 26 week TSH data, in summary form, in Table 21. In the thyroid tumor MOA discussion, the 12-fold significant increase of TSH for male rats at this time point was used as a support for thyroid perturbation as the MOA.

In this risk assessment, the dose-response assessment of oncogenic risk for MeI is based the overall tumor incidences at the end of the bioassay period, and includes both threshold and non-threshold approaches, as well as any promotional effects within the biological system. The threshold approach would accommodate MOA involving iodide-induced thyroid perturbation. With this approach, DPR scientists include a 10-fold factor to increase the certainty of protection against cancer effects (will be discussed in Section **V.C.2.a.**). The linear extrapolation (non-threshold) approach would include the genotoxic MOA, as well as any other factors which may have influence the final tumor outcome. The calculated risk values and RfCs will be different using these two approaches. As will be discussed under **V.C.2.b**., the need to reduce exposure will be based on the approach that showed a higher risk value, thus a lower allowed exposure.

IV.A.5.c. Other Tumors Mode of Action

There is clear evidence that salivary gland metaplasia in rats MeI exposure is caused by excess iodide. The result is consistent with the study by Takegawa *et al*. (2000). F344/CuCrj rats given KI in the drinking water, focal acinar atrophy and ductular proliferation, squamous metaplasia, and squamous cell carcinoma in the salivary gland were found in both genders of the high dose group (1000 ppm, average daily potassium iodide intake were 53 mg/kg/day and 67 mg/kg/day for males and females, respectively). In the study by French (1990) where rats and mice were given iodinated glycerol by gavage for two years, salivary gland squamous metaplasia was found in both genders and dose groups, affecting at >90% of the animals.

For astrocytomas and cervical/uterine fibromas, a genotoxic MOA would be a default assumption, in the absence of other plausible MOA. The presence of unmetabolized MeI in the brain may play a role in the cause of astrocytomas. This is suggested in the pharmacokinetic studies in the rat given ^{14}C-MeI (Sved, 2002 and 2003) where ^{14}C-radioactivity was detected in the brain (Tables 1 and 2). However, the chemical identity of the ^{14}C was not examined.

IV.A.5.d. Interspecies Extrapolation of Thyroid Tumors

An important issue related to the finding of thyroid tumors in rats is the relevance of the finding to humans. In the USEPA guidance on the assessment of thyroid tumors, the policy was to presume “chemicals that produce rodent thyroid tumors may pose a carcinogenic hazard for the human thyroid” (USEPA, 1998). The USEPA classified MeI as "Not likely to be carcinogenic to humans at doses that do not alter rat thyroid hormone homeostasis" in their risk assessment (USEPA 2005d, 2006a, and 2007). Rats were considered to be more sensitive than

humans to antithyroid agents because of their higher basal thyroid activity due to shorter half-lives and the absence of the high affinity thyroxine-binding globulin (TBG) to keep T4 bound to the protein and serve as a pool for free T4. Their basal TSH levels are elevated in an effort to maintain stable hormone levels.

A comparison of data presented in the USEPA document (1998) with available studies indicates that additional data are needed to support the species sensitivity difference (Table 58). The shorter half-life for rats is evident since rat serum hormone half-lives for T4 and T3 are less than 1 day, compared to one or more days in humans. But, the role of TBG levels in the interspecies difference is less certain. The assertion of TBG absence in rats (citing Dohler *et al.*, 1979) is not consistent with results from other studies. TBG in rats was already reported in 1970 (Davis *et al*., 1970). Molecular studies of the rat, mouse, and human TBG cDNA showed significant homology (Imamura *et al.*, 1991; Trent *et al*., 1987). In rats, the TBG level is negatively regulated by the T4 level, and is increased in response to decreased thyroid hormone levels during certain conditions such as early development, aging, fasting, and thyroidectomy (Savu *et al*., 1991; Imamura *et al*., 1991; Vranckx *et al*., 1990; Young *et al*., 1988). In humans, almost all T4, and about 46% of T3 are bound to TBG (Ganong, 2003). There are conditions which could alter TBG levels. Genetic mutation has lead to partial or complete TBG deficiency (TBG-CD) (Reutrakul *et al*., 2001), as well TBG variants with reduced T4 binding affinity (Janssen *et al*., 2000). In the TBG-CD cases, the total T4 and T3 levels were reported to be low, but free T4, free T3, and TSH were at normal levels (Miura *et al*., 2000; Reutrakul *et al*., 2001). TBG is reduced by anabolic steroids, and corticosteroids; but is increased during pregnancy, estrogen-containing medication, and infectious hepatitis (Ganong, 2003; The Merck Manual of Diagnosis and Therapy, 2004; Surks and Sievert, 1995).

Table 58. Comparison of rodent and human thyroid parameters.

Parameters	Human	Rat			Mouse	
		USEPA[a]	Other studies	MeI database[b]	USEPA[a]	MeI database[c]
Serum half-life T4 (days) T3 (days)	 5 to 9[a] 1 to 1.5[a]	 0.5 to 1 0.25		 NA NA	 0.5 to 0.75 0.45	 NA
Binding protein: High-affinity TBG Low-affinity	 Present[a] (2 mg/dL[e]) Present[a]	 Absent Present	 Present under some conditions[d] NA	 NA NA	 Absent Present	 NA NA
T4 Relative ratio PR µg/kg/day	1x[a] 1 to 9[f,g]	10x	 14 to 21[h]	NA	NA	NA
T3 PR µg/kg/day	 0.34[f]	 NA	 2.0 to 2.3[h]	NA NA	NA NA	NA NA
Serum Total T4 (µg/dL)	5 to 11[i]	NA	Wistar[j]: 4.9±0.6 SD[k,l]: 5	M: 2.2 to 3.9 F: 1.6 to 2.0	NA	M: 2.7 F: 1.8
Serum Total T3 (ng/dL)	95 to 190[i]	NA	Wistar[j]: 110±14 SD[k,l]: 73-90	M: 43 to 58 F: 68 to 82	NA	M: 71 F: 62
Serum Free T4 (ng/dL)	0.7-1.9[i]	NA	Wistar[j]: 0.89±0.04 SD[k,l]: 2	NA NA	NA NA	NA NA
Serum Free T3 (ng/dL)	0.2-0.52[i]	NA	Wistar[j]: 0.35±0.02 SD[k,l]: 0.18	NA NA	NA NA	NA NA
TSH Levels (ng/mL)	3-30[a]	200	SD[k,l]: 1.5-6.3	M: 2.3 to 2.5 F: 1.8 to 2.6	NA	M: 450 F: 280
TSH Gender difference	NA	M>F	Data for males only	M=F	M>F	M ≥ F
Carcinogenic tendency	Higher in rat than human[a]		NA	Tumors M>F	??	Tumors M>F

References: a. USEPA, 1998 and Jahnke *et al*., 2004 [(Human TSH level was calculated assuming a basal TSH value of 5 µIU/mL and a potency of human TSH of 1.5 to 15 IU/mg given in USEPA, 1998. The 200 ng/mL value for rats was stated as an assumed value in USEPA, 1998 (probably based on data from Dohler *et al*., 1979)]; b. Kirkpatrick, 2005 (Crl:CD(SD)IGS Br rats, ranges were either for different measuring time or for gender); c. Harriman, 2005a (Crl:CD-1(ICR) mice, ranges were for genders); d. Savu *et al*., 1991; Imamura *et al*., 1991; Vranckx *et al*., 1990; Young *et al*., 1988 (TBG are synthesized under some conditions); e. Ganong, 2003; f. Inada *et al*., 1975; g. Brown *et al*., 2004; h. Kinlaw *et al*., 1985; i. Greenspan and Dong, 2004; j. Shirpour *et al*., 2003; k. Hood *et al*., 1999; l. Christian and Trenton, 2003. Abbreviations: F=female, IU=international unit, M=male, NA=not available, PR=production rate, SD=Sprague-Dawley.

Another parameter considered important in the species difference in thyroid response is thyroid hormone levels. In the USEPA policy (USEPA, 1998), the T4 production rate in rats was supposed to be 10-fold higher than that for humans. This was not supported by results, which showed a 10-fold range for humans, and about a 2-fold difference between the highest values for rats and humans (Brown *et al*., 2004; Inada *et al*., 1975; Kinlaw *et al*., 1985). In addition, there are known age-related differences in hormone production. In human, the T4 production is highest during early infancy (7-9 μg/kg/day) and declines rapidly with age (3-5 μg/kg/day for 1-3 years old, 2-3 μg/kg/day for 3-9 years old, and 1 μg/kg/day for adults) (Brown *et al*., 2004). Since there were no production rate data available from the MeI toxicity studies, serum total T4 and T3 levels for humans (Greenspan and Dong, 2004), rats from published studies (Shirpour *et al*., 2003; Hood *et al*., 1999; Christian and Trenton, 2003), and rodents from MeI studies (Kirkpatrick, 2005; Harriman, 2005a) were compared. Because of the wide range, there were no distinct differences in these levels between species. The similarity in levels was also found for free T4 and T3 levels.

As for TSH level, rats are supposed to have more than 10-fold higher TSH than humans (USEPA, 1998). This was based on a human basal TSH of 3-30 ng/mL and rat TSH level of 200 ng/mL with higher levels in the male compared to the females. Though not directly cited, this value was probably based on results from Dohler *et al*. (1979) where the mean basal TSH levels in the serum for Sprague-Dawley male rats was about 300 ng/mL. On the other hand, the MeI database for control rats and published articles showed much lower values, ranging from 1.5-6.3 ng/mL (Hood *et al*., 1999; Christian and Trenton, 2003; Table 21; Kirkpatrick, 2005).

IV.A.5.e. Summary

There is sufficient evidence to consider MeI as a potential human oncogen based on the finding of thyroid tumors, astrocytomas, and cervical/uterine fibromas in laboratory animals. This oncogenicity may involve both genotoxic and non-genotoxic MOAs. Factors contributing toward the rat being more sensitive than human for thyroid tumors, as indicated by the USPA, are not sufficiently supported by available studies. Therefore, DPR scientists assume that formation of thyroid tumors in rats treated with MeI is a relevant concern for human exposure, and as a default assumption, humans are more sensitive than rats on a dose per body weight basis to the oncogenicity of MeI.

IV.A.5.f. Human Equivalent Concentration and Potency Factor

For the dose extrapolation, the approaches are nonlinear (threshold) and linear (non-threshold) for antithyroid MOA and genotoxic MOA, respectively. For the threshold approach, the POD was determined by benchmark dose analysis using the multistage cancer model and at 1% extra risk. The ED_{01} and LED_{01} are 18 ppm and 2 ppm, respectively. The HECs based on the LED_{01} of 2 ppm for thyroid tumors are 1.2 ppm and 0.39 ppm for 8-hour/day and 24-hour/day adult exposures, using the DPR methodology (**Appendix B** of **Volume I**).

For the nonthreshold approach, the potency slope factor for thyroid tumor in male rats is $5.0x10^{-3}$ mg/kg/day^{-1} from the multistage cancer model using animals at risk as determined by those who survived for at least 52 weeks (Table 22). The extrapolated human equivalent potency slope factor is 1.6×10^{-2} mg/kg/day^{-1} using an interspecies scaling factor of $(BWt_{human}/BWt_{rat})^{1/4}$ (Travis *et al.,* 1990) where the body weight (BWt) is 70 kg for human and 0.625 kg for rats from the MeI study (Kirkpatrick, 2005). Model output and equations for calculations are presented in **Appendix B** of **Volume I**. The unit risks (risk per ppb) are $6x10^{-6}$ for workers, and $2.5x10^{-5}$ for the general population.

The actual potency slope factor for astrocytoma in male rats from the current data is unknown because the incidence data are incomplete for the 5 and 20 ppm groups as discussed in the study summary (**III.D.1. Rat- Inhalation**). An estimate of the potency slope factor based on the current incidence data does not show a positive trend (linear regression analysis, p=0.068 at the high dose) for BMD modeling. It may be speculated that had all the animals were examined, the incidences at 5 and 20 ppm could increase to a point of significance. But it is also possible that they can decrease for these two groups (*i.e.*, greater increase in the denominator than the numerator). If the data are modeled as is, the potency slope (2×10^{-3} mg/kg/day^{-1}) is lower than the slope ($5x10^{-3}$ mg/kg/day^{-1}) for thyroid tumors which had higher overall incidences.

The potency slope factor for fibroma incidences in female mice is expected to be lower than those for thyroid tumors in male rats because of lower incidences. As shown in Table 27, the incidences are 0/50, 1/50/ 0/50, and 4/59 ($p<0.01$). Using these values, the potency factor is $2x10^{-4}$ mg/kg/day^{-1}.

Thus, the use of the higher thyroid potency slope factor to calculate the oncogenic risk for human exposure will protect against thyroid tumors as well as other tumors with lower incidences. The SRC recommended that the potency factor should be adjusted with age-dependent adjustment factors (ADAF) to account for potential increased sensitivity due to early childhood exposures (**Volume IV Part 1-A**). In cancer risk assessment practice, such factors are not applied to the potency. The appropriate place for the age-depended factors is in the calculation of the cancer risk and is presented in the Risk Characterization section (**IV.C.**).

IV.A.6. Summary of Human Equivalent Concentrations and Potency Factor

The critical endpoints, HECs, and potency slope factor for risk characterization are summarized in Table 59.

Table 59. Critical endpoints, HECs and potency factor for MeI risk characterization.[a]

Duration	Toxicity endpoints	Point of Departure or Potency	HEC or Unit Risk	
			Worker/ Worker bystander (8 hours)	**Bystander/ Resident (24 hours)**
Acute	Fetal death in rabbits (*Nemec, 2002d)	0.5 ppm (LED_{01})	0.23 ppm	0.081 ppm (women of child-bearing age)
	Olfactory epithelial degeneration in rats (*Kirkpatrick, 2002b)	21 ppm (NOEL)	17.1 ppm	5.7 ppm (adult) 3.5 ppm (child) 2.7 ppm (infant)
	Neurotoxicity in rats (*Schaefer, 2002)	12.8 ppm ($LED_{0.36\sigma}$)	10.4 ppm	3.5 ppm (adult) 2.2 ppm (child) 1.9 ppm (infant)
Sub-chronic	Decreased body weight in day 21 rat pups (*Nemec, 2002a)	3.0 ppm ($LED_{0.36\sigma}$)	NA	0.51 ppm (child) 0.39 ppm (infant)
	Neurotoxicity in rats (*Schaefer, 2002)	4.3 ppm (estimated LED from 12.8 ppm and MF of 3)	3.5 ppm	1.2 ppm (adult) 0.7 ppm (child) 0.5 ppm (infant)
Chronic	Salivary gland metaplasia in rats (*Kirkpatrick, 2005)	3.4 ppm (LED_{05})	2.0 ppm	0.66 ppm (adult) 0.41 ppm (child) 0.31 ppm (infant)
	Neurotoxicity in rats (*Schaefer, 2002)	1.3 ppm (estimated LED from 12.8 ppm and MF of 10)	1.0 ppm	0.35 ppm (adult) 0.22 ppm (child) 0.16 ppm (infant)
Lifetime	Thyroid tumors in rats (*Kirkpatrick, 2005)	Non-threshold: Potency 5.0×10^{-3} mg/kg/day^{-1} (rat) 1.6×10^{-2} mg/kg/day^{-1} (human)	Unit risk: 6×10^{-6} per ppb	Unit risk: 2.5×10^{-5} per ppb
		Threshold: 2 ppm (LED_{01})	1.2 ppm	0.39 ppm (adult)

a/ * indicates studies conducted under FIFRA guidelines and were acceptable to DPR. The basis for the HEC calculation was either the NOEL or the lower bound level (LED) from benchmark dose analysis for the POD, and interspecies pharmacokinetic adjustment based on DPR methodology described in **Appendix B** of **Volume I**. Under the "HEC or Unit Risk" column, all values are HECs except for unit risks from the non-threshold approach. MF=modifying factor.

IV.B. Exposure Assessment

The assessment for inhalation exposure to MeI in the air based on MeI-specific studies is summarized in this section (details are in **Volume II**). While the MeI exposure estimates are expressed both as air concentration and absorbed doses in the assessment, air concentrations are used for all exposure durations since the HECs are expressed in such term. Dermal exposure to MeI is considered negligible because the theoretical calculation indicated that dermal absorption would only add 0.01% to the total absorbed dose. Since no dermal absorption studies have been submitted to DPR, the amount of MeI absorbed through the dermal route could not be quantified. Dietary exposure is not included because the MeI intended use is preplant fumigation of the soil, and no MeI residues have been found in commodities grown on treated soil (Section **II.G.2. Residues in Soil and Plants**).

The aggregate risk for MeI exposure from multiple pathways (air, water, and diet) is not conducted because the primary route of dissipation for MeI is volatilization into the air. MeI residue levels in commodities grown on fumigated soils are generally below the LOQ. MeI is not expected to adversely impact ground water or surface water by both DPR (as discussed in **Volume III**) and USEPA (USEPA, 2007). The potential human exposure to iodide from MeI uses is discussed in **V.C.1.b. Cumulative Exposure to Iodide**.

IV.B.1. Workers

For workers directly involved in MeI fumigation, the exposure estimates are based on air concentrations measured for specific tasks using three MeI fumigation methods: tarped/raised-bed/shank injection, tarped/flat-fume/shank injection, and tarped/raised-bed/drip irrigation. The acute exposure is the upper-bound (95^{th} percentile) of measured air concentrations for an 8-hour work day. The arithmetic mean of the 8-hour TWA air concentrations for each task represents seasonal exposures of 3 months. The annual (chronic) exposure is the amortized seasonal exposure with a factor of 3-month season/12 months. The lifetime exposure is the amortized annual exposure with a factor of 40 working years over a 75 year lifetime. All exposures include a 90% protection factor for the use of air-purifying respirator by applicators, shovelmen, and tarp monitors.

For shank injection, tarp monitors have the highest 8-hour TWA acute air concentration (0.30 ppm) with a similar level for applicators (0.27 ppm) (Table 60). Other workers have much lower levels: shovelmen and shovelers and tarp handlers (0.08 ppm) and planters (0.006 ppm). For similar work tasks, the air concentrations from tarped-bed drip irrigation are much lower: 0.003 ppm (applicators), 0.015 ppm (hole punchers), and 0.004 ppm (planters). The seasonal and chronic exposures followed a similar trend as the acute exposure for these two methods, except that the planter repeated exposures are lower for drip irrigation (*e.g.*, 0.001 ppm for subchronic exposure) than for shank injection (*e.g.*, 0.004 ppm for subchronic exposure). The lifetime exposures are in the range of 0.0002 ppm to 0.008 ppm.

Table 60. Acute and repeated exposures for workers engaged in pre-plant field fumigation with MeI.[a]

Application Methods/ Workers	Air concentration (ppm)			
	Acute	Seasonal	Chronic[b]	Lifetime
Shallow Shank Injection-tarped (broadcast and bedded)				
Applicator	0.27	0.06	0.015	0.008
Shovelman and shoveler	0.08	0.02	0.005	0.003
Tarp monitor	0.30	0.04	0.01	0.005
Tarp hole puncher, cutter	0.08	0.03	0.0075	0.004
Planter	0.006	0.004	0.001	0.001
Drip Irrigation- tarped (bedded)				
Applicator	0.003	0.001	0.0003	0.0002
Hole puncher	0.015	0.01	0.0025	0.001
Planter	0.004	0.001	0.0003	0.0002

a/ Data from **Volume II**. The exposures of applicators, shovelmen, shovelers, tarp monitor include a respiratory protection factor.

b/ Chronic exposure in ppm is calculated by multiplying seasonal exposure in ppm by a factor of 3 months/12 months, the same factor used in **Volume II** for the absorbed dosage calculations.

c/ Lifetime exposure is chronic exposure amortized with a factor of 40 work years/75 year lifetime.

IV.B.2. Bystanders and Residents

People not directly involved in the fumigation are categorized into three groups: worker bystanders (working in the next field), non-worker bystanders (present at the 152 meter buffer zone), and residents who live next to application sites. Their exposures are determined by modeling of air data collected from samplers placed around treated fields using the 3 different fumigation methods in a total of 7 studies (Table 61). They are the air concentrations at the 152-meter buffer zone, the minimum buffer zone in the USEPA approved labels, and 48 hours after the application to a 40-acre field, the maximum acreage allowed per day. For acute exposures, an individual is assumed to be located downwind throughout the exposure interval at the maximum TWA air concentration. The 24-hour exposure duration assumes that the indoor and outdoor air concentrations are the same. The seasonal exposure is 0.07 μg/L (0.012 ppm) based on the 2-week average concentration calculated from all air monitoring studies and an adjustment for changing wind directions. Chronic and lifetime exposures are not calculated for bystanders because they are not expected to be in the same location continuously. For bystanders, the highest exposures are those from drip irrigation (Table 61).

Residents living in the region where MeI is used are potentially exposed throughout the year. Their chronic exposures are calculated by reducing the seasonal values by a factor of 3 months of use over a 12-month period. The lifetime exposure is the same as the chronic exposure with the assumption that a resident would live in a home adjacent to the field for a lifetime of 70 years.

Worker Bystanders

For exposure only during the 8-hour work day, the TWA air concentrations for acute exposure range from 0.6 to 1.6 ppm (Table 61). The seasonal air concentration is 0.012 ppm for all application methods.

Non-worker Bystanders

For 24-hour of exposure, the TWA air concentrations for acute exposure are 0.3 ppm (drip irrigation) and 0.2 ppm (both shank injection methods) (Table 61). The seasonal air concentration is 0.012 ppm for all application methods.

Residents

For residents living next to application sites, the air concentration for acute exposure is 0.3 ppm from drip irrigation, the method resulting in the highest MeI 24-hour TWA air concentration (Table 61). The 24-hour TWA air concentrations are 0.012 ppm (seasonal exposure) and 0.003 ppm (chronic exposure). The lifetime exposure is the same as that (0.003 ppm) for chronic exposure.

Table 61. Acute and repeated exposures to MeI for bystanders and residents.[a]

Groups/ Application Methods	Air concentration (ppm)			
	Acute	**Seasonal**	**Chronic**	**Lifetime**
Worker bystanders				
Drip irrigation, raised bed	1.6	0.012	NA	NA
Shank injection, raised bed	0.6	0.012	NA	NA
Shank injection, flat-fume	1.0	0.012	NA	NA
Drip irrigation, raised bed	0.3	0.012	NA	NA
Shank injection, raised bed	0.2	0.012	NA	NA
Shank injection, flat-fume	0.2	0.012	NA	NA
Bystander children (3-5 years old)				
Drip irrigation, raised bed	0.3	0.012	NA	NA
Shank injection, raised bed	0.2	0.012	NA	NA
Shank injection, flat-fume	0.2	0.012	NA	NA
Bystander infants (<1 year old)				
Drip irrigation, raised bed	0.3	0.012	NA	NA
Shank injection, raised bed	0.2	0.012	NA	NA
Shank injection, flat-fume	0.2	0.012	NA	NA
Residents living next to application sites				
Adults	0.3	0.012	0.003	0.003
Children	0.3	0.012	0.003	NA
Infants	0.3	0.012	0.003	NA

a/ Data are from **Volume II**. Seasonal ppm is derived from 0.07 μg/L. Chronic ppm is calculated multiplying 0.07 μg/L (0.012 ppm) by a factor of 3 months/12 months, the same factor used in the calculation of absorbed dose. Lifetime exposure for resident is the same as that for chronic exposure. NA=exposure available or expected.

IV.C. Risk Characterization

The potential health risk associated with the use of MeI is considered for workers, bystanders, and residents is calculated as the margin of exposure (MOE), a ratio of toxicity represented by HECs, and human exposure levels. The risk for lifetime exposure is calculated as a MOE as well as probability for excess cancer risk. For the residents, the concern for potential increased cancer susceptibility due to early childhood exposure to carcinogens is addressed using age-dependent adjustment factors (ADAF). The recommended ADAFs are: 10 (last trimester/ birth up to 2 years old) and 3 (2 to < 16 years old) in the calculation of risks associated with carcinogens with a mutagenic MOA by the USEPA (2005e), and for all carcinogens by the OEHHA (2009). The appraisal of these MOE and risk values is discussed under **V.C.** after the discussion on the need for an additional uncertainty factor.

IV.C.1. Workers

For workers, the lowest acute MOEs are calculated for the fetal toxicity endpoint. The acute MOEs for fetal death are 1 (applicators, tarp monitors) to 37 (planters) for shallow shank injection and 15 (hole puncher) to 77 (applicator) for drip irrigation (Table 62). Higher acute MOEs are calculated for nasal toxicity; they range from 57 (tarp monitors) to 2,850 (planters) for shank injection, and from 1,140 (hole punchers) to 5,700 (applicators) for drip irrigation. For neurotoxicity, the acute MOEs range from 35 (tarp monitors of shallow shank injection) to 3,467 (applicators of drip irrigation). The seasonal MOEs range from 58 to 875 for shank injection, and 350 to 3,500 for drip irrigation. The chronic MOEs range from 67 to 6,667 for both types of application method and both toxicity endpoints. The lifetime MOEs range from 150 to 7,500, and probability of risks range from $1x10^{-6}$ to $5x10^{-5}$ for the application methods.

Table 62. Margins of exposure and lifetime risks for workers engaged in pre-plant field fumigation with MeI.[a]

Application Methods/ Workers	Acute MOE			Seasonal MOE	Chronic MOE		Lifetime	
	Fetal Death	Nasal Toxicity	Neuro-toxicity	Neuro-toxicity	Salivary metaplasia	Neuro-toxicity	MOE	Risk
Shallow Shank Injection-tarped (broadcast and bedded)								
Applicator	1	63	39	58	133	67	150	$5x10^{-5}$
Shovelman, shoveler	3	214	130	175	400	200	450	$2x10^{-5}$
Tarp monitor	1	57	35	88	200	100	225	$3x10^{-5}$
Tarp hole puncher, cutter	3	214	130	117	267	133	300	$2x10^{-5}$
Planter	38	2,850	1,733	875	2,000	1,000	2,250	$3x10^{-6}$
Drip Irrigation-tarped (bedded)								
Applicator	77	5,700	3,467	3,500	6,667	3,333	7,500	$1x10^{-6}$
Hole puncher	15	1,140	693	350	800	400	900	$8x10^{-6}$
Planter	58	4,275	2,600	3,500	6,667	3,333	7,500	$1x10^{-6}$

a/ The MOEs were calculated with HECs and unit risks as specified in Table 59 and equations in **Appendix B** of **Volume I**.

IV.C.2. Bystanders and Residents

Worker Bystanders

For worker bystanders, the acute MOEs for fetal death are 0.1 to 0.4 (Table 63). The acute MOEs for nasal toxicity are 11 (drip irrigation), 17 (shank injection, flat fume) and 29 (shank injection, raised bed). For neurotoxicity, the acute MOEs range from 7 (drip irrigation) to 17 (shank injection, raised bed). The MOE for seasonal exposure is 292 for all three methods.

Other Bystanders

For adult bystanders, the acute MOE for fetal death ranges from 0.3 to 0.4 (Table 63). When based on nasal toxicity, the acute MOEs for all age groups range from 9 to 29. For neurotoxicity, the MOEs range from 6 to 18. The lowest seasonal MOEs are 100 (adults, neurotoxicity endpoint), 43 (children, reproductive toxicity endpoint), and 33 (infants, reproductive toxicity endpoint).

Residents

For residents living next to application sites, the acute MOEs for adults are 0.3 (fetal death), 19 (nasal toxicity), and 12 (neurotoxicity) (Table 63). For children and infants, they are 9 and 12 (nasal toxicity) and 7 and 6 (neurotoxicity), respectively. The seasonal MOEs based on neurotoxicity are 100 (adults), 58 (children) and 42 (infants). When based on reproductive toxicity, the MOEs are 43 for children and 33 for infants, with slightly higher MOEs for neurotoxicity. The chronic MOEs are 103 to 220 for salivary gland metaplasia, and 53 to 117 for neurotoxicity. The lifetime risks are MOE of 130 and a risk probability of $8x10^{-5}$ when calculated based on adult exposure. The age-adjusted risk is 1.8-fold higher at $1.4x10^{-4}$ using the following equation and the risk calculated for adult exposure:

$(10 \times 2.25/70 \text{ years} \times 8 \times 10^{-5}) + (3 \times 14/70 \text{ years} \times 8 \times 10^{-5}) + (54/70 \text{ years} \times 8 \times 10^{-5}) = 1.4x10^{-4}$

Table 63. Margins of exposure and lifetime risks for bystanders and residents exposed to MeI.[a]

Groups/ Application Methods	Acute MOE			Seasonal MOE		Chronic MOE		Lifetime	
	Fetal Death	Nasal Toxicity	Neuro-toxicity	Neuro-toxicity	Repro-toxicity	Salivary gland meta-plasia	Neuro-toxicity	MOE	Risk
Worker bystanders									
Drip, raised bed	0.1	11	7	292	NB	NA	NA	NA	NA
Shank, raised bed	0.4	29	17	292	NB	NA	NA	NA	NA
Shank, flat-fume	0.2	17	10	292	NB	NA	NA	NA	NA
Non-worker bystander adults									
Drip, raised bed	0.3	19	12	100	NB	NA	NA	NA	NA
Shank, raised bed	0.4	29	18	100	NB	NA	NA	NA	NA
Shank, flat-fume	0.4	29	18	100	NB	NA	NA	NA	NA
Bystander children (3-5 years old)									
Drip, raised bed	NB	12	7	58	43	NA	NA	NA	NA
Shank, raised bed	NB	18	11	58	43	NA	NA	NA	NA
Shank, flat-fume	NB	18	11	58	43	NA	NA	NA	NA
Bystander infants (<1 year old)									
Drip, raised bed	NB	9	6	42	33	NA	NA	NA	NA
Shank, raised bed	NB	14	10	42	33	NA	NA	NA	NA
Shank, flat-fume	NB	14	10	42	33	NA	NA	NA	NA
Residents living next to application sites									
Adults	0.3	19	12	100	NA	220	117	130	$8x10^{-5}$
Children (3-5 years old)	NB	12	7	58	43	137	73	NB	$1.4x10^{-4}$ (age-adjusted)[b]
Infants (<1 year old)	NB	9	6	42	33	103	53	NB	

a/ The acute MOEs were calculated with HECs and unit risks as specified in Table 59 and equations in **Appendix B** of **Volume I.** Abbreviations: NA=chronic exposure not expected, NB=not calculated because exposure duration was not lifetime.

b/ Age adjusted risk takes into consideration of age-related sensitivity using the following equation:

$$(10 \times 2.25/70 \text{ years} \times 8 \times 10^{-5}) + (3 \times 14/70 \text{ years} \times 8 \times 10^{-5}) + (54/70 \text{ years} \times 8 \times 10^{-5}) = 1.4x10^{-4}$$

V. RISK APPRAISAL

Every risk assessment has inherent limitations on the application of existing data to estimate the potential risk to human health. Therefore, certain assumptions and extrapolations are incorporated into the hazard identification, dose-response assessment, and exposure assessment processes. These, in turn, result in uncertainty in the risk characterization, which integrates all the information from the previous three processes. The degree or magnitude of the uncertainty can vary depending on the availability and quality of the data, and the types of exposure scenarios being assessed. The appraisal of the calculated risk considers the data and approaches used in the risk assessment process, and makes recommendations regarding the risks associated with the exposure to the chemical.

V.A. Hazard Identification

The main uncertainty in hazard identification is the lack of sufficient data to address toxicity in the young. NOELs or threshold benchmark doses generated from observations of adult animals may not be sufficiently protective, if young animals are more sensitive from direct exposure to MeI. While developmental toxicity and reproductive toxicity included *in utero* and lactational exposures of the fetuses and newborn, respectively, they provide limited information about potential post-natal effects. For MeI, studies which examine the developmental neurotoxicity for animals exposed *in utero*, as well as those examining the postnatal effects of MeI on the nervous system of young animals are not available. The absence of such studies can lead to the underestimation of the toxicity based on the current database.

At the recommendation of SRC, this risk assessment has replaced the POD for rabbit pre-natal fetal death at the 2 ppm (6 hr/day) NOEL used in the August 2009 draft risk assessment with the LED_{01} of 0.5 ppm from nested BMD approach. As noted, the 2 ppm is at approximately LED_{04}. The choice of BMR at 1% excess death recommended by the SRC is generally within the DPR's practice for considering the seriousness of the effect. However, with the wide data variability for this endpoint (*e.g.*, 1.8±6.4% death per litter at the controls), the application of 1% BMR to this dataset carries some uncertainty of being well within the at normal designation in the background distribution.

A clarification is needed for the application of an interspecies 10-fold UF in the context of its application. The SRC noted that DPR should "restore" the interspecies UF to 10-fold or "raise" it to 10-fold (page 7 and **Appendix B** in **Volume IV Part 1-A**). These comments may imply that DPR scientists have failed to implement the convention of applying the default 10-fold UF when in fact this convention has been fully utilized. The confusion may have stemmed from the steps in risk assessment at which the UF is applied. The convention for the 10-fold factor is that it can be divided into two components (*i.e.*, PK and PD factors) and that each can have equal contribution (*i.e.*, 3-fold factor, or 3.16-fold more precisely). Thus, a full 10-fold factor is used when the starting point is the POD established from animal studies. On the other hand, a 3-fold factor is used when applying the interspecies UF to the HEC. As the term HEC would indicate, it is a human instead of animal exposure level that came from either PBPK model or by dividing the animal POD by first 3-fold interspecies UF for interspecies PK difference. The confusion may have also stemmed from looking at the apparent magnitude of reduction from NOEL to HEC. A comparison of HECs from DPR's PBPK and DPR's default approaches were previously presented and further illustrated in Section VI.A that includes the

application of interspecies UF. Suffice to note that care should be taken to conceptually tracking the use of UF by numerically comparing between NOEL and HEC since other multipliers may be involved, *e.g.*, the exposure for the former is usually for a fraction of day while the latter was derived for a 24-hr period.

It should be noted that the use of 3-fold UF on HEC from PBPK model was recognized in by the SRC in one place (page 7) but not the second (**Appendix B)** of their comments (**Volume IV Part 1-A**). The latter comment would imply that no interspecies adjustment was accounted for in the PBPK model, when in fact the model is designed precisely for this purpose. Thus, when the PBPK model is accepted for use, a clear rationale is needed for deviating from the default 3-fold UF. If the question of adequacy for this 3-fold UF comes from concerns about variability in humans, it is noted that the default 10-fold inter-individual UF is subsequently applied. For transparency sake, the above discussion pertains only to issues regarding the interspecies UF and does not include considerations for any possibility of inter-individual variation greater than 10.

With respect to the use of MeI formulations in field fumigation, an additional toxicity concern is co-exposure to chloropicrin, which can be up to 75% of total active ingredient in the formulations. Chloropicrin is a sensory and respiratory irritant in humans and has systemic toxicity including reduced body weight and food consumption, genotoxicity, and lung tumors in laboratory animals (DPR, 2009). Several developmental and reproductive effects were seen in laboratory animal studies; they are reduced number of implantation sites, increased pre- and post-implantation losses, late-term abortions, and visceral and skeletal variations in fetuses. Chloropicrin's mechanism of toxicity is not well understood, but it may be related to its reaction with thiol groups in proteins like glutathione and hemoglobin, and inhibition of pyruvate and succinate dehydrogenase. Since MeI and chloropicrin are applied to the field at the same time, the combined toxicity of these two pesticides need to be considered. The few studies available (described under Sections **III.B.7** and **III.B.8**, Table 5) are insufficient to determine if there is any potentiation of toxic effects when humans are exposed to both pesticides at the same time. Since the concentrations of MeI and chloropicrin are relative in the formulations, there should be greater concern about chloropicrin toxicity when the MeI formulation contains 75% of chloropicrin, compared to the one containing 2% chloropicrin.

V.B. Exposure Assessment

The uncertainty associated with the exposure estimates is discussed in details in **Volume II**, and is summarized briefly in this section. Sources of uncertainty included the use of single default breathing rates for different age groups, use of field spike data, and estimating exposure with the assumption of a linear relationship between number of acres treated and worker exposure. These could lead to over- or under-estimation of exposures.

Some assumptions in air modeling likely lead to overestimation of bystander acute exposures. They were: location (present directly downwind at the buffer zone), meteorological condition (constant wind speed, wind direction, and atmospheric stability), exposure duration (present at the buffer zone for the entire 8 or 24 hours), and constant flux with application size. The bystander long-term exposures are likely intermittent since MeI is used only as a pre-plant fumigant. The exposure assessment did not estimate potential iodide exposures from MeI.

V.C. Risk Characterization

Uncertainties in the risk estimates are the result of limitations in the pharmacokinetic and toxicology study designed to address specific exposure scenarios, and inadequate exposure data to derive the actual human exposure. To be health protective, conservative assumptions are made in the application of the NOELs and in the exposure estimates, and the evaluation of estimates. Because a default methodology was used to derive the HEC, they do not include the potential 16-hour of exposure to MeI at ambient concentrations during non-working hours by workers.

In this section, the basis for the benchmarks to evaluate the MOEs and potency slope factors are discussed. The emphasis is on why an additional uncertainty factor needs to be added to the conventional benchmark level.

V.C.1. Non-Cancer Effects

When the HEC is used in the MOE calculation, a benchmark MOE of 30 is considered health protective such that any exposure with a MOE $\geq$ 30 would not be of significant health concern. This benchmark of 30[22] assumes that humans are more sensitive than the most sensitive laboratory animal to MeI toxicity, with a default factor of 3 for interspecies pharmacodynamic differences (PD_{animal}, a factor of $10^{0.5}$, rounded to 3), and a default factor of 10 for interindividual differences in the PK and PD within the human population (PK_{human} and PD_{human}).

In the risk characterization for MeI, the benchmark MOE of 30 may be insufficient because of the following:

(1) The lack of data for the evaluation of potential neurodevelopmental effects, in the presence of evidence for MeI perturbation of maternal and fetal thyroid functions,

(2) The substantial post-natal death in neonates of rats and rabbits associated with pre- and post- natal exposure to NaI and KI, and

(3) The high iodide levels from inhalation exposure to MeI at the Reference Concentration (RfC), when compared with current health-based limits of iodide intake.

V.C.1.a. Pre- and Post-natal Sensitivity

The current MeI database with rabbits is limited to an examination of pre-natal survival as late resorption or dead fetuses (see studies under **III.G.** Developmental Toxicity). There is insufficient information on the potential of MeI to cause pre- and post-natal developmental neurotoxicity.

[22] Mathematically, the benchmark MOE is 31.6 ($10^{0.5}$ x 10) instead of 30. But for simplicity, it is referred to as 30-fold. Thus, the RfCs (Table B-2) are the result of 3 (pharmacodynamic) x 10 (interspecies) uncertainty factors.

V.C.1.a.(1) Thyroid Perturbation and Developmental Effects

There is a concern for potential developmental toxicity from MeI exposure because neurodevelopmental effects associated with thyroid toxicity is well documented (Howdeshell, 2002; Zoeller *et al*., 2002; Zoeller, 2003). Thyroid hormone dysfunction affects many fetal organs, *e.g.*, heart, liver, muscle, and development. Before the onset of fetal thyroid functions, maternal thyroid hormone is especially critical for the development of the fetal brain (Morreale de Escobar *et al*., 2004). While adults may recover from transient thyroxinemia without permanent consequences, the effects on developing fetuses can be permanent. Many of these effects (*e.g.*, mental retardation, neurological deficit) are neither clinically overt nor necessarily detected immediately after birth, especially in laboratory animals. So far, early intervention alone has not been able to eliminate all effects stemming from fetal hypothyroxinemia in humans (Zoeller, 2003). The manifestation of thyroid-related effects on the fetal brain is highly specific to the timing and region of brain development. A threshold, the smallest change in thyroid hormone required for observing significant effects on various gene expressions, has not been delineated (Table 1 in Zoeller, 2003).

Excess iodide may result in neurological damage causing altered neurobehavioral effects. PBPK modeling for MeI predicted an extraordinarily high accumulation of iodide in the fetal thyroid (**Appendix A** of **Volume I**). In the study with KI by Vorhees *et al.* (1984), Sprague-Dawley rats were fed diets containing 0.025, 0.05, or 0.1% KI 14 days before mating and during mating. The treatment continues for pregnant dams throughout gestation and lactation periods, and for offspring up to 90 days of age. The corresponding iodide levels were 22, 44-46, or 92-93 mg iodide/kg/day during pre-mating and gestation periods, and 34, 66, or 140 mg iodide/kg/day during lactation period. No fetal death occurred (with respect to number of litters with <8 live offspring, and numbers of born fetus per litter) at 0.025% and 0.05% KI. However, many significant ($p<0.05$) developmental effects were reported at these two dose levels. At 0.025% KI, effects reported during post-weaning period were: higher errors in swimming M-maze, lower mean number of wheel revolutions during the dark cycle, and increased number of trials to criterion on rotorod performance. Additional effects were reported during the pre-weaning periods at the next higher dose of 0.05% KI. They included: decreased body weight, 1 day delay in the development of auditory startle response, delayed olfactory orientation towards home-cage scent, and reduced swimming limb movements. Post-weaning body weight was also reduced.

Another illustration for the need of evaluating post-natal MeI toxicity is in a report by Morales de Villalobos *et al*. (1986) at an apparently lower maternal iodide dose than the above study by Vorhees *et al*. (1984). Changes in brain enzyme levels were detected during post-natal days 5 - 30 in rat pups of dams that received 1.1 mg/day iodide in drinking water during pregnancy and lactation period. These marker enzymes include glucose dehydrogenase, phosphofructokinase, malic enzymes, succinate dehydrogenase, and hexokinase. The authors suggested that the brain enzyme profile indicated a bimodal thyroid status in pups that received iodide indirectly (pre-natal via maternal exposure, post-natal via breast milk) or directly (post-natal via drinking water).

V.C.1.a.(2) Post-natal Death

Published literature suggests that post-natal death in rabbits from MeI exposure should also be of concern. Current MeI studies were conducted with sacrifice up to GD 29 (Nemec, 2002d) and not post-natally. Marked reduction in the survival of neonates associated with pre- and post-natal iodide exposure was reported by Ammerman *et al.* (1964) and Arrington *et al*. (1965). From the data for post-natal survival, Arrington *et al*. (1965) reported a 30% survival of 3 days old rabbit pups from does that received the lowest tested level of 250 ppm iodide in the diet (9 mg iodide/kg/day) for 2 days before parturition (*i.e.*, equivalent to GD 29-30), while the pup survival in the control group was 91%. This iodide level in the diet is comparable to the total iodide at the MeI LOEL of 10 ppm (7.6 mg MeI/kg/day, or 6.8 mg iodide/kg/day; Nemec, 2002d). The same authors also reported a mere 3% survival to day 3 among rabbit pups from does that received 500 ppm iodide in the diet (18 mg iodide/kg/day) starting 5 days before parturition (presumably GD 26-30). In a cross-fostering study, Ammerman *et al.* (1964) reported a 33.3% survival to day 10 for rat pups that received pre-natal iodide exposure through the maternal diet at 2,500 ppm (150 mg/kg/day) but were fostered by non-treated dams. This is much lower than the 93.8% survival of non-iodide treated pups fostered by non-treated dams. The lactational effect is evident in the 65.6% survival of non-treated pups fostered by iodide-treated dams.

V.C.1.b. Cumulative Exposure of Iodide

DPR scientists are concerned with the additional iodide body burden from the conversion of MeI to iodide in the body after MeI inhalation exposure, and iodide in the water from the degradation of MeI after soil treatment. Excess iodide may cause a transient reduction in circulating T4, T3, and an increase in TSH (ATSDR, 2004). In addition to pre- and post-natal developmental toxicity already discussed, excess iodide may contribute to autoimmune thyroid disease in susceptible individuals. Thyroid autoimmunity may contribute to miscarriages, fetal death, and possibly childhood cognition, and postpartum depression (Smallridge *et al*., 2005).

The need to ensure safety of exposure to halides from pesticides has been addressed in the USEPA and DPR risk assessments for sulfuryl fluoride (SF), which included total fluoride intake from the use of SF and from other sources (USEPA, 2006b; DPR, 2006). With MeI, the USEPA is apparently only concerned with iodide in the air, as a result of MeI degradation after application (USEPA, 2007). This level was considered to be "lower than those expected to cause toxic effects," but the data to support this statement were not provided in their risk assessment. In the USEPA evaluation of MeI in the drinking water, no risk was identified for MeI but it was not clear if iodide contamination was considered.

V.C.1.b.(1) Health-based Standards

Major sources of human iodide intake include drinking water, iodide-containing table salt, natural occurrence in food, inclusion in food additives, vitamin and mineral supplements, and therapeutics. The current iodide Recommended Daily Intake (RDI) for vitamins and minerals is 150 μg/day, as specified in 21CFR 101.9 (CFR, Code of Federal Regulation). A drinking water Maximum Contamination Level (MCL) for iodide has not been established by USEPA. No iodide Reference Dose (RfD) or RfC for inhalation is available.

Table 64 summarizes the current health-based standards for iodide intake from (1) the dietary reference intakes published by the Institute of Medicine (IOM) of National Academy of Sciences (IOM/NAS; NAS, 2000), (2) as proposed for updating WHO (World Health Organization) standards (Delange, 2007), and (3) 21 CFR 172.375 that provides the maximum single day iodide intake for food additives. The iodide thresholds for young children are proportionally calculated from the standards for adults based on age-specific body weights.

The NAS Recommended Dietary Allowance (RDA) is the average daily dietary intake "sufficient to meet the nutrient requirement of nearly all (97 to 98 percent) healthy individuals in a particular life stage and gender group" (NAS, 2000). The Tolerable Upper Intake Level (UL) is the highest average daily intake that is "likely to pose no risk of adverse health effects to almost all individuals in the general population" (NAS, 2000). The NAS report emphasized that there is no established benefit for intakes above the RDA or tolerable UL.

In comparison, the Center for Disease Control (CDC) ATSDR established the Minimum Risk Level (MRL) for an estimated daily exposure that is "likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure" (ATSDR, 2004). The acute (1-14 days) and chronic MRL for iodide is 0.01 mg/kg/day. This level is 113 - 153 µg/day for an 11.3 - 15.3 kg child (1-3 years old) (USEPA, 1997) and 700-800 µg/day (including a background of 200 µg/day exposure) for a 70 kg reference adult. The MRLs are comparable to, but slightly lower than, the tolerable UL established by NAS (Table 64). Thus, for the following discussion on the excess iodide exposure from MeI, the RDA can be viewed as the approximate population background intake while the tolerable UL is the level that should not be exceeded. It is understood that sensitive individuals are not included in these standards (NAS, 2000), and the subject is further discussed in the section **V.C.1.b.(2)**.

Table 64. Current health criteria for iodide intake.

Population Groups	Iodide intake (µg/day)				
	NAS 2000[a]		Delange 2007[b]	21 CFR[c]	ATSDR, 2004
	RDA	Tol-UL	Optimal	Maximum	MRL
Infants	-	-	90	45	-
1 - 3 years	90	200	-	105	113-153
4 - 8 years	90	300	-	225	
9 - 13 years	120	600	-	-	
14 - 18 years	150	900	-	-	
19 - >70 years	150	1,100	-	-	700-800 (70 kg adult, includes 200 µg/day background)
Pregnancy ≤ 18 years- 50 years	220	900 - 1,100	250-300	300	
Lactation ≤ 18 years- 50 years	290	900- 1,100	225-350	300	

a/ RDAs: Recommended Dietary Allowances; Tolerable UL: maximum intake likely to pose no risk of adverse effects in healthy individuals.

b/ The levels for pregnancy and lactation periods are estimated based on the increased demand for fetuses and the optimal amount in breast milk, but they may reach a point of maternal side effects (Delange, 2007)

c/ Maximum single day iodide intakes established for food additive for KI as in CFR 172.375.

V.C.1.b.(2) Sensitive Populations

The following remarks regarding sensitive individuals to excess iodide are stated in the IOM/NAS summary table of Dietary Reference Intake table:

> "Individuals with autoimmune thyroid disease, previous iodine deficiency, or nodular goiter are distinctly susceptible to the adverse effect of excess iodine intake. Therefore, individuals with these conditions may not be protected by the UL for iodine intake for the general population." (IOM/NAS, 2000)

Depending on the level of excess iodide exposure, people in areas of deficient, mild, or moderate iodide without underlying thyroid disease may also have greater risk. Oral ingestion of iodide can also produce allergic reactions in sensitive individuals. Iodide is actively concentrated in the lactating mammary gland due to increased expression of sodium/iodide symporter (NIS) (Pearce *et al*., 2008). Thus, nursing infants can receive excess iodide exposure through breast milk from maternal MeI exposures.

Based on the effects of thyroid perturbation by MeI, people with clinical and subclinical thyroid disease[23] or a lack of adaptation to the antithyroid action of iodide are expected to be at greater risk to further thyroid perturbation. They include patients with Graves disease, receiving exogenous thyroid hormone therapeutics or thyroid active drugs, recovering from treatment of hyperthyroidism, pregnancy, fetal thyroid precondition, genetic defects, or people taking other medications (*e.g.*, dopamine, glucocorticoids, dobutamine) (Surks and Sievert, 1995; Wilson and Curry, 2005; Fisher 1997).

[23] Defined by Wilson and Curry (2005) as having lowered serum thyroid-stimulating hormone concentration, 0.1-0.45 µU/mL) when serum free T3 and T4 is within normal range.

Higher sensitivity may also be related to a low capacity for oxidative stress. Preterm neonates are at greater risk of oxidative stress because the maternal-to-fetal transfer is incomplete during the final gestation period, and their antioxidant defense is not yet matured (Robles *et al*., 2001). Included in other age groups that have lower GSH are young adults and older people (Lavoie and Chessex, 1997 and 1998; Erden-Inal *et al*., 2002; Hussain and Ali, 1998). Individuals with a genetic low expression of GSH may also be more sensitive.

Active or very active persons with higher breathing rates than the values used in this risk assessment may result in higher MeI exposure, thus associated increase in iodide intake. Thus they are expected to have greater risk from MeI exposure.

V.C.1.b.(3) Additional Iodide Exposure from MeI

DPR's evaluation of MeI environmental fate showed a potential for iodide contamination of the ground water under certain conditions (detailed discussion in section C. of **Volume III**). The scenario is where the soil is known to be vulnerable to ground water contamination and the ground water is shallow, which exists on the east side of the San Joaquin Valley in Fresno County. Under worst-case ground water scenario assumptions, the upper-bound estimate of iodide in the ground water is 18 ppm. Using this 18 ppm iodide level as the residue levels in all sources of water for human consumption, the human exposure to iodide (expressed as mg/kg/day) was calculated using the Dietary Exposure Evaluation Model (DEEM™, version 7.74), and The DEEM™- Food Commodity Ingredient Database (DEEM-FCID™, version 2.03[24]) (Table 65). The DEEM-FCID 50th percentile and 95th percentile water consumption rates for adults are 0.8 L/day and 2.7 L/day, respectively. The exposures to iodide in the ground water far exceeded the ATSDR acute (1-14 days) and chronic minimal risk level (MRL) of 0.01 mg iodide/kg/day (Table 64). This result indicates that DPR needs to have additional information for the evaluation of ground water contamination if MeI is to be used for soil fumigations. As a comparison, the U.S. Geological Survey detected iodide in 234 of 256 wells in California (2004-2007) with concentrations ranging from 0.001 to 2.4 mg/L, and a mean of 0.08 mg/L (0.08 ppm).

[24] DEEM™ - FCID version 2.03, Exponent <http://www.exponent.com/home.html>. DEEM™ is a mathematical model that contains a version of the USDA Continuing Survey of Food Intake by Individuals (CSFII), which reports food consumption from a representative sample of the U.S. population, including California residents. CSFII translated into basic units of agricultural commodities or commonly analyzed food form.

Table 65. Exposure to iodide in the ground water from the use of MeI.

Population groups	Exposure[a] mg iodide/kg/day (based on 18 ppm in water)		% MRL[b] (MRL= 0.01 mg iodide/kg/day)	
	50th percentile	95th percentile	50th percentile	95th percentile
All infants	0.337	1.929	3,370	19,294
Children 3-5 years	0.360	1.152	3,600	11,520
Adults	0.198	0.720	1,980	7,200

a/ Human exposure to iodide (expressed as mg/kg/day) was calculated using the Dietary Exposure Evaluation Model (DEEM™, version 7.74), and The DEEM™- Food Commodity Ingredient Database (DEEM-FCID™, version 2.03).

b/ ATSDR acute (1-14 days) and chronic MRL (ATSDR, 2004). Exposure/MRL x 100%.

For the evaluation of iodide exposure from MeI inhalation exposure, potential iodide limit was extrapolated from existing health standard. Assuming a tolerable additional iodide (TAI) intake for MeI can be estimated as the difference between the NAS RDA and the tolerable UL, the maximum iodide allowed from MeI exposure is 110 µg/day for 1 - 3 years old and 210 µg/day for 4 -8 years olds. A MeI RfC of 1 ppb would result in an estimated additional iodide intake of 42 µg/day and 50 µg/day, levels well below the TAI, using the following equation:

Additional iodide exposure = RfC (ppb) x 5.65 (µg/m^3)/ppb x BR x (127/142)

The ratio of molecular weight of iodide (127) to MeI (142) is used to account for the molecular weight of iodide in MeI. The breathing rates (BR) are: 8.3 m^3/day for 1 - 3 years old and 10 m^3/day for 4 - 8 years old.

DPR scientists are recommending that the MeI RfC be set at no higher than 1 ppb level because these iodide calculations from the RfC do not include the additional iodide exposure through breast milk from maternal exposure to the same MeI concentration, nor do they include considerations for sensitive individuals within each population age category. In addition, the rates for active and very active persons (infants to 70 years old) are 15 - 30% higher, resulting in higher iodide exposure (USEPA, 2008b).

V.C.1.c. Additional Uncertainty Factor

An additional uncertainty factor is considered for young children exposed to MeI because of the serious and irreversible nature of neurodevelopmental effects that have not been studied, the post-natal mortality from excess iodide that needs further study in the context of MeI exposure, and the level of excess iodide in MeI being added to the background iodide intake. The current default risk assessment approach for taking into account data gaps, especially lacking information for pre- and post- natal developmental toxicity for chemicals with evidence of neurodevelopmental potential, is to apply an additional uncertainty factor ($UF_{additional}$), or modifying factor, to the final RfC determination. This $UF_{additional}$ is usually 3- or 10-fold, depending on the weight of evidence for the concern, data availability, and adversity of effects of concern.

In the previous and current risk assessment documents, DPR scientists have applied a 10-fold $UF_{additional}$ toward the determination of the MOE benchmark and the calculation of the reference concentration for the fetal death endpoint. This factor is applied to the fetal death endpoint because this effect is the most sensitive endpoint as a result of fetal exposure to MeI. Fetal death and the potential for developmental neurotoxicity are most likely not caused by the same MOA. When an effect that has not been tested (*i.e.* developmental neurotoxicity) but can realistically be expected to be more sensitive than the most sensitive endpoint detected (*i.e.* fetal death), an additional UF is applied to the detected endpoint. This default approach does not necessarily imply the same MOA for the two endpoints. The SRC (**Volume IV Part 1-A**) concurred that this additional uncertainty factor to address developmental neurotoxicity is necessary

In addition, the SRC indicated that a10-fold factor should also be applied to the neurotoxicity because of deficiency in the data for neurotoxicity concerns (**Volume IV Part 1-A** and **-B**). The acute neurotoxicity study (Schaefer, 2002) did not fully investigate the neurotoxicity potential of MeI, and the lack of neurotoxicity testing after repeated exposures. There is clear evidence in human reports that MeI causes neurotoxicity (see **III.I. Human Toxicity Case Reports**). After consideration of the SRC comments, this risk assessment incorporates a modifying factor of 10-fold for the MOE benchmark and reference concentration calculation.

Table 66. Reference concentrations for MeI inhalation exposure.[a]

Duration	Toxicity endpoints	HECs	RfC[c]	
			UF=30	UF=300
Acute	Fetal death in rabbits[1]	Worker (8 hr)=0.23 ppm GP_W (24 hr)=0.081 ppm		0.8 ppb 0.3 ppb
	Olfactory epithelial degeneration in rats[2]	Worker (8 hr)= 17.1 ppm Adult (24 hr)= 5.7 ppm Child (24 hr)= 3.5 ppm Infant (24 hr)= 2.7 ppm	570 ppb 190 ppb 118 ppb 90 ppb	
	Neurotoxicity in rats[3]	Worker (8 hr)= 10.4 ppm Adult (24 hr)= 3.5 ppm Child (24 hr)= 2.2 ppm Infant (24 hr)= 1.9 ppm		35 ppb 12 ppb 7 ppb 6 ppb
Sub-chronic	Decreased day 21 body weight in rat pups[4]	Child (24 hr)= 0.51 ppm Infant (24 hr)= 0.39 ppm	17 ppb 13 ppb	
	Neurotoxicity in rats (extrapolated)	Worker (8 hr)= 3.5 ppm Adult (24 hr)= 1.2 ppm Child (24 hr)= 0.7 ppm Infant (24 hr)= 0.5 ppm		12 ppb 4 ppb 2 ppb 2 ppb
Chronic	Salivary gland metaplasia in rats[5]	Worker (8 hr)= 2.0 ppm Adult (24 hr)= 0.66 ppm Child (24 hr)= 0.41 ppm Infant (24 hr)= 0.31 ppm	66 ppb 22 ppb 14 ppb 10 ppb	
	Neurotoxicity in rats (extrapolated)	Worker (8 hr)= 1.0 ppm Adult (24 hr)= 0.35 ppm Child (24 hr)= 0.22 ppm Infant (24 hr)= 0.16 ppm		4 ppb 1 ppb 0.7 ppb 0.5 ppb
Lifetime	Thyroid tumors in rats[5]	Non-threshold: Worker (8 hr)= unit risk $6x10^{-6}$/ppb GP= unit risk $2.5x10^{-5}$/ppb		Risk benchmarks[d]: 1.7 ppb 0.04 ppb
		Threshold: Worker (8 hr)= 1.2 ppm GP_A= 0.39 ppm	 NA NA	 4 ppb 1 ppb

a/ * indicates studies conducted under FIFRA guidelines and were acceptable to DPR. References: 1. Nemec, 2002d*; 2. Kirkpatrick, 2002b*; 3. Schaefer, 2002*; 4. Nemec, 2002a*; 5. Kirkpatrick, 2002b*.

b/ The basis for the HEC calculation was either the NOEL or the lower bound level from benchmark dose analysis for the POD, and DPR methodology as described in **Appendix B** of **Volume I**.

c/ For threshold effects, total UF from the HEC is 300 for fetal death and thyroid tumors, and 30 for all other endpoints.

d/ For nonthreshold effect, the unit risk and RfCs are based on acceptable risk probabilities of $1x10^{-5}$ for workers, and $1x10^{-6}$ for the general population.

Abbreviations: GP=general population all ages, GP_W=women of child-bearing age in general population, GP_A=general population adult, NA=not applicable.

V.C.1.c.(1) Assessment of Non-cancer MOEs from MeI Inhalation Exposure

For the assessment of MOEs, the inclusion of an $UF_{additional}$ of 10 means the MOE benchmark should be set at 300 for the fetal death (acute exposure) and neurotoxicity (all exposure durations) endpoints. The default benchmark is 30 for other endpoints after acute or repeated exposures. However, it should be noted that the total uncertainty factor of 30 associated with this benchmark MOE, would result in RfCs that may not be sufficiently protective against excess iodide intake.

General Population (Bystanders and Residents)

The lowest MOEs for each exposure scenario are those for the fetal death after acute exposure. For the HEC of 0.081 ppm for fetal death endpoint, the MOEs (0.1 to 0.4, Table 63) for adults are all below this benchmark of 300. The MOEs for neurotoxicity (range from 6 to 18 for acute, 42 to 292 for subchronic, and 53 to 117 for chronic exposures) are also below the benchmark.

The acute MOEs (range from 9 to 29) for nasal toxicity are below this benchmark for all age groups (Table 63). The seasonal and chronic MOEs based on reproductive toxicity and salivary gland metaplasia, respectively, are above the benchmark.

Workers

For the assessment of worker MOEs, the MOE benchmark should also be set at 300 for the fetal death and neurotoxicity. The lowest MOEs are those for the fetal death after acute exposure. For the HEC of 0.23 ppm for the fetal death, the MOEs for all workers (range from 1 to 77) are below this benchmark (Table 62). For neurotoxicity, MOEs for workers (with the exception of planters) involved in shallow-shank injection are below the benchmark for almost all durations. For other endpoints, the MOEs for these endpoints are all above this benchmark (Table 62).

V.C.1.c.(2) Recommended MeI Reference Concentrations

When a 10-fold $UF_{additional}$ is included in deriving the RfCs for MeI in the air, the lowest RfC for noncancer effects are 0.8 ppb for the HEC of 0.23 ppm (occupational) and 0.3 ppb for the HEC of 0.081 ppm (general population) for the fetal death endpoint (Table 66). These reference concentrations are below the 1 ppb limit calculated based on iodide concerns in children exposed to MeI. For other endpoints and durations, the RfCs derived from an UF of 30 listed in Table 66 are sufficiently protective only for the associated toxicity endpoints. They are higher than the 1 ppb RfC based on iodide concerns, would not be sufficient for protection of children against excess iodide intake.

V.C.2. Cancer Effects

V.C.2.a. Evaluation Benchmarks

For MeI oncogenicity, risks associated with MeI lifetime exposures are calculated based on two approaches: threshold and non-threshold for tumor formation. For risks associated with

the threshold approach and expressed as MOEs, an additional UF of 10 should be applied to the default benchmark of 30. This is necessary for the possible need of greater protection against cancer endpoints. Exposures with MOEs lower than this 300 benchmark would be of health concern.

For the probability of oncogenic risk based on the non-threshold approach, the DPR default probabilities are $1x10^{-5}$ and $1x10^{-6}$ for workers and general population, respectively. Exposures with risk values higher than these benchmarks are of health concern. The SRC recommended consideration of a factor for human inter-individual variability applied to the cancer potency, citing the National Research Council (NRC) report Science and Decisions (NRC, 2008) in the evaluation of the USEPA risk analysis approaches (**Volume IV Part 1-A**). While noting such a factor is lacking in the current potency approach, the NRC recommended a phase-in of a unified framework for the dose-response assessment of cancer and non-cancer endpoints. As a short-term goal for USEPA, initial test cases would be used as a proof of concept with different conceptual models applied to the unified framework. DPR scientists will evaluate the use of such factor and models when guidelines for their use are available. In this document, the oncogenic risk includes an age-dependent adjustment to the cancer risk and showed about a 2-fold difference for potential sensitivity due to age.

V.C.2.b. Assessment of Cancer Risks from MeI Inhalation Exposure

The MOEs for lifetime exposures showed some workers (applicators and tarp monitors of shallow shank injection) with MOEs (150 and 225; Table 62) and resident adult with MOE of 130 (Table 63) at below the benchmark level of 300. When probabilistic risk is used for the evaluation, all workers involved in shallow shank injection had oncogenic risks (range from $2x10^{-5}$ to $5x10^{-5}$; Table 62) greater than the $1x10^{-5}$ benchmark. For residents, the oncogenic risks were $8x10^{-5}$ based on adult exposure only, but a much higher risk of $1.4x10^{-5}$ when age-dependent adjustment factors are applied (Table 63). For both risk calculations, the risks are higher than the $1x10^{-6}$ benchmark.

The difference in conclusion from these terms (MOE or probability of risk) is due to the assumptions regarding the MOA for the thyroid tumor induced by MeI as discussed in section **IV.A.5. Oncogenicity Weight of Evidence**. The likelihood is that both non-genotoxic and genotoxic MOAs are involved with the oncogenic susceptibility of the thyroid due to MeI as a methylating agent, enhanced by the MeI effect on thyroid function due to iodide. The risk associated with the genotoxicity MOA yields a higher risk potential, thus a lower exposure limit or risk benchmark (1.7 ppb and 0.04 ppb for workers and general populations, Table 66). In comparison, the reference concentration from the non-genotoxic MOA and threshold approach for extrapolation resulted in reference concentrations of 4 ppb and 1 ppb for these groups (Table 66). Thus, this risk assessment recommends the use of the risk calculated based on the genotoxic MOA for evaluation of exposure to be more protective against cancer effect. Accordingly, a reduction of exposure 5 to 140-folds is needed in order for the risk to be at the benchmark level. Since this reduction level is lower than that (up to 3,000-fold) for acute exposure, mitigation of acute exposure should also address lifetime exposure.

VI. CONCLUSION

This risk characterization document assesses the human health risk associated with the inhalation exposure to MeI from its proposed use in preplant field fumigation. The exposure groups examined are: workers directly involved in the application of MeI, workers in the adjacent fields, bystanders present at the buffer zone of 152 meters, and residents living next to application sites. Their exposures are estimated from MeI field monitoring studies. The toxicity of MeI is available from laboratory animal studies and human case reports. The main toxicity endpoints of concerns are: fetal death, nasal toxicity (olfactory epithelial degeneration), neurotoxicity, reproductive toxicity (delayed growth), salivary gland effect (metaplasia), and oncogenicity (thyroid tumors). These effects may be caused by MeI as a result of a direct effect or related to its effects on the thyroid in conjunction with iodide, a metabolite of MeI. Analysis of the database supports the need for a more thorough investigation on developmental neurotoxicity and neurotoxicity of MeI.

For non-cancer effects, the most sensitive endpoints are fetal death in rabbits and neurotoxicity in rats from acute exposure to MeI. The acute MOEs are 0.1 to 77 for adults (fetal death endpoint) and 6 to 7 for young children (neurotoxicity endpoint) exposures. For lifetime MeI exposure and cancer risk, the risks based on the genotoxic MOA for thyroid tumors in rats are $1x10^{-6}$ to $5x10^{-5}$ and $1.4x10^{-4}$, respectively, for workers and residents.

This risk assessment recommends the acute MOEs evaluated with a benchmark MOE of 300, an additional uncertainty factor of 10-fold applied to the conventional value of 30, because of concerns about MeI causing potential pre- and post-natal developmental neurotoxicity and adequacy of neurotoxicity testing. For some acute exposure scenarios, the calculated MOEs of these endpoints are well below this benchmark indicating that significant reduction of exposure, up to 3,000 fold, is needed. Exposure reduction is also necessary for some acute exposure scenarios evaluated using a benchmark of 30 for other endpoints as well as for repeated exposures. The recommended RfCs for human exposures based on the fetal death endpoint with the additional 10-fold uncertainty factor are 0.8 ppb and 0.3 ppb for women of child-bearing age in the workplace and in the general population, respectively. When they are applied for all durations, these levels are also protective of young children against excess iodide, which should not exceed 1 ppb based on available iodide intake standards. The lifetime cancer risks of worker and general population exposures, when compared to benchmarks of $1x10^{-5}$ and $1x10^{-6}$, respectively, exceed the benchmarks by 5- and 140-fold. The associated MeI RfCs are 1.7 ppb and 0.04 ppb for worker and general population, respectively. This risk assessment concludes that the application of MeI in field fumigation under the conditions evaluated could result in significant health risks for workers and the general population.

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