Methyl Iodide
Human Health Risk Assessment

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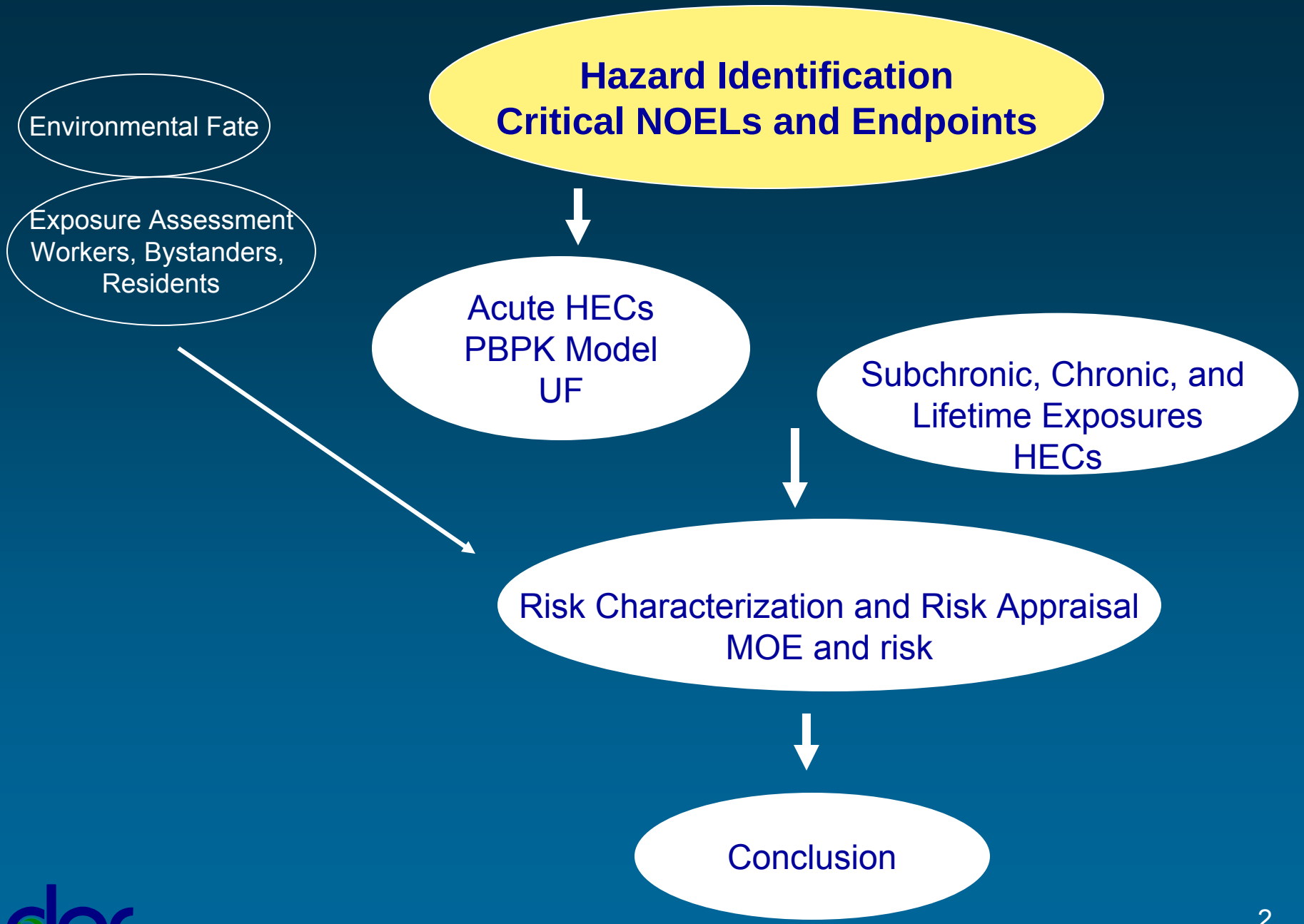
Hazard Identification
Critical NOELs and Endpoints
Environmental Fate
Exposure Assessment
Workers, Bystanders, Residents
Acute HECs
PBPK Model
UF
Subchronic, Chronic, and Lifetime Exposures
HECs
Risk Characterization and Risk Appraisal
MOE and risk
Conclusion

Hazard Identification

- Identify critical NOELs and Endpoints
  - Durations
    - Acute, subchronic, chronic, and lifetime
  - Applicable groups
    - Workers and general population
    - Women of child-bearing age

Acute Inhalation Toxicity

- Neurotoxicity in rats
- Nasal tissue toxicity in rats
  - Port of entry effect
- Developmental toxicity in rabbits
  - Increased late resorption
  - Endpoint applicable for women of child-bearing age

Acute Neurotoxicity

- Adult rats (Schaefer, 2002)
  - MeI 0, 27, 93, or 401 ppm; single day 6 hours
- FOB and motor activity assessment
  - ‘within’ 3 hours after treatment
  - Effects
    - Reduced body temperature
    - Clonic convulsion
    - Decreased motor activity
  - Acute NOEL=27 ppm
  - No FOB or motor activity on day 7 or 14 post treatment
- Histopathology of CNS and PNS tissues
  - No treatment related lesions

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Modified Table 6. Effects in male rats after acute inhalation exposure to MeI.

Effects	Doses (ppm)			
	0	27	93	401
FOB parameters- Observations on Day 0, within 3 hours after treatment				
Mean body temp. (°C)	38.3±0.23	38.3±0.28	37.2±0.74**	34.2±1.07**
Home Cage Observations Convulsions, clonic	0/12**	0/12	1/12	3/12
Total Motor Activity Counts (in 60 minute session)				
Pretest Day 0 (after exposure) % Day 0 Control % Pretest	969±513 800±323 100% 83%	809±438 637±288 80% 79%	777±396 201±78** 25% 26%	1015±523 102±65** 13% 10%
Mean ambulatory motor activity counts (in 60 minute session)				
Pretest Day 0 (after exposure) % Day 0 Control % Pretest	324±220 260±116 100% 80%	247±151 194±102 75% 79%	249±140 58±32** 22% 23%	313±197 8±8** 3% 3%

Schaefer, 2002

Acute Nasal Toxicity

- Adult rats (13-week study; Kirkpatrick, 2002b)
  - MeI 0, 5, 21 or 70 ppm; 6 hrs/day; 5 days/week
- Olfactory epithelial degeneration
  - NOEL= 21 ppm
  - Acute effect
    - Slight increase in severity from 4 weeks to 13 weeks of exposure
    - Consistent with moderate (4 hours) and marked (6 hours) damage at 100 ppm (Reed et al., 1995)

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Modified Table 11 and 12. Nasal effects in rats after inhalation exposure to 70 ppm MeI for 4 and 13 weeks.

Olfactory epithelial degeneration	Males		Females	
	4 weeks	13 weeks	4 weeks	13 weeks
Level II minimal	1/10	3/10	3/10	3/10
Level III minimal mild	4/10* 0/10	4/10* 4/10*	4/10* 0/10	6/10** 1/10
Level IV minimal mild moderate	4/10* 1/10 0/10	4/10* 5/10* 1/10	6/10* 0/10 0/10	5/10* 4/10* 0/10
Level V minimal mild moderate	9/10** 1/10 0/10	3/10 2/10 2/10	7/10** 0/10 0/10	5/10* 2/10 0/10
Level VI minimal mild	4/10* 1/10	2/10 2/10	0/10 1/10	1/10 2/10

Incidences for control, 5 and 21 ppm were 0/10 or 1/10.
Kirkpatrick, 2002b

Developmental Toxicity

- Pregnant rabbits (Nemec, 2002d)
  - MeI 0, 2, 10, or 20 ppm; 6 hrs/day; GD 6 to 28, sacrificed on GD 29
- Maternal effect
  - NOEL= 10 ppm
    - Body weight reduction
- Development effects
  - NOEL= 2 ppm, LOEL=10 ppm
    - Reduced fetal body weight
    - Increased late resorption and dead fetuses (fetal death)
    - Data variability

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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%

Historical data (36 studies) average is 1.1±1.0% (range of 0 - 3.7%) (WIL Res. Lab. 1999-2004).

Nemec, 2002d

Modified Table 34. Effects in fetal rabbits after GD 6-28 gestational exposure to Mel.

Effects	0	2 ppm	10 ppm	20 ppm
Fetal body weight Mean male (g, % C) Mean female (g, % C)	 46.8±5.70 46.9±5.48	 45.6±6.7(97%) 44.6±7.1(95%)	 44.3±7.4 (95%) 41.3±7.4* (88%)	 39.5±7.1** (84%) 37.0±7.5** (79%)
Viable fetuses -mean fetus/litter -% fetus/litter	 6.1±2.6 86.2±26.47%	 5.5±2.6 87.9±24.50%	 4.6±2.6 82.1±26.28%	 3.6±2.2** 67.7±29.96%**
Late resorptions -affect. litter/total litter -affect. fetus/total litter -% fetus/litter	 2/23* 3/23 1.7±6.2%	 2/20 6/20 3.1±10.7%	 6/20 17/20 11.1±21.2%	 11/21** 33/21 21.5±26.9%**
Dead fetus -dead fetus/total litter -% fetus/litter	 0/23 0%	 0/20 0%	 1/20 0.6±2.8%	 1/20 0.8±3.6%
Fetal Death (Exclusion of litters with 100% fetal loss due to early resorption)				
Late resorption+dead fetuses -affect. litter/total litter -affect.fetus/total fetus -% fetus/litter	 2/22* 3/143* (2%) 1.8±6.4%	 2/19 6/115 (5%) 3.3±10.9%	 6/20 18/109** (17%) 11.1±21.2%	 11/20** 34/110** (31%) 22.5±27.2%**

Nemec, 2002d

Developmental Toxicity

- Pregnant rabbits (During gestation; Nemec, 2003)
  - MeI 0 or 20 ppm, 6 hrs/day; sacrificed on GD 29
- Window of vulnerability on GD 23-26

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

Effects	Control	20 ppm					
	GD29	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
Late resorption and dead fetus							
-affect. litter/Total' litter	2/18	**10/19****	2/23	0/20	**5/17**	**6/21**	0/20
-affect. fetus/Total' fetus	2/129	**25/114****	2/121	0/131	**11/119****	**16/143****	0/131
-% fetus/litter	1.1%	**18.3****	1.1	0.0	**6.3**	**9.6**	0.0

Subchronic Inhalation Toxicity

- Systemic effects
  - Liver weight and body weight changes in rats
- Reproductive and developmental effects
  - Reduced pup weight, delayed development in rats
  - Endpoint applicable for women of child-bearing age

Subchronic Inhalation Toxicity

- Rats (13-week study, Kirkpatrick, 2002b)
  - MeI 0, 5, 21 or 70 ppm; 6 hrs/day; 5 days/week; NOEL= 21 ppm

Modified Table 11. Effects in male rats exposed to MeI by inhalation for 13 weeks.

Effects	Dose (ppm)			
	0	5	21	70
Food consumption (% decrease)				
Week 0-1 Week 11-12	0 0	4.5% 4.2%	4.5% 8.3%	13.6%** 8.3%
Cumulative group mean body weight changes (g) (% of control)				
Weeks 0-1 Weeks 0-13	43 234	34 (79%)* 220 (94%)	36 (84%) 212 (91%)	29 (67%)** 199 (85%)
Group mean relative liver weights/final body weight ratios x 100 (% of control)				
Week 4 Week 13	2.903 2.436	2.965 2.513	2.923 2.639	2.991 2.809 (115%)**

Reproductive and Developmental Toxicity

- Rats (2-generation reproductive toxicity; Nemec, 2002a)
  - MeI 0, 5, 20 or 50 ppm; 6 hrs/day
    - Parental generation: premating (10 weeks), mating to GD 20, and LD 5 to 21
      - F1 pups
    - Second generation: PND 28 to GD 20, LD 5 to 21
      - F2 pups
    - Pup exposure: *in utero* during gestation and postnatal via milk
  - Reproductive NOEL=20 ppm
    - Reduced live litter size for both generations
  - Developmental NOEL=5 ppm
    - Reduced mean pup body weights
    - Delayed development

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Modified Table 33. Effects in pups exposed to MeI in utero and lactation.

Effects	Parental Doses (ppm)			
	0	5	20	50
Mean pup weight in grams (% control)				
F2 pups Day 14-males	29.7	28.7 (97%)	26.8** (90%)	24.3** (82%)
-females	28.3	26.4*(93%)	25.3** (89%)	23.3** (82%)
Day 21-males	45.1	44.4 (98%)	38.7** (86%)	36.2** (80%)
-females	42.9	40.6 (95%)	37.2** (87%)	35.0** (82%)
Balanopreputial Separation, F1 male pups				
Days to separation	46.5±2.58	45.1±2.97	46.4±2.82	47.0±2.82
Body weight (g) at separation	219.5±20.6	218.5±16.1	213.6±20.4	203.4±14.7**
Vaginal patency, F1 female pups				
Days to patency	37.0±2.34	37.9±2.68	38.8±3.38*	40.0±3.17**
Body weight (g) at patency	119.8±14.1	125.4±12.8	130.2±18.5	128.3±18.1

Nemec, 2002a

Chronic Inhalation Toxicity

- Rats (2-year study; Kirkpatrick, 2005)
  - MeI 0, 5, 20, or 60 ppm; 6 hr/day; 5 days/week
  - Salivary gland squamous metaplasia, NOEL=5 ppm

Modified Table 22. Histopathological findings in rats exposed to MeI for 2 years.

Effects (main group)	Doses (ppm)							
	Males				Females			
	0	5	20	60	0	5	20	60
Metaplasia	1/50**	4/49	22/49**	47/50**	0/50**	3/50	22/50**	40/48**

Oncogenicity Weight of Evidence

- Evidence in human and laboratory animals
  - Human
    - No information
  - Laboratory animals (Kirkpatrick, 2005; Harriman, 2005a)
    - Thyroid tumor in male rats (inhalation) and male mice (oral)
    - Astrocytoma in male rats (inhalation)
    - Cervical/uterus fibroma in female mice (oral)

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Modified Table 22: Tumor data in rats after inhalation exposure to MeI for 2 years (6 hrs/day, 5 days/week)

Effects (Main group)	Dose (ppm)							
	Males				Females			
	0	5	20	60	0	5	20	60
Thyroid follicular cell tumor								
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+CA	4/45**	2/45	4/49	12/42*	2/50	1/48	1/48	3/38
Astrocytoma								
Benign	0/48	0/25	0/25	1/44	0/50	0/26	0/28	1/39
Malignant	0/48	1/25	0/25	2/44	0/50	0/26	0/28	0/39
Benign+Malignant	0/48*	1/25	0/25	3/44	0/50	0/26	0/28	1/39

Kirkpatrick, 2005

Modified Table 27: Tumor data in mice after oral exposure to MeI daily for 2 years.

Effects (main group)	Dose (ppm)							
	Males				Females			
	0	60	200	600	0	60	200	600
Thyroid follicular tumor								
Adenoma	0/50*	0/50	1/50	2/49	0/50	0/50	0/50	1/50
Carcinoma	0/50	0/50	0/50	1/49	1/50	0/50	0/50	0/50
Adenoma+CA	0/50*	0/50	1/50	3/49	0/50	0/50	0/50	1/50
Cervix/Uterus								
Cervical fibroma	NA	NA	NA	NA	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

Harriman, 2005a- microencapsulated MeI mixed in the diet

Oncogenicity Weight of Evidence

- Mode of action
  - Thyroid tumors
    - Non-genotoxic MOA
      - Perturbation of thyroid function by excess iodide
    - Genotoxic MOA
      - Gene mutation, chromosomal aberration and DNA alkylation by MeI
  - Other tumors
    - Possible genotoxic MOA (default)

Genotoxicity

- Positive studies
  - Gene mutation
    - Salmonella strain in closed system
    - Chinese hamster ovary cells at the HGPRT locus
  - Structural chromosomal aberration
    - Chinese hamster ovary cells (chromatid breaks, exchanges)
    - Mouse lymphoma cells (TK^- colonies)
  - DNA alkylation
    - Human lymphoblasts and lymphocyte DNA
    - Rat tissues DNA after gavage or inhalation exposure
- Negative studies
  - Gene mutation (Salmonella and HGPRT assay)
  - Chromosomal damage (bone marrow micronuclei assay)

HGPRT=hypoxanthine-guanine-phosphoribosyl transferase

Oncogenicity – NOEL and Potency Factor

- Thyroid tumors
  - Non-genotoxic MOA (Threshold)
    - NOEL = 20 ppm (6 hr/day, 5 days/week)
  - Genotoxic MOA (Non-threshold, BMD)
    - Potency factor = 5.0×10^{-3} mg/kg/day^{-1} (rat)
      1.61×10^{-2} mg/kg/day^{-1} (human equivalent)

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Hazard Identification
Critical NOELs and Endpoints

Acute HECs
PBPK Model
UF

No-observed -effect Level (NOEL) → **Human Equivalent Concentration (HEC)** → **Risk**

Uncertainty Factor (UF)

Interspecies extrapolation
Pharmacokinetic difference
(Physiologically-based pharmacokinetic Model, PBPK)

Acute HECs - PBPK Model and UF Application

1. Model Overview
   - To account for interspecies PK differences
   - Match human dose metric to animal's at NOELs
2. HEC from PBPK Model
   - Mode of action
   - Model application
   - HEC dose metric
3. Acute HECs
   - 24-hr HEC for general public
   - "8-hr" HEC for workers (additional 16-hr as general public)
4. Uncertainty Factors for using HEC in Risk Assessment

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PBPK Model Overview

Arysta Model

- Developed by Sapphire Group
- Reviewed by National Center for Computational Toxicology, USEPA (2007)
- Rabbit model - Simplified with no nose uptake

Model Description and Parameters:

- May 2009 Inhalation Toxicology Issue 21(6)
- Endpoint specific model issues

DPR HECs

- Iterative runs using DPR input parameters and dose metric
- Model runs repeated by NCCT USEPA (May 2009)
- Comparison to USEPA's HECs

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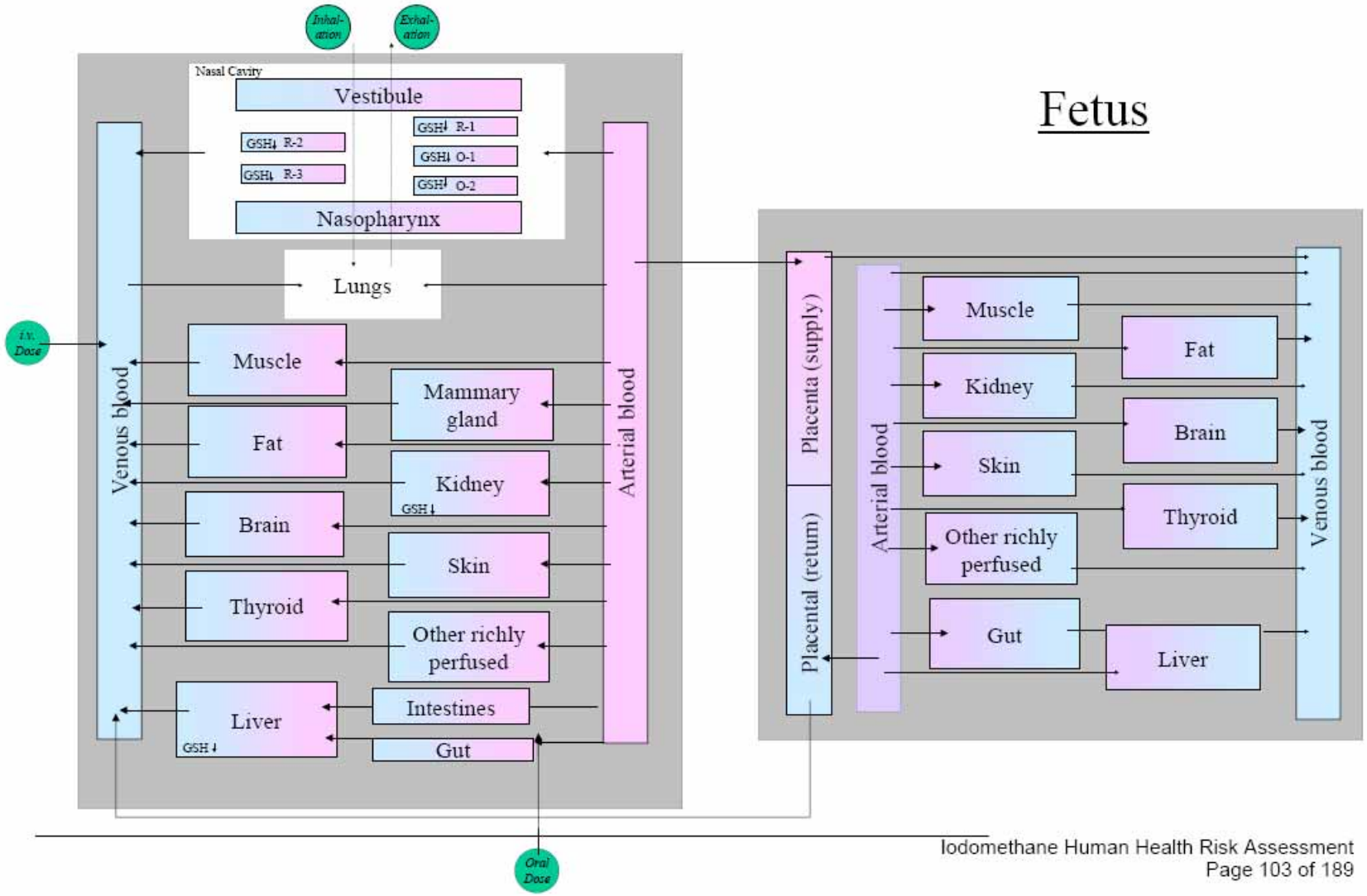
Arysta Rabbit PBPK Model



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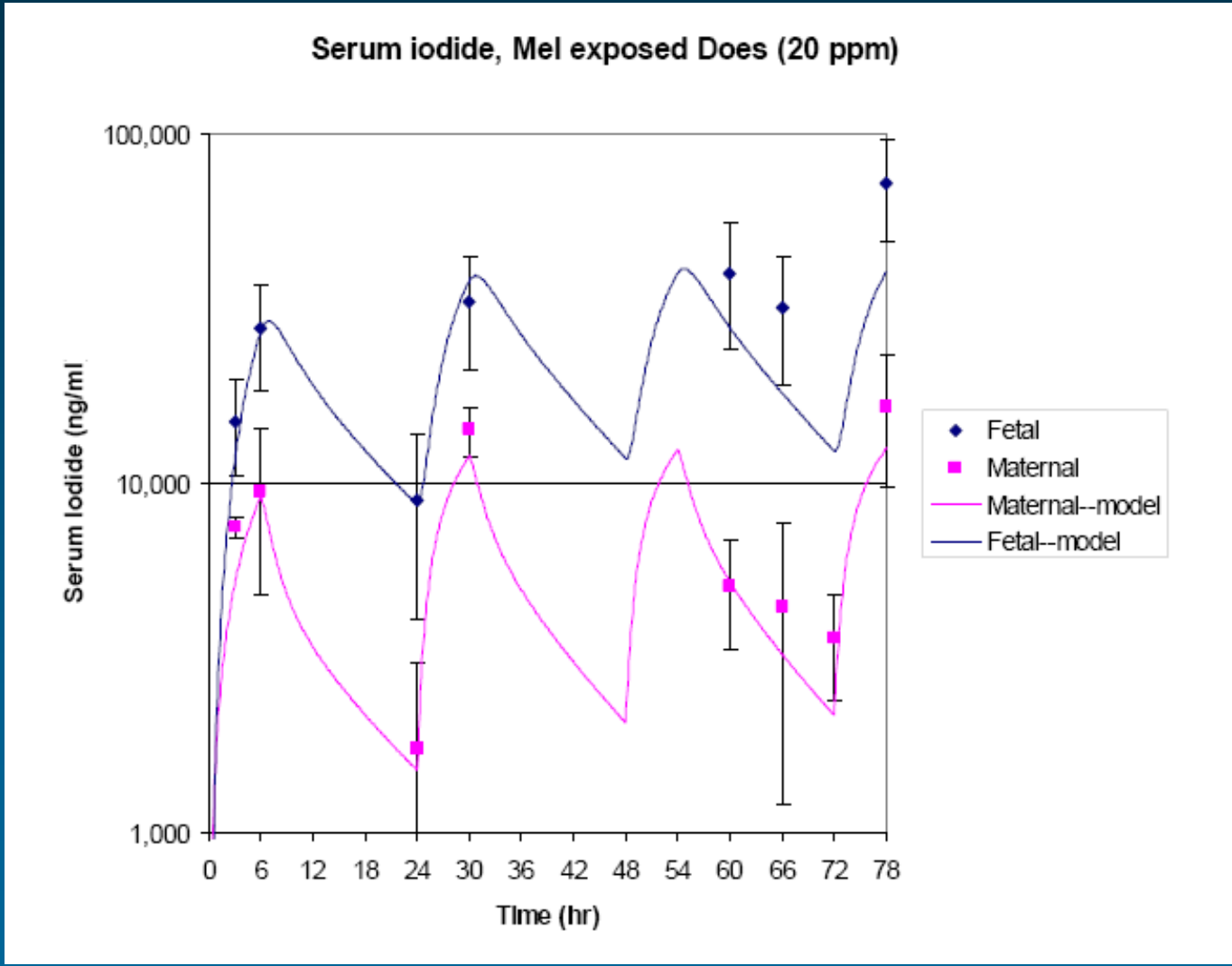
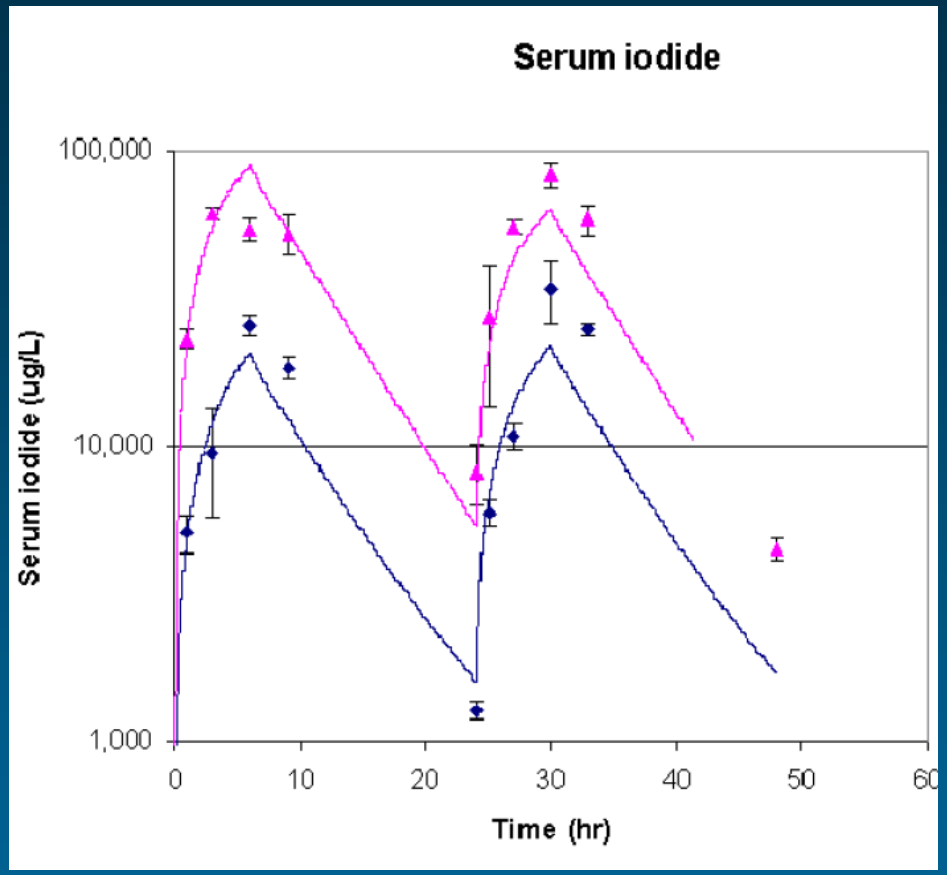
PBPK Model Fit - Rabbit Model (Vol. I Fig A-2)



PBPK Model Fit – Rat Model (Vol. I, Fig A-11)



Ethmoid 25 ppm
Dorsal Meatus 25 ppm

Ethmoid 100 ppm
Dorsal Meatus 100 ppm

25 ppm
100 ppm

Rabbit Fetal Death - MOA

Possible MOA(s)

1. Fetal thyroid perturbation from excess iodide
2. GSH depletion and oxidative stress
3. Direct alkylation
4. Altered cholesterol homeostasis

Available Data

- Maternal vs. fetal data during GD23 to GD26
- Lack data on dose-response and pre-natal interspecies comparison

MOA Implication - Dose Metric Selection

- Maternal or Fetal?
- Serum Iodide or MeI?
- AUC or Peak concentration?

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MOA 1: Perturbed Fetal Thyroid from Excess Iodide

Available Data

- Thyroid hormones TSH, T3, T4
- Thyroid histopathology (colloid depletion, hypertrophy)
- Serum iodide
- Studies with iodide
- In rats and rabbits (MeI, Iodide)

Key Questions on Thyroid Perturbation MOA

- Causal effect – fetal or maternal thyroid or both?
- Chemical form - MeI or Iodide or both?
- Temporal focus - fetal death within 30 hr (earliest observation immediately after the 2nd 6-hr exposure)

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Volume I, Table 56, Sloter 2005a

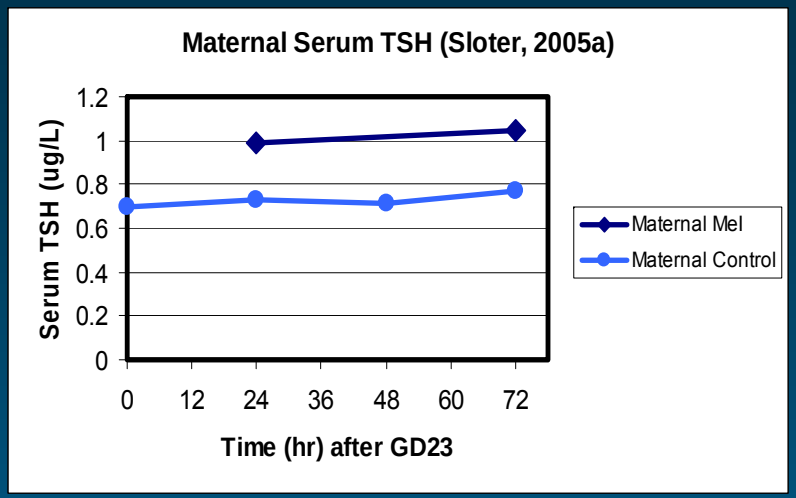
Effects	MeI (6 hr/day) on GD 23-24		MeI (6 hr/day) on GD 23-26	
	0 ppm	25 ppm	0 ppm	25 ppm
Maternal				
TSH; ng/mL	0.73 ± 0.13	0.99 ± 0.32*	0.77 ± 0.11	1.05 ± 0.30*
T3; μg/dL	0.190 ± 0.021	0.144 ± 0.030*	0.154 ± 0.025	0.122 ± 0.026*
T4; μg/dL	1.9 ± 0.5	1.4 ± 0.5	1.8 ± 0.5	1.6 ± 0.6
Serum I; mg/L	0.027 - <0.1	17.2 (9.8-22.7)	<0.02 - <0.1	26.4 (10.2-78.0)
Fetal				
TSH; ng/mL	1.70 ± 0.23	1.47 ± 0.42	1.37 ± 0.27	9.71 ± 8.94*
T3; μg/dL	0.007 ± 0.0028	0.003 ± 0.003*	0.011 ± 0.005	0.012 ± 0.006
T4; μg/dL	0.09 ±0.07	0.05 ± 0.10	0.26 ± 0.13	0.06 ± 0.07*
T-c depletion	0/79 (0%)	10/73 (14%)	0/99 (0%)	72/81 (89%)
T hypertrophy	0/79 (0%)	27/73 (37%)	0/99 (0%)	76/81 (94%)
Serum I; mg/L	0.18 (0.12-0.26)	37.1 (21.6-55.9)	<0.1 - 0.165	70.6 (33.5-128.0)
Fetal Late Resorption immediately after the 2 or 4 days of exposure				
% Fetus/Litter	1.8±3.9	5.7±9.2	1.7±3.7	5.2±7.6
% Litter	2/10 (20%)	3/9 (33.3%)	2/10 (20%)	4/10 (40%)

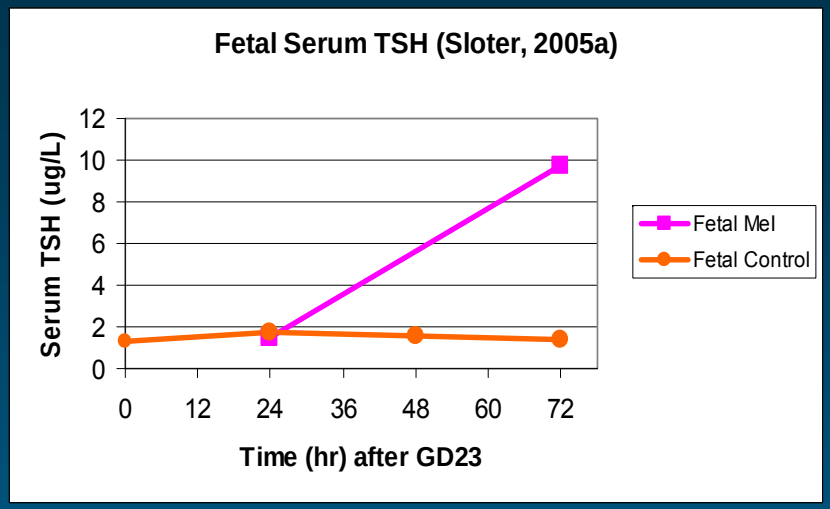
Volume I, Table 57, Sloter 2005b
(% viable fetus/litter on GD29 from MeI exposure on GD23-26: controls 93%, MeI 47%, NaI 88%)

Effects	GD 23-24			GD 23-26		
	0 ppm	20 ppm MeI	iv NaI	0 ppm	20 ppm MeI	iv NaI
Maternal						
TSH; ng/mL	0.46±0.11	0.62±0.04*	0.62±0.08*	0.58±0.24	0.58±0.15	0.60±0.07
T3; μg/dL	0.17±0.016	0.16±0.020	0.13±0.022*	0.122±0.024	0.114±0.025	0.123±0.016
T4; μg/dL	1.43±0.42	1.44±0.46	1.15±0.71	0.60±0.38	0.84±0.89	0.61±0.66
T-c depletion	-	-	-	0/5 (0%)	3/5 (60%)	1/5 (20%)
T hypertrophy	-	-	-	0/5 (0%)	2/5 (40%)	0/5 (0%)
Serum I mg/L	-	14.3(12.9-18.7)	6.29(5.75-6.75)	0.0052-0.049	16.6(11.1-29.6)	9.63(3.33-29.2)
Fetal						
TSH; ng/mL	1.9±0.5	1.7±0.4	2.0±0.6	1.9±0.9	5.1±1.5*	5.2±2.9*
T3; μg/dL	0.010±0.002	0.014±0.005	0.008±0.002	0.015±0.003	0.027±0.013	0.016±0.002
T4; μg/dL	0.05±0.04	0.08±0.05	0.03±0.03	0.06±0.04	0.03±0.05	0.01±0.01
T-c depletion	0/20(0%)	1/20(5%)	0/20(0%)	0/20(0%)	13/20(65%)	17/20(85%)
T hypertrophy	0/20 (0%)	16/20 (80%)	12/20 (60%)	0/20(0%)	16/20(80%)	18/20(90%)
Serum I; mg/L	-	33.2(14.8-46.4)	23.0(15.4-30.3)	0.124-0.217	72.6(53.9-110)	35.9(14.4-55.3)
Fetal Late Resorption assessed on GD 29						
% Fetus/Litter	-	-	-	4.7±6.48	50.4±28.09*	6.8±10.9
Litter Affected	-	-	-	2/5 (40%)	4/4 (100%)	2/5 (40%)

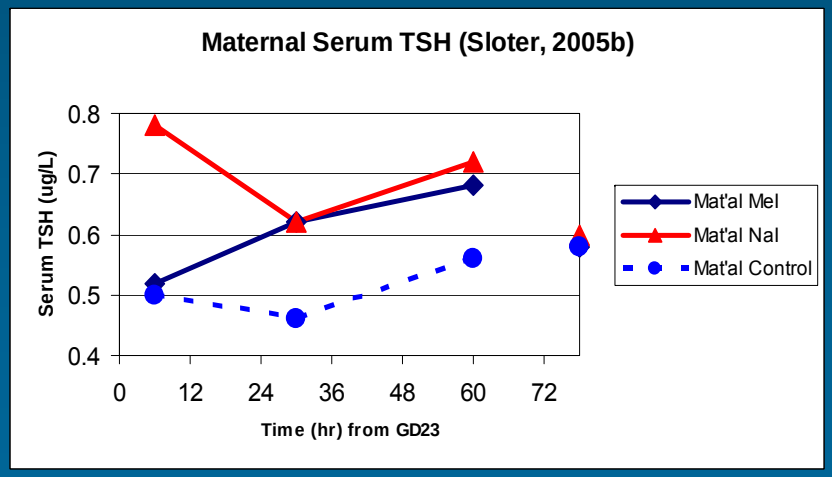
Maternal and Fetal TSH

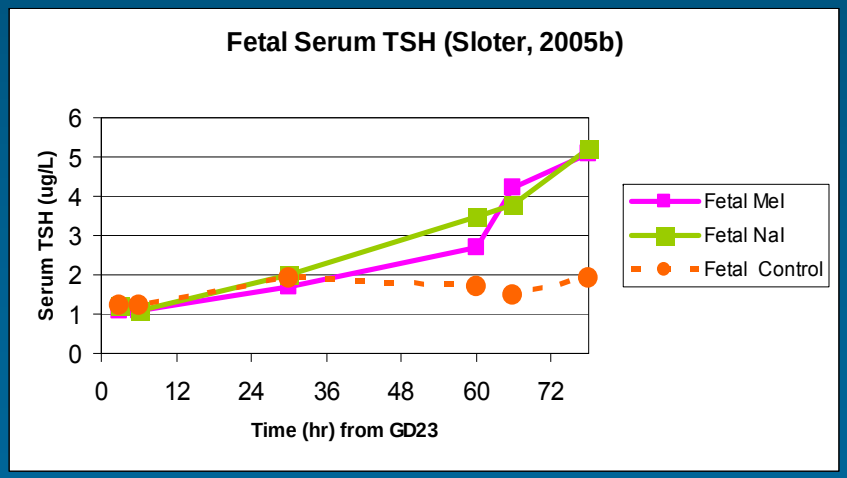
25 ppm MeI, 6 hr/day (Sloter 2005a)





20 ppm MeI 6 hr/day; 3.04 mg/kg/day NaI (Sloter 2005b)





Summary Data on Fetal Thyroid MOA

1. GD23-24 Fetal death (Sloter 2005a,b)
   - TSH: maternal showed consistent concordance
   - T3, T4: data less consistent
   - Histopathology: no maternal data, fetal no clear difference to NaI
   - Iodide F/M ratio: decreased with MeI exposure
   - Iodide MeI treated/control ratio: maternal ~350X; fetal ~200X

2. Thyroid Iodide (Morris *et al*, 2004; i.v. at 0.75 and 10 mg/kg NaI)
   - Iodide accumulation in maternal but not fetal thyroid

3. Conclusions
   - Fetal: Lack consistency; fetal thyroid unlikely immediate or sole MOA
   - Maternal: Showed better temporal concordance with fetal death

4. Uncertainty: Fetal data are from those who survived

Additional Data: Species Comparison, MeI vs. Iodide

1. MeI Fetal Death
   - Rabbit (GD6-29) : 11.1% fetal death/litter @10 ppm
   - Rat: No GD6-19 fetal death @60 ppm; ↓live pup born/day 1 @50 ppm

2. NaI Increased Postnatal Death (Arrington *et al*, 1965)
   - Rabbit: day 3 to week 4 survival
   - Rat: day 3 survival

3. Placental Iodide Transport
   - Rabbit F/M
     - Controls : 9 - 11X; MeI: 2X (Mileson *et al*, 2009)
   - Rat: no data
   - Human C/M
     - No excess Iodide: 0.35 - 5.4 (Rayburn *et al*, 2007)
     - Iodomethylsparteine: 0.5 - 3.4 (Cottino *et al*, 1972)

MOA 2: Oxidative Stress

Marker: GSH Depletion

Available Data

- GSH depletion in rabbits
  - Evident within 3 hr of MeI exposure
  - Greater depletion in fetal than maternal blood
- GSH depletion in cultured rat cerebellar granule cells
  - Evident within 15 minutes after 5 min MeI
  - Cell death long after recovery of GSH concentration
- Rabbit pre-natal observations
  - Fetal death
  - A single mid-coronal brain section mentioned in rabbit pre-natal study with no data reported

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Rabbit Blood GSH (mM) (Vol. I, Table 59)

Mel Treatment	Controls	Mel	% Control	Study
Maternal				
GD23-24; 25 ppm	0.599±0.12	0.469±0.06*	78%	Sloter, 2005a
GD23-26; 25 ppm	0.387±0.15	0.460±0.15	119%	Sloter, 2005a
GD23; 20 ppm	0.565±0.097	0.451±0.100	80%	Sloter, 2005b
GD23-24; 20 ppm	0.642±0.045	0.413±0.051**	64%	Sloter, 2005b
Fetal				
GD23-24; 25 ppm	0.473±0.08	0.338±0.12*	72%	Sloter, 2005a
GD23-26; 25 ppm	0.382±0.09	0.216±0.09*	57%	Sloter, 2005a
GD23; 20 ppm	0.410±0.104	0.253±0.098*	62%	Sloter, 2005b
GD23-24; 20 ppm	0.411±0.115	0.227±0.056*	55%	Sloter, 2005b

MOA 3: Direct Alkylation

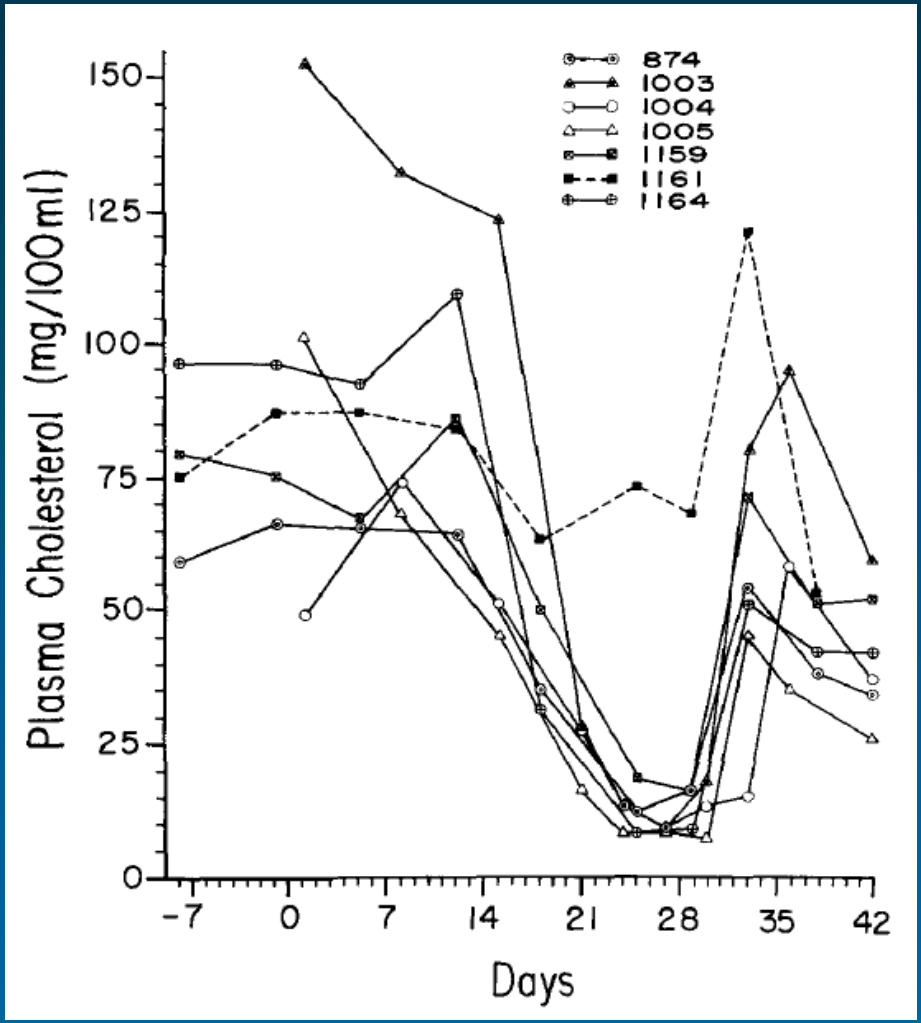
Marker: Hemoglobin S-Methylcysteine Adduct in rabbits

Available Data

- Indicate systemic distribution and fetal transport of MeI
- Fetal may be slightly higher than maternal
- No further data for MOA evaluation

MeI Treatment	Hemoglobin S-methylcysteine adduct (nmol/g globin)				Study
	Maternal		Fetal		
	Control	MeI	Control	MeI	
GD23-24; 25 ppm	70.2±33.1	101.5±22.1 (145%)	81.2±20.4	116.3±34.3 (143%)	Sloter, 2005a
GD23-26; 25 ppm	48.4±6.3	103.4±27.8 (214%)	60.1±9.2	98.7±17.5 (164%)	Sloter, 2005a
GD23-26; 20 ppm	69.7±9.3	93.4±5.0 (134%)	86.9±20.1	131.1±11.0 (151%)	Sloter, 2005b

MOA 4: Altered Cholesterol Homeostasis



<u>Pregnant Rabbit Cholesterol</u>

- Zilversmit *et al*, 1972a
- Controls (Cholesterol-free diet)
- #1161 inseminated but had no young

MOA 4: Altered Cholesterol Homeostasis

Marker: Cholesterol Profile

Available Data

- Maternal cholesterol lowest during GD23-28 (Zilversmit *et al,* 1972a)
- Hypercholesterolimic Does (fed high cholesterol diet)
  - ↑Fetal cholesterol
  - ↑Fetal death (late stage, not malformed)
  - ↓Fetal weight
- MeI increased maternal and fetal cholesterol
- No further data for MOA evaluation

Rabbit Model Issues

1. Rabbit QAC (Alveolar Ventilation Rate) at 20 L-hr/kg$^{3/4}$
   - Biologically appropriate for pregnant rabbit
   - Closer prediction to maternal data, overestimate fetal serum Iodide

2. Maternal versus Fetal Serum Iodide
   - Rabbit: Higher predicted fetal-to-maternal ratio
   - Human: data somewhat varied

3. High Modeled Fetal Thyroid Iodide Accumulation – Rabbit and Human

4. Human Gestation Stage – Impact on serum profile
   - 0.24 ppm HEC modeled for fetal weight 0.6 lb (end of 1st trimester)
   - Modeled serum iodide for 6 lb fetal weight at 0.24 ppm:
     12% higher in maternal blood, 42% higher in fetal blood

5. Conclusion: Greater modeling confidence with maternal serum iodide dose metric which also better describes exposure with no clear MOA

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Rabbit Fetal Death – Dose Metric and HEC

Dose Metric – Maternal Serum Iodide

- Single day versus steady state incremental change
  - Model limitation: poorer prediction beyond one day
  - Kinetic: days to steady state > 4-day window of vulnerability
- AUC: to account for 6 hr rabbit versus 24-hr human exposures

HEC

- DPR HEC
  - Maternal serum iodide AUC from a single day exposure
  - 24 hr HEC at 0.24 ppm, 8-hr HEC at 0.22 ppm
- USEPA HEC
  - 5X higher NOEL (@10 ppm) than DPR's
  - use fetal serum iodide AUC dose metric
  - 24-hr HEC at 7.4 ppm, 8-hr HEC at 23 ppm

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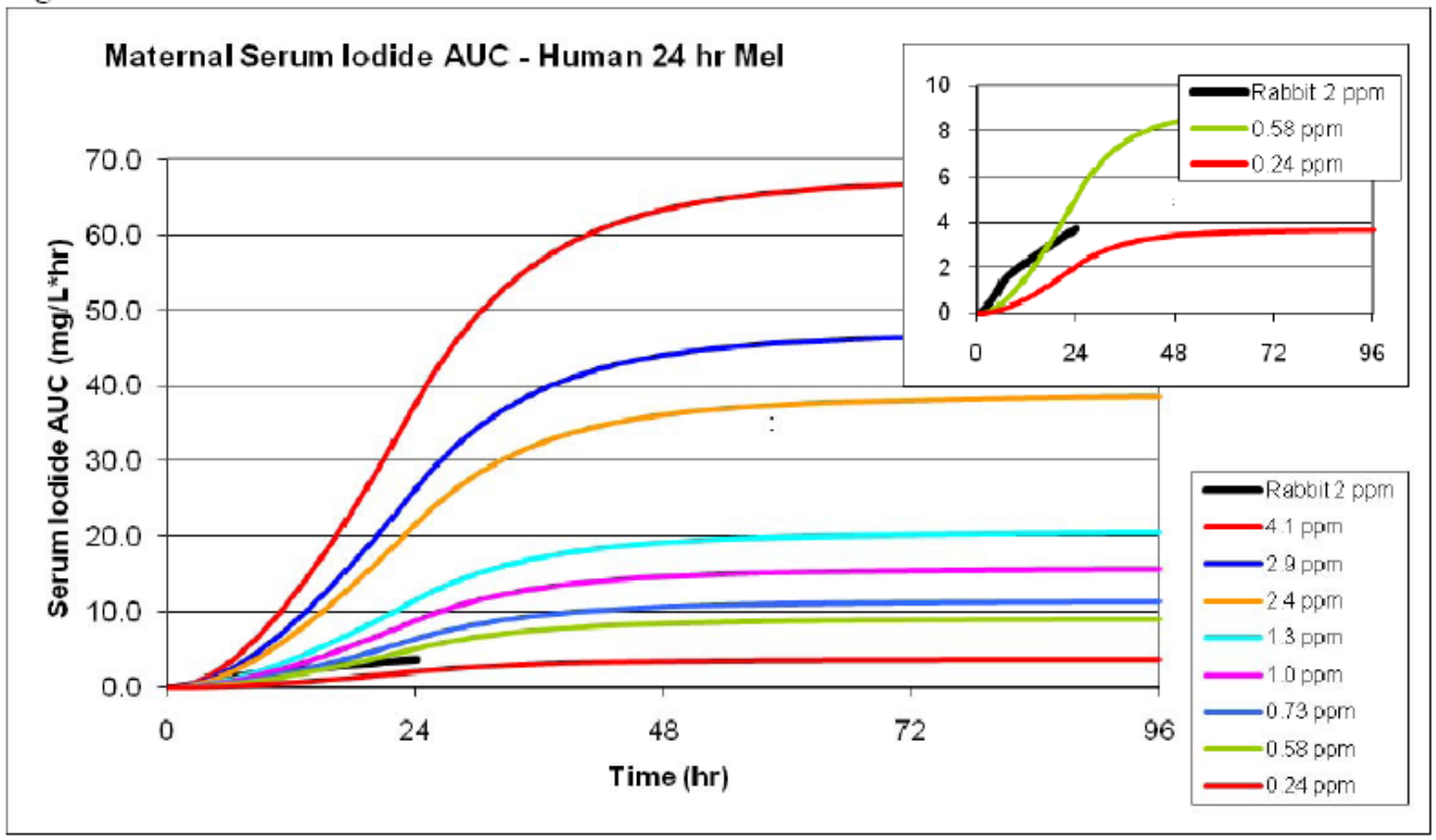
Rabbit Fetal Death 24-hr HEC – 0.24 ppm

Figure A-9a



Rat Nasal Effect - MOA

Possible MOA

- Direct alkylation
- Cytotoxic metabolites, e.g., methanethiol (from GSH conjugation) or formaldehyde (from CYP450)

Available Data

- GSH data in nasal epithelium at 25 and 100 ppm
- Degeneration attenuated by replenishing (GSH isopropyl ester) or depleting (phorone, buthionine sulphoximine) GSH

Conclusion: GSH depletion a likely early marker associated with toxicity

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Rat Nasal Effect Dose Metric - %GSH Depletion

1. Available Data

   - Olfactory vacuolization and early degeneration at as little as 48% GSH depletion 1 hr after 100 ppm MeI
   - 35% GSH depletion at 25 ppm for 6 hours
   - GSH depletion is exposure time-dependent

2. Model: 25% (ethmoid) and 34% (meatus) depletion at 21 ppm

3. Conclusion: 25% regional GSH depletion as benchmark for no effect in human nasal olfactory region

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Rat Nasal Effects - HEC

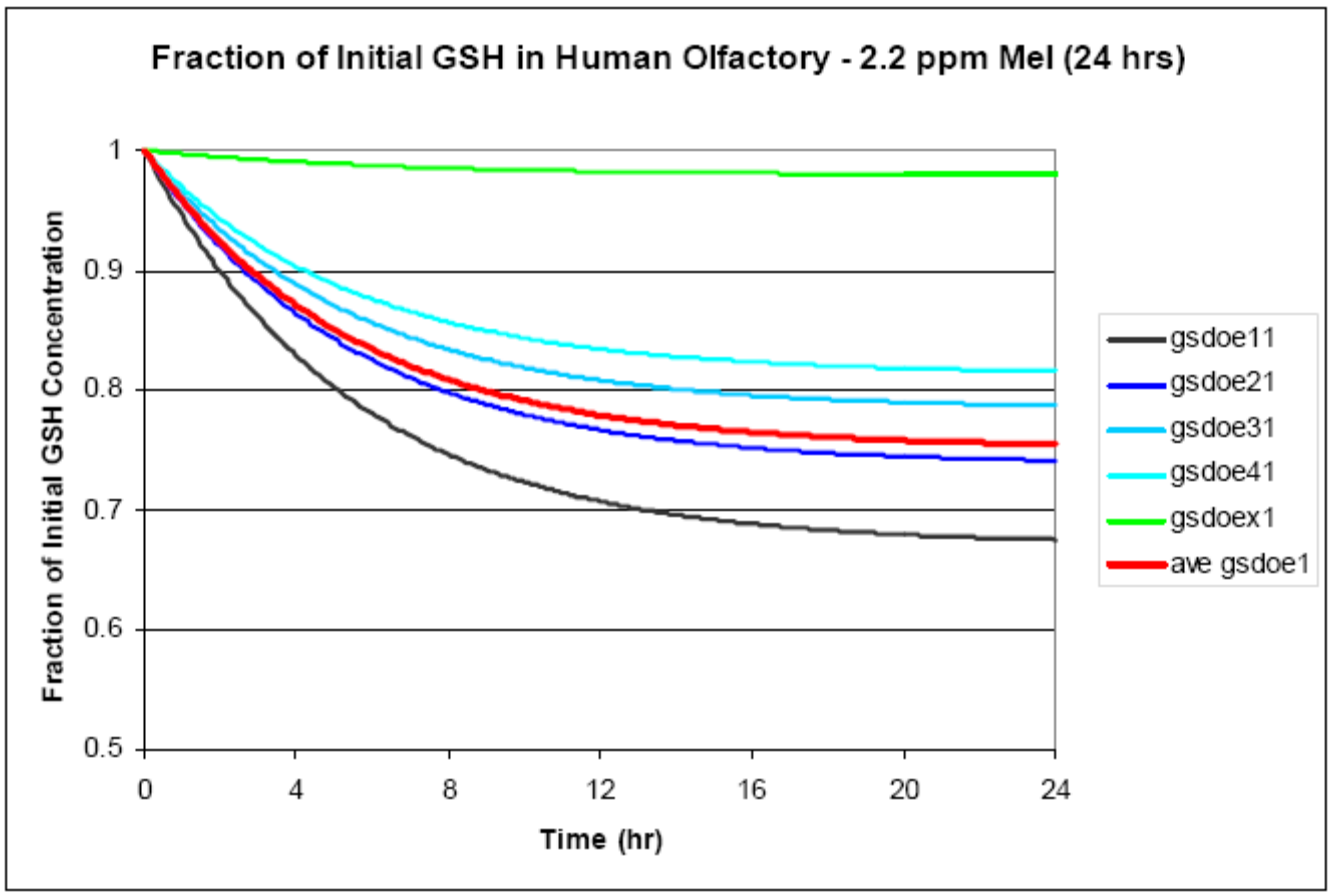
DPR HEC

- 25% GSH depletion dose metric
- 24-hr HEC at 2.2 ppm; 8-hr HEC at 2.8 ppm
- Depletion at outermost nasal epithelial layer could be greater than the regional average of 25%

USEPA HEC

- Same NOEL as DPR
- 50% GSH depletion dose metric
- 24-hr HEC at 4.5 ppm (lowest USEPA HEC); 8-hr HEC at 5.8 ppm

Rat Nasal Effect 24-hr HEC at 2.2 ppm



Rat Neurotoxicity – MOA and Dose Metric

Possible MOA

- GSH depletion in brain (Chamberlain *et al*, 1998a,b)
  - 20-30% ↓non-protein sulphydryl after 6-hr 100 ppm MeI
  - GSH depletion in cultured neural cells
- Direct effect of MeI
  - cell membrane disruption as organic solvents

Modeled MeI in brain

- Peak is reached within 30 minutes of exposure
- AUC is proportional to time of exposure thereafter

Conclusion: MeI AUC in brain can be used as HEC dose metric with no clear MOA

Rat Neurotoxicity - HEC

DPR HEC

- AUC dose metric accounts for 6 hr rat NOEL versus 24-hr human exposure
- 3.4 ppm for 24-hr and 8-hr HEC
- 2.8 ppm by National Center for Computational Toxicology, USEPA

USEPA HEC

- Same NOEL as DPR
- Peak MeI in brain dose metric
- 10 ppm for 24-hr and 8-hr

Uncertainty Factors

1. Default UFs

- Interspecies 10 (PK x PD) from NOEL or 3 (PD) from HEC
- Inter-individual 10 (PK x PD)

2. Additional UF of 10

- Neurodevelopmental concern
  - Lack data beyond GD29 from pre- and post-natal exposure
  - Maternal thyroid effects
  - Fetal thyroid effects (histopathology, ↑TSH)
  - Post-natal death from excess iodide

- Excess iodide from MeI – Total iodide burden for children

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Current Health Criteria for Iodide Intake (Vol. I, Table 70)

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

- NAS stated no benefit for above RDA (Recommended Daily Allowance) and Tol-UL (Tolerable Upper Intake Level); these levels may not protect sensitive individuals
- These guidance/standards are applicable to short and long term excess iodide exposure; however, subchronic and chronic HECs are all higher than acute HEC of 0.24 ppm

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Excess Iodide Body Burden from MeI

Source of Iodide Daily Intake	Additional Iodide from MeI
➢ Drinking water ➢ Salt ➢ Natural occurrence in food ➢ Food additives ➢ Vitamin and mineral supplements ➢ Therapeutics ➢ Breast milk for infants	➢ Inhalation ➢ Drinking water

Sensitive Individuals

- Thyroid disease, Previously iodine deficiency
- Pre-term neonates sensitive to oxidative stress
- Low GSH – genetic polymorphic, young adults, seniors

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Application of UFs

1. UF = Acceptable MOE

$$RfC = \frac{HEC}{UF}; \qquad MOE = \frac{HEC}{Exposure}$$

2. DPR Proposed MeI RfC

$$RfC = \frac{0.24\ ppm}{3 \times 10 \times 10} = 1\ ppb$$

3. Additional Iodide for Children 1 – 3 yrs old @1 ppb MeI:
   - 42 µg/day (or 34 µg/day at 0.8 ppb from Vol.1, Table 73)
   - NAS Tol-UL – RDA = 110 µg/day
   - ATSDR MRL – RDA = 23 to 63 µg/day

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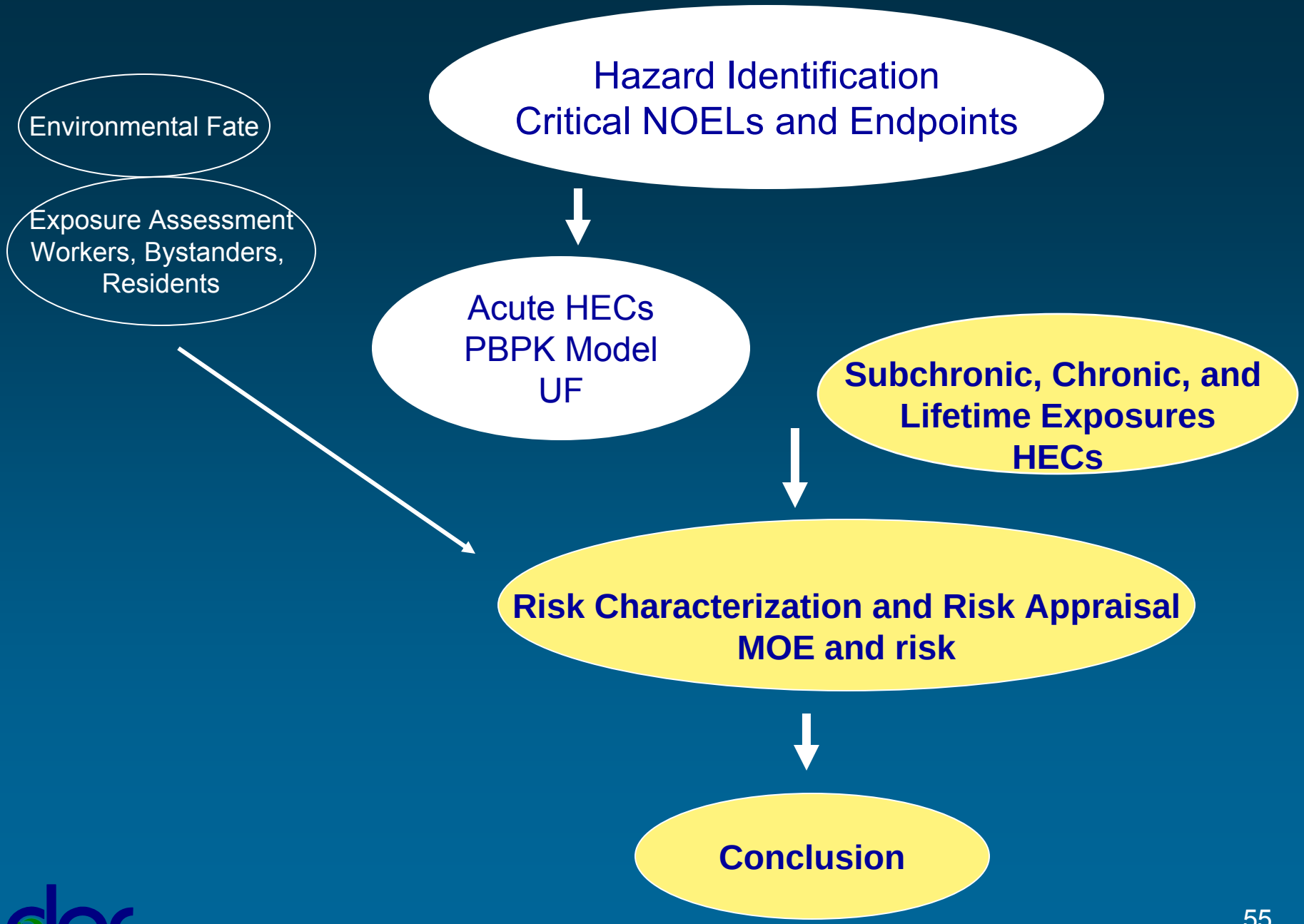
Hazard Identification
Critical NOELs and Endpoints
Environmental Fate
Exposure Assessment
Workers, Bystanders, Residents
Acute HECs
PBPK Model
UF
Subchronic, Chronic, and Lifetime Exposures
HECs
Risk Characterization and Risk Appraisal
MOE and risk
Conclusion

Interspecies Pharmacokinetic Differences

- PBPK modeling
  - Acute exposure NOELs
- DPR default methodology
  - Repeated exposure NOELs
  - Species breathing rate ratio (Human, age- adjusted)
  - PK_{animal} of $10^{0.5}$

$$HEC = NOEL \times \frac{\text{Animal Breathing Rate}}{\text{Human Breathing Rate}} \times \frac{1}{PK_{animal}}$$

Modified Table 65. Critical endpoints, HECs, and potency factor for MeI risk characterization.

Duration	Toxicity endpoints	NOEL	HECs	
			Worker/Worker bystander	Bystander/ Resident
Acute	Fetal death in rabbits	2 ppm	0.22 ppm	0.24 ppm (women of child-bearing age)
	Olfactory epithelium degeneration in rats	21 ppm	2.8 ppm	2.2 ppm (all ages)
	Neurotoxicity in rats	27 ppm	3.4 ppm	3.4 ppm (all ages)
Sub-chronic	↓ Pup wt, delayed development in rats	5 ppm	4.1 ppm	1.4 ppm (adult)
	↑ Relative liver wt, ↓ body wt gain in rats	21 ppm	NA	2.4 ppm (child) 1.9 ppm (infant)
Chronic	Salivary gland metaplasia in rats	5 ppm	4.1 ppm	1.0 ppm (adult) 0.6 ppm (child) 0.5 ppm (infant)
Lifetime	Thyroid tumors in rats	20 ppm	16.3 ppm	3.9 ppm (adult)
		Potency factor: 1.61×10^{-2} mg/kg/day^{-1} (human eq.)		

Risk Characterization

- Margin of Exposure (MOE)

  MOE= HEC ÷ Human exposure level

- Cancer probability of risk

  Risk = Potency factor x Human exposure level

Risk Appraisal

- MeI non-cancer MOE benchmarks
  - Conventional MOE benchmark
    =30 (PD_{animal} 3, PK_{human} x PD_{human} 10)
  - Acute fetal death: 300 ($UF_{additional}$ of 10)
  - All other acute endpoints: 30*
  - Repeated exposure endpoints: 30*

- MeI cancer risk benchmarks
  - MOE
    - 300 (Conventional UF 30 and $UF_{additional}$ of 10)
  - Cancer risk probability (DPR policy)
    - Workers: 1×10^{-5}
    - General population: 1×10^{-6}

* Does not include consideration of excess iodide intake

Table 68. MOEs and lifetime risks for workers exposed to MeI.

Application Methods/ Workers	Acute MOE			Seasonal MOE	Chronic MOE	Lifetime	
	Fetal Death	Nasal Toxicity	Neuro-toxicity			MOE	Risk
Shallow Shank Injection-tarped (broadcast and bedded)							
Applicator	1	10	13	68	273	2,038	$7x10^{-5}$
Shovelman and shoveler	3	35	43	205	820	6,113	$3x10^{-5}$
Tarp monitor	1	9	11	103	410	3,056	$6x10^{-5}$
Tarp hole puncher, cutter	3	35	43	137	547	4,075	$3x10^{-5}$
Planter	37	467	567	1,025	4,100	30,563	$5x10^{-5}$
Drip Irrigation-tarped (bedded)							
Applicator	73	933	1,133	4,100	13,667	101,875	$1x10^{-5}$
Hole puncher	15	187	227	410	1,640	12,225	$9x10^{-5}$
Planter	55	700	850	4,100	13,667	101,875	$9x10^{-5}$

Table 69. MOEs for bystanders exposed to MeI.

Groups/ Application Methods	Acute MOE			Seasonal MOE	Chronic MOE	Lifetime	
	Fetal Death	Nasal Toxicity	Neuro-toxicity			MOE	Risk
Worker bystanders							
Drip irrigation, raised bed	0.1	2	2	342	NA	NA	NA
Shank injection, raised bed	0.4	5	6	342	NA	NA	NA
Shank injection, flat-fume	0.2	3	3	342	NA	NA	NA
Non-worker bystander adults							
Drip irrigation, raised bed	0.8	7	11	117	NA	NA	NA
Shank injection, raised bed	1	11	17	117	NA	NA	NA
Shank injection, flat-fume	1	11	17	117	NA	NA	NA

Table 69. MOEs for bystanders exposed to Mel. (continued)

Groups/ Application Methods	Acute MOE			Seasonal MOE	Chronic MOE	Lifetime	
	Fetal Death	Nasal Toxicity	Neuro-toxicity			MOE	Risk
Bystander children (3-5 years old)							
Drip irrigation, raised bed	NB	7	11	200	NA	NA	NA
Shank injection, raised bed	NB	11	17	200	NA	NA	NA
Shank injection, flat-fume	NB	11	17	200	NA	NA	NA
Bystander infants (<1 year old)							
Drip irrigation, raised bed	NB	7	11	158	NA	NA	NA
Shank injection, raised bed	NB	11	17	158	NA	NA	NA
Shank injection, flat-fume	NB	11	17	158	NA	NA	NA

Table 69. MOEs and lifetime risks for residents exposed to MeI.

Groups/ Application Methods	Acute MOE			Seasonal MOE	Chronic MOE	Lifetime	
	Fetal Death	Nasal Toxicity	Neuro-toxicity			MOE	Risk
Residents living next to application sites							
Adults	0.8	7	11	117	333	1,300	9×10^{-5}
Children (3-5 years old)	NB	7	11	200	200	NA	NA
Infants (<1 year old)	NB	7	11	158	167	NA	NA

Reference Concentration

- RfC = HEC ÷ UF_{total}
- Evaluate iodide intake at the RfCs

Mel HEC	Total UF	RfC	Iodide intake for 1-3 year old
Acute 0.24 ppm	300	1 ppb	42 µg/day
Subchronic 1.4 ppm	30	45 ppb	1,887 µg/day
Chronic 0.5 ppm	30	15 ppb	629 µg/day

TAI=(NAS UL 200 µg/day) – (RDA 90 µg/day)

TAI= 110 µg/day for 1-3 years old

Iodide = ppb x 5.65 µg/m^3-ppb x BR x 127/142

Conclusion

- The potential health risks of workers and general population exposed MeI are assessed.
- Many human exposure scenarios are of health concern because of noncancer and cancer effects of MeI and iodide
- MeI reference concentrations for all durations (acute, subchronic, and chronic) should not exceed 1 ppb to protect against MeI and excess iodide toxicity
- Under conditions evaluated (available data, approaches, assumptions), proposed use of MeI in field fumigation results in significant health risks for workers and the general population

dpr