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Methyl Iodide (Iodomethane)

**RISK CHARACTERIZATION DOCUMENT
FOR INHALATION EXPOSURE**

Appendices to Volume I (Health Risk Assessment)

External Panel Review Draft

**Medical Toxicology Branch
Department of Pesticide Regulation
California Environmental Protection Agency**

August 2009

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Appendices to Volume I:

Appendix A. Review of Physiologically Based Pharmacokinetic Model for Human Equivalent Concentration

Appendix B. Calculations

Appendix C. U.S. Environmental Protection Agency Risk Assessment

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**Appendix A. Review of Physiologically Based Pharmacokinetic Model
For Human Equivalent Concentration**

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1 **I. INTRODUCTION**

2
3 This review on acute Human Equivalent Concentrations (HECs) of methyl iodide (MeI) derived
4 from Physiologically Based Pharmacokinetic (PBPK) modeling pertains to three sets of
5 endpoints: 1) fetal death in rabbits from maternal exposure, 2) nasal olfactory epithelial
6 degeneration in rats, and 3) neurotoxicity in rats. Data and discussions already presented in
7 Volume I are briefly mentioned but not repeated here in detail.

8
9 For deriving the HECs, the PBPK model is expected to account for interspecies pharmacokinetic
10 differences. A diagram of the basic model taken directly from Arysta (2007) is included in
11 Figure A-1. The same basic PBPK model structure is used for all three endpoints but the rat
12 model contains an enhanced nose compartment for simulating the nasal endpoint HECs. It is
13 also used for the neurotoxicity endpoint. The same basic model and endpoints are also used by
14 U.S. Environmental Protection Agency (USEPA). However, the final HECs presented in this
15 review differ from USEPA (2007) due to different modeling baselines and dose metrics. They
16 are highlighted herein.

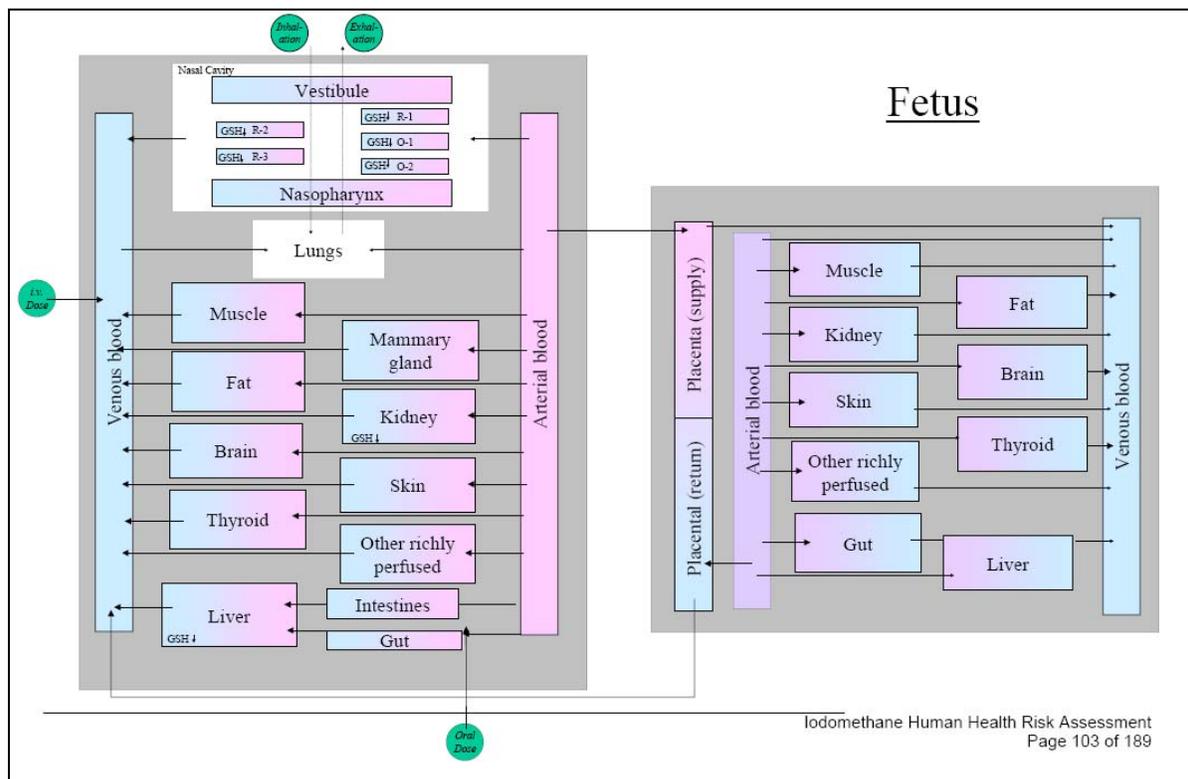
17
18 The iterative PBPK model runs presented in this review were conducted by Arysta (2008a, b, c,
19 d, e, f). To avoid confusion, instead of the term “bystander” used in the Arysta modeling reports
20 that was applicable to both “bystander” and “resident” in Volume I and II, the term “General
21 Population” is used in this Appendix for anyone who does not receive occupational exposure as
22 being a part of the work task associated with the MeI use. This review also includes discussions
23 of occupational HECs that consider a worker’s 16-hour MeI exposure as a member of the general
24 public in addition to the 8-hour work exposure in the Arysta model. They are termed as “8-hour
25 occupational HEC” or “8-hour HEC” in short.

26
27 In this review document, sources for detailed information on the Arysta model are cited. The
28 rabbit and rat model codes were initially submitted by Arysta (2007). The source codes and
29 model input and output for the specific model iterations presented in this review are in Arysta
30 (2008a, b, c, d, e, f). Additional model description can also be found in Sweeney *et al.* (2009)
31 which became publicly available after the DPR model review. Further information related to
32 supporting data for the model construct and application previously submitted to DPR are also
33 published within an entire issue of the Journal of Inhalation Toxicology (2009 issue 6, volume
34 21); many of these articles are added to the citations in Volume I for additional sources of
35 information. For ease of cross reference between this review and Volume I, the same literature
36 citation designation is used throughout both documents. This may mean, for example, a
37 publication is designated as “b” while it is “a” for the same authors in the same year appearing
38 later in sequence or not be used at all in this review.

39
40
41 **II. FETAL DEATH IN RABBIT**

42
43 Aspects of the modeling framework that are important to establishing the HEC specifically for
44 the fetal death endpoint include input parameters and model validation and the dose metric(s) for
45 the HEC. A key issue in selecting the dose metric for the HEC is the exposure duration and

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Figure A-1. Diagram of MeI PBPK model. Taken directly from Arysta (2007).

1 frequency associated with the NOEL. These essential determinants are discussed before the final
2 presentation of the HEC.

3 4 **II.A. Model and Parameters**

5
6 The rabbit model was reviewed by USEPA (2007) for establishing HECs corresponding to a
7 NOEL of 10 ppm, 5-fold higher than the 2 ppm established by DPR. The model description,
8 codes, and parameters are in Arysta (2007) and Mileson *et al.* (2007). They are subsequently
9 published in open literature (Sweeney *et al.*, 2009). This section provides only a very brief
10 description of the model, mainly as a backdrop for focusing on some key issues that could
11 significantly impact the modeling outcome.

12
13 Comparison of model output to the experimentally measured values is used to calibrate and
14 adjust input variables for model fit. The iodide level in blood is designated as “plasma” in all
15 Arysta model runs, while it is referred to as “serum” in toxicity studies. To simplify, “serum” is
16 used in this review for the model output. Key determining variables involved in the initial model
17 fit to data from NaI exposures in the study by Morris *et al.* (2004) (see: Table 50 and Section
18 III.J.2. of Volume I) are: placental and maternal uptake, urinary elimination rate, and maternal
19 and fetal iodide transfer (Mileson *et al.*, 2007). The model documentation stated that further
20 parameter adjustments (unspecified) to fit data from the MeI study by Slotter (2005a, b)
21 compromised the fit to the Morris data. Mileson *et al.* (2007) further speculated that model
22 parameters that may be iodide concentration-dependent (e.g., transfer between maternal and fetal
23 blood) may need dose-dependent correction but this adjustment was not carried out due to the
24 modeler’s conclusion that the current model provided a reasonable fit.

25
26 The specific input parameters and simulation patterns highlighted below are identified for their
27 importance to biological considerations in establishing the HEC and their potential to
28 significantly impact the model outcome. Validation against measured data is included in these
29 discussions.

30 31 **II.A.1. Alveolar Ventilation Rate (QAC)**

32 33 Rabbit simulation

34
35 The Arysta pregnant rabbit HEC model initially used the QAC of 12 L-hr/kg^{3/4} from non-
36 pregnant rabbits. This is only approximately 70% of the pulmonary ventilation rate measured by
37 DeLorme (2004) for non-pregnant females during 18.5 ppm MeI exposure. On the other hand, a
38 higher QAC of 20 L-hr/kg^{3/4} for GD20-30 rabbits was used for comparing model output to
39 experimental data from the Slotter studies (Slotter 2005a, b) in which rabbits received MeI on
40 GD23-26. The justification for the use of a lower QAC in single day simulation is as a “health
41 protective” or “conservative” input for the HEC determination (Mileson *et al.*, 2007) and for
42 targeting an early pregnancy stage (Mileson, 2008). Nevertheless, DPR considers it more
43 important that a biologically valid parameter is used in PBPK modeling.

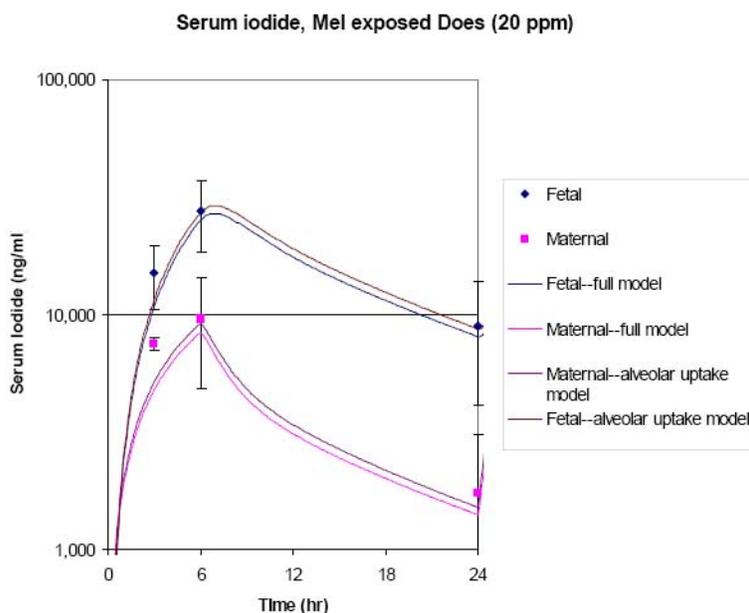
1 The illustration of the model fit to the data from the Slotter studies is provided by Mileson *et al.*
2 (2007) and given in Figure A-2a (a single exposure in 24 hours) and A-2b (4 repeated daily MeI
3 exposures). These figures are taken directly from Figures 4a, b in Mileson *et al.* (2007). The
4 model showed reasonable fit to the 3 data points for fetal serum levels within 24 hours but
5 underestimated the maternal data, especially at hour 3. The fit for both maternal and fetal data
6 became poorer as time progressed (Figure A-2b). No experimental data are available for model
7 validation beyond a few days. The poor model fit in time indicates increasing uncertainty for
8 extending the model beyond 24 hours, especially for accommodating the assumption by Mileson
9 *et al.* (2007) that the NOEL should represent a single-day incremental exposure after the steady
10 state of fetal blood iodide is reached on day 13. This issue on defining a single-day HEC
11 corresponding to the NOEL is discussed in Section II.B.1.

12
13 Table A-1 presents the model output at 20 ppm MeI exposure but using the non-pregnant 12 L-
14 hr/kg^{3/4} QAC. As expected, the lower QAC results in further deviation from the experimental
15 measurements. During the first 24 hours, the maternal serum iodide concentrations were only 32
16 - 53% of the measured values. The fetal concentrations were lower at hour 3 (48% of measured
17 values) and hour 6 (66% of measured values), but caught up with the measured values at hour
18 24. Thus, the use of lower QAC would significantly impact the HEC especially when maternal
19 serum iodide is used as the dose metric. A comparison of HECs is available in Table A-4.

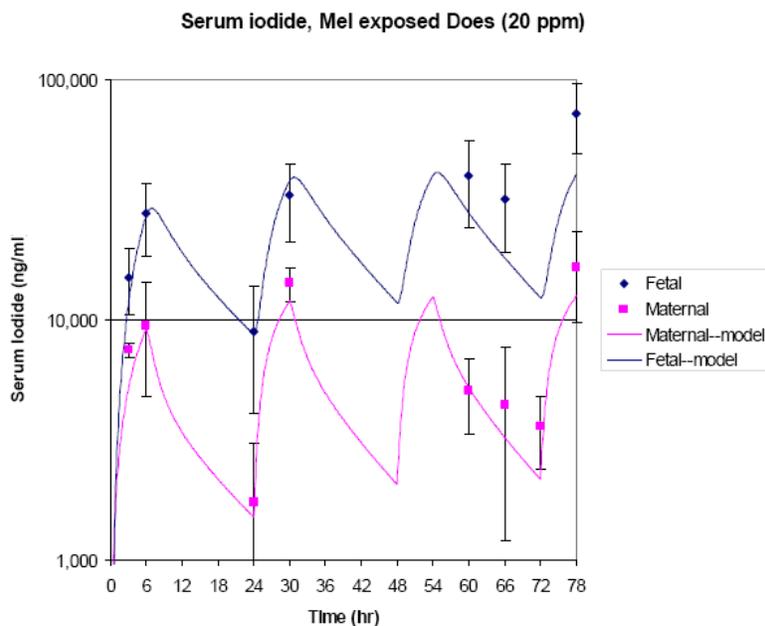
20
21 After being informed of the above concerns by DPR, Arysta provided a revised model simulation
22 using the QAC of 20 L-hr/kg^{3/4} in September 2008 (Arysta, 2008e). This model output became
23 available when DPR's model review was near its completion and the majority of model
24 presentations from the lower QAC runs were already in place, and only at 2 ppm. DPR did not
25 consider it necessary to delay the review process by requesting further model runs from Arysta
26 (i.e., at 20 ppm) nor invest substantial resources to re-do a different set of basic model behavior
27 illustrations. The value of QAC is clearly labeled for all data presented in this review. It should
28 be emphasized that the DPR preferred 20 L-hr/kg^{3/4} QAC is used for generating model runs for
29 DPR's final HECs for this endpoint. They are presented in Section II.C.

30
31 The lower QAC was used in the final single-day HEC modeled by USEPA (USEPA, 2007;
32 Mileson, 2008) at the NOEL of 10 ppm. Model output at 20 ppm using 20 L-hr/kg^{3/4} QAC was
33 recently provided by Rodriguez (2009) as a part of USEPA's comments to the March 2009 draft
34 of this DPR model review. The graphic comparisons of model fit at both QACs are presented in
35 Figure A-3, taken directly from Rodriguez (2009). The modeled maternal serum iodide was 67 -
36 91% of the measured values in the 24 hours. The modeled fetal serum iodide was 95% of
37 measured level at hour 3, but exceeded the measured levels by 31% at hour 6 and 81.3% at hour
38 24. Thus, the higher estimation of fetal serum iodide profile would be a concern if it is used as
39 the dose metric for HEC determination. While data are not directly available for any AUC
40 comparison, the use of lower QAC might be somewhat justified for USEPA's HEC based on the
41 fetal serum iodide dose metric because of the better model fit than at the higher QAC
42 (Rodriguez, 2009). However, the issue remains regarding the physiological incongruity of using
43 a low non-pregnant QAC for the window of vulnerability during GD23-26. Apparently the
44 inability to achieve a good fit at both maternal and fetal serum iodide levels is beyond the
45 adjustment of QAC parameter and is further evident from the standpoint of fetal-to-maternal
46 (F/M) iodide ratio as presented in the next section.

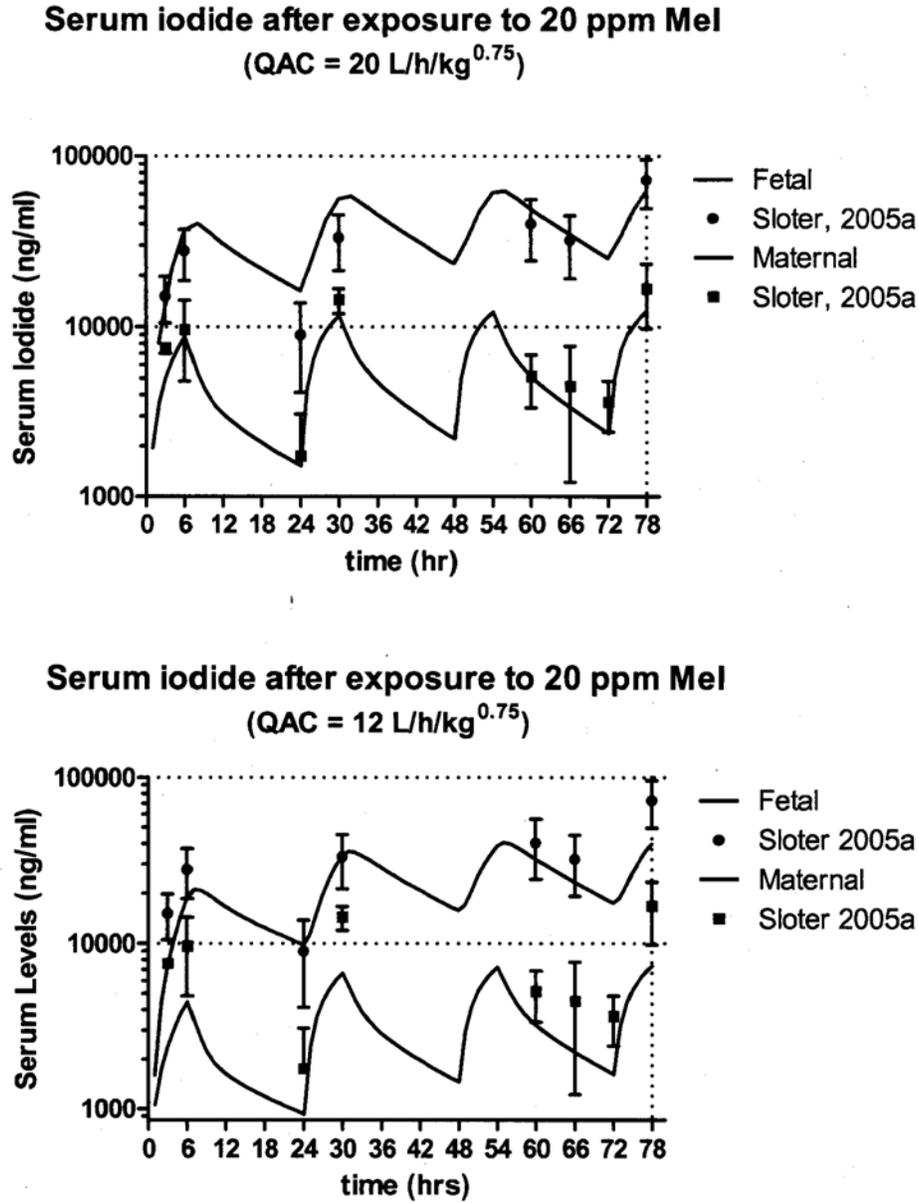
1 Figure A-2a



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4 Figure A-2b



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6 Figure A-2. Modeled versus measured data in rabbits (Taken from Mileson *et al.*, 2007, Figure
7 4a and 4b). The measured data are from Slotter, 2005a. The “full model” in 4a
8 includes both alveolar and nasal MeI uptakes. Lines: simulations; Symbols:
9 experimental data. The QAC for this simulation is 20 L-hr/kg^{3/4}. Using the lower
10 QAC of 12 L-hr/kg^{3/4} would result in much poorer model fit than demonstrated
11 here (see Table A-1).



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Figure A-3. Model rabbits at QAC 12 and 20 L-hr/kg^{3/4} (Taken from Rodriguez, 2009, Figure 1). The measured data (points) were from Slotter, 2005a. QAC at 20 L-hr/kg^{3/4} was used in the top simulation (lines) while 12 L-hr/kg^{3/4} was used in the bottom simulation (lines).

1 Table A-1. Modeled versus measured rabbit serum iodide concentrations after repeated 20 ppm
 2 MeI (6 hour/day) exposure.^a

Hour	Modeled ^b (mg/L)		F/M	Measured ^c (mg/L)		F/M
	Maternal	Fetal		Maternal	Fetal	
3	2.39	7.22	3.0	7.50 ± 0.49	15.10 ± 4.62	2.0
6	4.41	18.45	4.2	9.57 ± 4.75	27.80 ± 9.25	2.9
24	0.92	9.77	10.6	1.74 ± 1.34	8.96 ± 4.83	5.2
30	6.55	33.33	5.1	14.30 ± 2.36	33.20 ± 11.90	2.3
60	3.19	32.09	10.1	5.11 ± 1.76	40.10 ± 15.70	7.9
66	2.19	23.35	10.7	4.47 ± 3.25	32.00 ± 11.90	7.2
72	1.61	17.50	10.9	3.61 ± 1.20	-	-
78	7.28	39.67	5.5	16.60 ± 6.80	72.60 ± 23.20	4.4

3 a/ The beginning of MeI treatment is hour zero. “F/M” is the fetal-to-maternal ratio.

4 b/ The QAC for model output was 12 L-hr/kg^{3/4} for a non-pregnant rabbit. A separate
 5 simulation by Rodriguez (2009) showed that changing the QAC to 20 L-hr/kg^{3/4} did not
 6 significantly alter the modeled F/M ratios.

7 c/ The corresponding measured values are from a Slotter study (Slotter, 2005b) in which
 8 pregnant rabbits received 20 ppm exposure starting on GD23. The maternal and fetal
 9 levels from another Slotter study at 25 ppm MeI exposure, 6 hr/day (Slotter, 2005a, data in
 10 Table 56 of Volume I) are: 17.2 and 37.1 mg/L at hour 30 and 26.4 and 70.6 mg/L at
 11 hour 78.

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17 Human Simulation

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19 A QAC of 16.5 L-hr/kg^{3/4} is used in simulating exposure scenarios for pregnant women. It was
 20 noted that a very slightly lower QAC of 16.4 L-hr/kg^{3/4} was used by USEPA in their HEC
 21 simulation (Rodriguez, 2009). In the Arysta model, the minute volume for the 24-hour MeI
 22 exposure is 567 L/hr (tidal volume at 630 ml/breath, 15 breath/minute). This rate is close to the
 23 0.5 m³/hr recommended in the USEPA Exposure Factors Handbook (EFH) (USEPA, 1997) for
 24 short-term sedentary activities. While USEPA used the same breathing rate for modeling its
 25 occupational exposure scenarios, DPR’s current default breathing rate is 833 L/hr. This default
 26 is lower than the 1.0 m³/hr given in the EFH for light activities (USEPA, 1997). Subsequent to
 27 the above considerations, Arysta provided revised model simulations by changing the tidal
 28 volume (TVol) from 630 to 925 ml/breath to match the 1.47-fold higher DPR default breathing
 29 rate of 833 L/hr (Arysta, 2008e). The revised model outputs are presented in Section II.C. and
 30 used in this review for establishing DPR’s final occupational HECs.

31
32 One question exists in how the higher breathing rate for workers is incorporated into the model.
 33 Rodriguez (2009) opined that the 1.47-fold change should instead be reflected on the QAC
 34 which resulted in an 8-hour occupational HEC of 0.5 ppm based on the maternal serum iodide
 35 AUC dose metric and the NOEL of 2 ppm in rabbits. However, this “8-hour only” HEC did not

1 account for the 16 hours of additional exposure for these workers as a member of the general
2 public at the HEC of 0.24 ppm.

4 **II.A.2. Maternal versus Fetal Iodide Levels**

6 The transfer between maternal and fetal iodide was one of the three key factors that determined
7 the maternal and fetal serum iodide profile (Sweeney *et al.*, 2009). The other two factors were
8 placental and mammary uptake and urinary elimination rate. In the model, CLTRANS1C
9 denotes placenta to fetus transfer and CLTRANS2C denotes fetus to placenta transfer. General
10 illustrative model outputs for both rabbits and humans are presented in Table A-2 and discussed
11 below in the context of their respective simulations.

13 Rabbit Simulation

15 The rabbit model used CLTRANS1C of 0.07 L/hr-kg^{0.75} and CLTRANS2C of 0.015 L/hr-kg^{0.75}.
16 The resultant fetal-to-maternal serum iodide ratios (F/M) are compared to the two sets of
17 experimental data.

19 The first comparison is to the measurements by Slotter (2005b) after 20 ppm MeI exposure. As
20 shown in Table A-1, at the same MeI exposure level, the modeled F/M ratios are higher than the
21 experimental data at all time points. A separate simulation by Rodriguez (2009) showed that
22 changing the QAC to 20 L-hr/kg^{3/4} did not significantly alter the modeled F/M ratios.

24 The second comparison is to the measurements from a NaI study by Morris *et al.* (2004).
25 Although these data are used for model adjustment, the resultant F/M ratios at 2 and 10 ppm MeI
26 exposure (Table A-2) show significant overestimation of the relative distribution of iodide to the
27 fetal blood. The blood F/M ratios between 2 - 24 hours after a single i.v. injection of NaI on
28 GD25 from Morris *et al.* (2004) are 2.6-5.8 at 0.75 mg/kg and 1.6-2.8 at 10 mg/kg (Table 58 in
29 Volume I). The ratios from model output during the similar period are 3.1-8.2 at 2 ppm MeI and
30 3.4-10.0 at 10 ppm MeI exposure (Table A-2). Although the NaI study and MeI simulation
31 differ in many respects (NaI given via i.v. versus MeI given via inhalation), the F/M comparison
32 is possible since the NaI dose range in the Morris study was designed to encompass the range of
33 iodide from toxicologically relevant MeI exposure levels. In this case, the range of total amount
34 of iodide in the simulated 2-10 ppm MeI exposure is 1.5-7.6 mg/kg/day MeI, or 1.3-6.8
35 mg/kg/day iodide at 100% MeI inhalation absorption. The comparison is of value because it is
36 based on the level of iodide in circulation and not the external NaI or MeI dose.

38 No other experimental data are available for similar validation comparisons. The general pattern
39 is a higher simulated F/M ratio than the results from the two model calibration studies, even
40 within the first 24 hours of MeI exposure. This indicates that a more holistic adjustment of
41 transfer rates and other input parameters within the model construct would be desirable
42 especially if fetal serum iodide is used as the dose metric for the HEC.

1 Table A-2. Modeled fetal-to-maternal serum iodide (F/M) ratio in rabbits and humans exposed
2 to MeI.^a

Hour	Modeled ^a – Rabbits						Modeled ^a – Humans		
	2 ppm			10 ppm			3.7 ppm		
	M	F	F/M	M	F	F/M	M	F	F/M
3	0.16	0.50	3.1	0.94	3.20	3.4	0.53	0.53	1.0
6	0.21	0.91	4.4	1.57	6.98	4.5	0.95	0.95	1.0
24	0.06	0.50	8.2	0.41	4.14	10.0	2.20	2.06	0.9
30	0.29	1.44	5.0	2.72	14.2	5.2	1.36	1.40	1.0
60	0.20	1.63	8.1	1.53	15.5	10.2	0.11	0.17	1.6
66	0.18	1.47	8.0	1.13	11.9	10.5	0.071	0.13	1.8
72	0.17	1.33	8.0	0.89	9.40	10.6	0.049	0.097	2.0
78	0.42	2.33	5.5	3.38	19.7	5.8	0.037	0.078	2.1
96	0.20	1.63	8.1	0.93	9.94	10.6	0.021	0.049	2.4

3 a/ Data from Mileson *et al.*, 2007. “M” and “F” are mg/L iodide concentrations in maternal
4 and fetal serum, respectively. The rabbit simulation represents daily 6 hours of MeI
5 exposure for 4 days using the lower QAC of 12 L-hr/kg^{3/4}. The human simulation represents
6 a single 24-hour MeI exposure.
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13 Human Simulation

14
15 The ratio of cord-to-maternal blood iodide concentration was reported in an earlier study by
16 Cottino *et al.* (1972) with 18 women who received iodomethylsparteine through i.v. injection at
17 termed delivery. The time between the injection and delivery ranged from 15 minutes to 48
18 hours, and the paired cord-to-maternal blood iodide concentration ranged from 0.5 to 3.4. More
19 recently, Rayburn *et al.* (2007) conducted a survey on plasma iodide concentration of paired
20 maternal and cord blood at delivery (Table 51 in Volume I). These data are subsequently
21 published in the open literature (Rayburn *et al.*, 2008). The surveyed subjects did not have any
22 documented exposure to any test substances nor povidone iodine. The results are summarized in
23 Table A-3. The average cord-to-maternal blood iodide ratio of 1.2 from this study was used to
24 adjust the CLTRANS1C (placenta to fetus) and CLTRANS2C (fetus to placenta) parameters to
25 0.15 and 0.12 L/hr-kg^{0.75} respectively in the model (Mileson *et al.*, 2007; Barton, 2007). Mileson
26 *et al.* (2007) considered this 1.2 ratio as “conservative” compared to using the pre-term ratio of
27 0.9. In this consideration, Arysta regarded the 0.9 ratio as a possibly better alternative for
28 representing the end-of-first-trimester stage which they assumed to be the window of
29 vulnerability to MeI toxicity and thus the target for their HEC simulation. However, it is DPR’s
30 view that even if the end of first trimester is the only target period for fetal death from MeI
31 exposure, data are unavailable for determining how well iodide levels collected from deliveries
32 during gestation week 29 – 36 may represent the early gestation stage when excess iodide is
33 introduced through exposure to MeI. The related issue of fetal stage at the weight of 0.27 kg is a
34 subject of separate discussion in Section II.A.4.

1 Table A-3. Plasma iodide concentration in human maternal and cord blood at delivery.^a

Delivery	N	Blood Iodide (µg/dL)		Cord-to-Maternal	
		Maternal	Cord	Ratio	Range
Pre-term (29-36 week)	29 ^b	1.6±0.4	1.4±0.5	0.9±0.4	0.35 – 2.11
Term (37-41 week)	92	1.5±0.5	1.7±0.7	1.3±0.8	0.35 – 5.4
All subjects	121 ^b	1.5±0.7	1.6±0.7	1.2±0.7	0.35 – 5.4

2 a/ Data as reported by Rayburn *et al.* (2007)

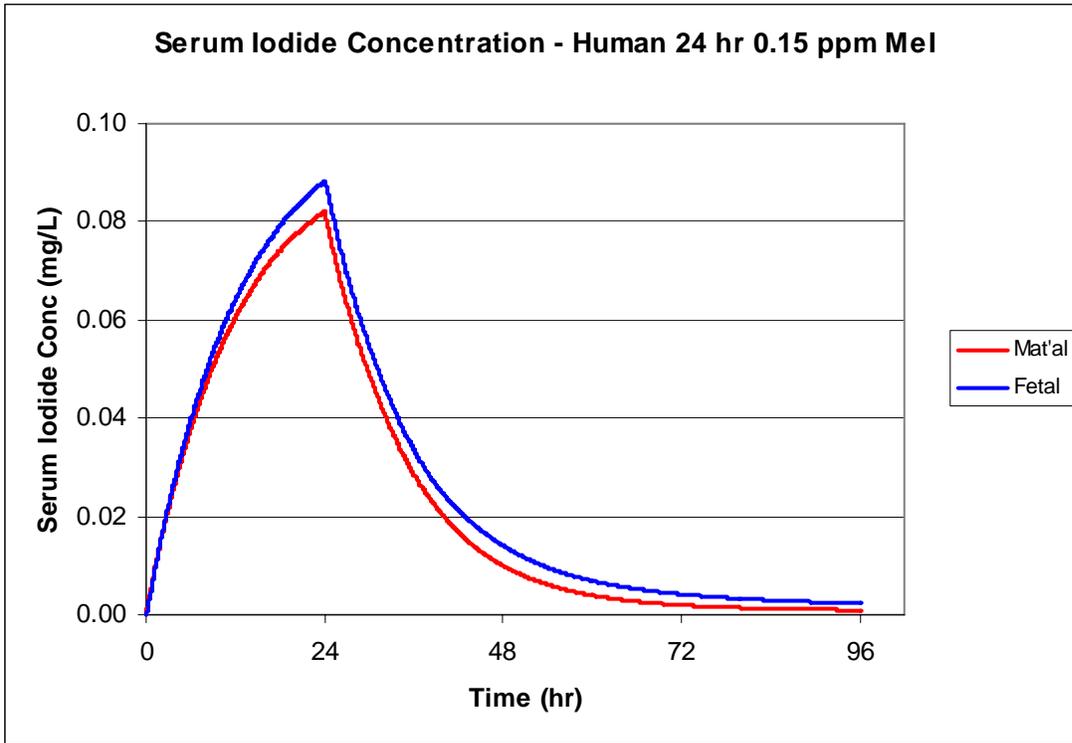
3 b/ Excludes 2 data pairs both at gestation week 33 delivery. One pair with extreme cord blood
 4 concentration suspected as contamination, resulted in a cord-to-maternal ratio of 255.9. The
 5 other with high maternal blood concentration reported as requiring antiarrhythmic therapy,
 6 resulted in a cord-to-maternal ratio of 0.41. They are not included in the statistical analysis.

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 15 Another important observation regarding the F/M ratio is that it is dynamic, not a fixed value.
 16 This can be demonstrated in two scenarios: by comparing simulation results from two MeI
 17 exposure levels and by following the time of diminishing serum iodide concentrations after MeI
 18 exposure. Figure A-4 illustrates the first scenario at 0.15 and 3.4 ppm MeI exposure levels.
 19 These levels are parts of a large set of simulations from Arysta (2008c) and are used here only
 20 for illustration purposes. While the fetal iodide concentration is consistently higher than the
 21 maternal level at 0.15 ppm MeI exposure, this relationship is reversed near the peak
 22 concentration at 3.4 ppm MeI.

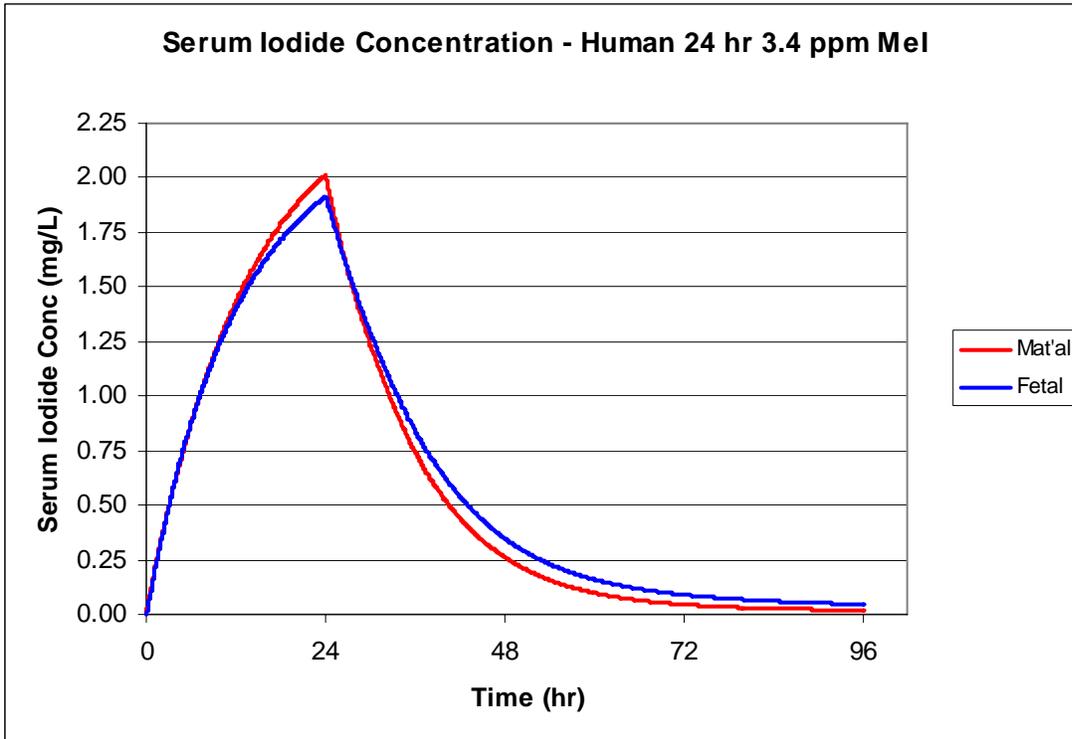
23
 24 Table A-2 illustrates the second scenario at 3.7 ppm MeI exposure. The F/M ratio gradually
 25 increases with decreasing serum iodide level after the end of 24 hours of exposure, from 1.0
 26 within hour 24 to 2.1 - 2.4 by hour 78 - 96. The higher simulated F/M ratio is of interest
 27 because the corresponding serum iodide levels are down at the range reported by Rayburn *et al.*
 28 (2007) but with 2-fold higher F/M ratio in the simulation output. The discrepancy raises
 29 uncertainty about how well either the Rayburn study or the model can describe the dynamics of
 30 iodide distribution between maternal and fetal compartments after MeI exposure.

31
 32 Overall, data in both rabbits and humans indicate greater uncertainty at the fetal compartment
 33 level. In the rabbit model, the F/M ratios did not compare well with measured data at 20 ppm
 34 MeI. Nor did they compare well with data from the only available NaI study. In the human
 35 model, it is uncertain how well data from the Rayburn study can adequately represent the
 36 modeled MeI exposure scenarios, specifically regarding the unmatched gestation stage (i.e.,
 37 applying data from beyond gestation week 29 to model the end of the first trimester stage) and
 38 the iodide exposure status (i.e., applying data from non-iodide exposure conditions to
 39 substantially high excess iodide exposure scenarios). The simulation shows that the ratio is not
 40 constant after MeI exposure and can be much higher than the targeted ratio at a comparable
 41 range of serum iodide concentrations in the Rayburn study.

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Figure A-4. Modeled human serum iodide concentration at 0.15 and 3.4 ppm MeI for 24 hours. Data from Arysta (2008c).

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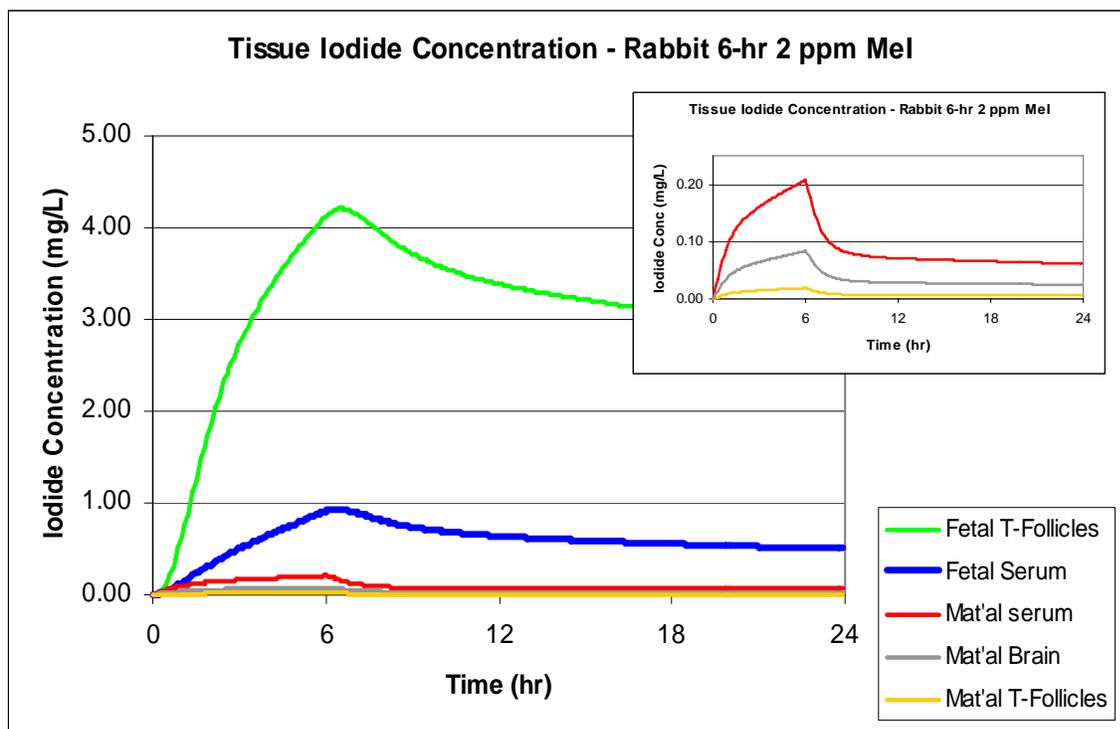
II.A.3. Fetal Thyroid Iodide Level

Arysta used data from the Morris *et al.* (2004) rabbit study with NaI as starting points for modeling iodide disposition variables. The stated model assumption was that when blood kinetics are accurately predicted, tissue-specific parameters are sufficiently accurate without needing further adjustment (Milesen *et al.*, 2007). Although the modeling focuses on the serum MeI and iodide profiles, iodide distribution to fetal thyroid is of specific interest because fetal thyroid is the target tissue of the Arysta proposed mode of action (MOA) (Arysta, 2007). However, since no single MOA for fetal death can be clearly supported (Section IV.A.1.a. of Volume I), the following discussion is mainly on the concerns for the extremely high iodide accumulation in this biologically relevant tissue, and not necessarily for considerations that would directly influence the HEC dose metric selection.

The Morris study showed that within 24 hours of NaI injection on GD25, fetal thyroid did not accumulate iodide as compared to levels in fetal trachea. In fact, at 0.75 and 10 mg/kg NaI, fetal thyroid iodide level is substantially lower than the maternal level (Table 58 and Figure 4 in Volume I). Thus, it is surprising that the model predicted a 4.2 mg/L peak iodide level in fetal thyroid follicles at the end of the 6 hour MeI exposure, a level that is 217-fold higher than the maternal level at 0.02 mg/L (Figure A-5). The fetal-to-maternal ratio is further increased to 513-fold after 18 hours of no exposure. Regarding the ratio of fetal to maternal iodide in rabbit thyroid follicles, model output from different sets of runs indicated that compared to the ratio of 217 at the end of 6-hour of 2 ppm MeI exposure, the ratio is 37 at 20 ppm MeI (maternal 0.4 mg/L, fetal 14.9 mg/L) and 68 at 10 ppm (maternal 0.14 mg/L, fetal 9.8 mg/L) MeI. Thus, within the 2 to 20 ppm MeI range, the iodide concentrations in fetal thyroid follicles are substantially higher than the maternal, contrary to the lack of fetal thyroid iodide accumulation reported in the Morris study from NaI iv injection. Further comparison to rabbit data cannot be made due to the difference in dosing regimen and the NaI versus MeI exposure.

The human model shows an even more distinct pattern of iodide accumulation to the fetal thyroid follicles and at a much higher level than rabbits (Figure A-6). For a single 24-hour exposure to 0.15 – 3.4 ppm MeI, the fetal thyroid iodide saturates at 208 mg/L. Unlike the decline in rabbits after the exposure (Figure A-5), this level remains unchanged in human fetal thyroid after MeI exposure, for at least up to hour 96; i.e., 3 days after the exposure. This plateau is 50-fold above the already seemingly high modeled rabbit fetal thyroid level at the end of 6-hour exposure. Within the human model, the fetal plateau is 1,800-fold higher than the maternal level at the end of the 24-hour exposure to 0.15 ppm MeI.

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 3 Figure A-5. Modeled iodide tissue distribution in rabbits at 2 ppm MeI for 6 hours (simulation
 4 using the lower QAC of 12 L-hr/kg^{3/4}). Data from Arysta (2008c). “T-follicles”:
 5 thyroid follicles. The reduced figure at upper right corner magnified the maternal
 6 patterns. The maternal profiles are enlarged at the upper right box.

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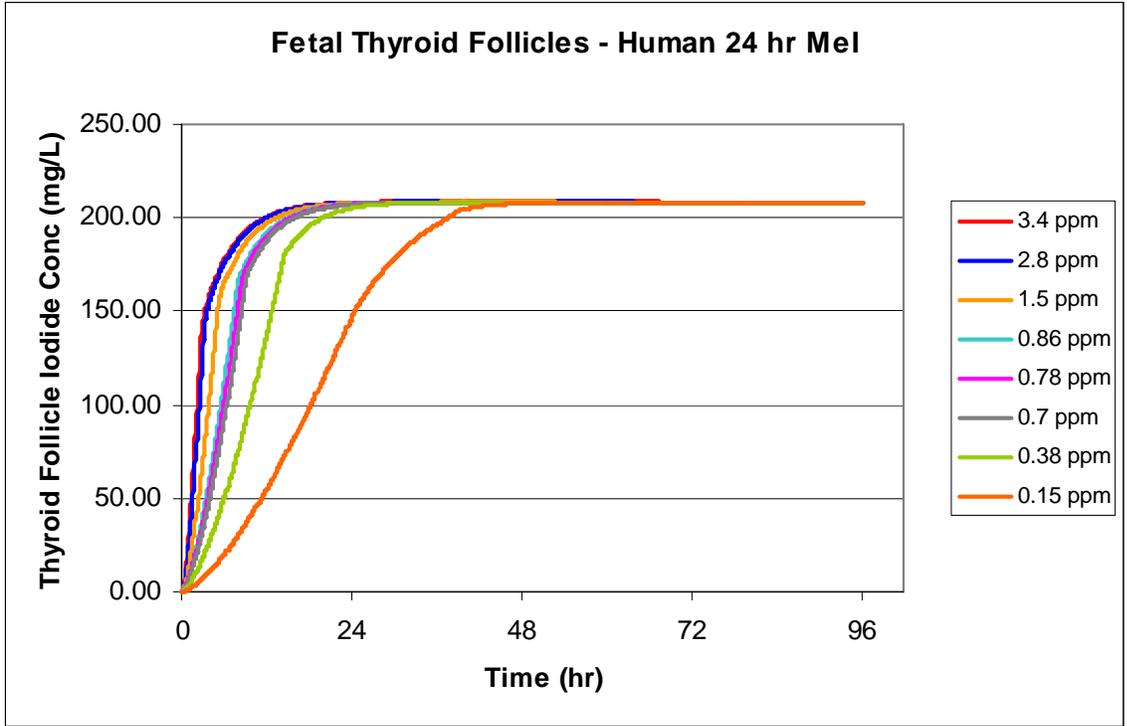


Figure A-6. Modeled iodide concentration in human fetal thyroid follicles at 0.15 - 3.4 ppm MeI. Data from Arysta (2008c).

1 The high predicted level of iodide in human fetal thyroid can be a serious concern. On the one
2 hand, its high simulated level may merely indicate the need to further adjust the model construct
3 or parameters. The model documentation mentioned that the lack of modeling stability in
4 predicting fetal thyroid iodide resulted in abandoning the initial attempt to use it as the dose
5 metric for HEC determination (Arysta, 2007). On the other hand, although no tissue distribution
6 data from MeI exposure are available for validation, these high levels could have some
7 likelihood of reality since the model description stated that the iodide transfer rates were derived
8 based on the fit to human fetal thyroid iodide levels as used in the models for perchlorate risk
9 assessment (Gargas *et al.*, 2005).

10
11 Further investigate may be needed for applying the basic human iodide submodel used for
12 assessing the thyroid inhibition by perchlorate to scenarios of excess iodide from MeI exposures.
13 This is desirable even if merely to ensure that the higher level of iodide sequestered into fetal
14 thyroid would not significantly impact the dose metric selection for the HEC modeling. More
15 importantly, if such high fetal thyroid iodide is indeed reflective of human consequence from
16 MeI exposure, its human fetal health implication would be of great concern at the range of 0.15 –
17 3.4 ppm MeI demonstrated in Figure A-6. In fact, by applying USEPA’s default uncertainty
18 factor of 30 to their acute HEC of 4.5 ppm MeI (for 50% GSH depletion in nasal tissue)
19 (USEPA, 2007), the acute RfC would be 0.15 ppm, exactly the level illustrated in Figure A-6.

20 21 **II.A.4. Human Fetal Stage**

22
23 The human model is represented by a maternal body weight of 61.1 kg and a fetal weight of 0.27
24 kg (i.e., a single fetus at maternal weight fraction “VFETC” of 0.0044). The model targets the
25 stage of fetal thyroid ontogeny (Milesion, 2008). Human free T4 and T3 in cord blood begin to
26 increase in gestation week (GW) 12, and the iodide uptake to follicular cells begins to increase in
27 GW18-20 (Howdeshell, 2002). However, fetal thyroid vulnerability should not be limited only
28 to the onset of its ontogeny. The development of iodide autoregulation takes place much later,
29 during GW36-40 (Fuse, 1996; Howdeshell, 2002). Thus, human fetal thyroid vulnerability
30 would not be limited to the end of the first trimester, even when the model is used in the context
31 of the MOA proposed by Arysta (2007), i.e., excess fetal iodide perturbs fetal thyroid function as
32 in a typical Wolf-Chaikoff effect. Instead, the period of vulnerability would extend to any time
33 before the full development of thyroid autoregulation (Fisher and Klein, 1981).

34
35 It is also important to consider the impact of MeI exposure at a higher VFETC for the gestation
36 period beyond the end of the first trimester because there is no compelling evidence for a single
37 proposed MOA. In this case, assuming the applicability of the low normalized sensitivity
38 coefficient¹ for VFETC (given as “<0.05” in Table 11 of Milesion *et al.*, 2007), a 5- to 10-fold
39 higher value for the VFETC (from 0.27 kg, or 0.6 pounds, to 3 to 6 pound fetuses) for later
40 gestation period may still be significant. A more precise estimate on the effect of VFETC was
41 provided in the Arysta comments to DPR March 2009 draft Volume I (Arysta, 2009). A 10-fold
42 higher VFETC would result in decreased iodide level by 12% in the maternal but 42% in the

¹ Normalized sensitivity coefficient (SC) is the change to the predicted dose metrics from changes in model parameter values. It is calculated as the ratio of fractional change in the model prediction to 1% change in the model parameter.

1 fetal serum at 0.24 ppm MeI exposure. Given the uncertainties regarding the choice of fetal
2 stage in modeling, its huge impact on the fetal dose metric would also support the use the
3 maternal instead of fetal serum iodide dose metric in HEC determination.
4

5 **II.A.5. Time Course Profile**

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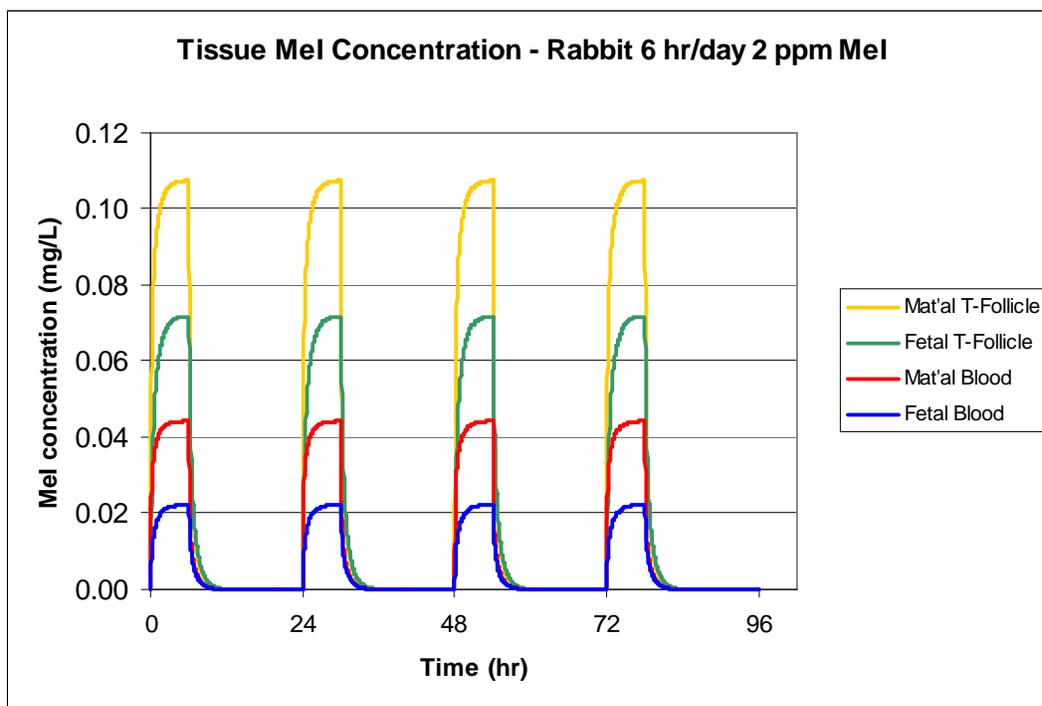
7 Patterns from multiple days of exposure for the dose metrics of interest provide the necessary
8 context for simulating single-day HECs. The general patterns of blood and thyroid distribution
9 of MeI and iodide in rabbits after multiple days of 2 ppm MeI exposure (6 hr/day) are illustrated
10 in Figure A-7 for MeI and Figure A-8 for iodide. Figure A-7 shows that the concentration of
11 MeI diminishes after the 6 hours of exposure without a day-to-day accumulation. Figure A-8
12 shows that the rise of serum iodide from the first 6 hours of exposure does not return to the
13 baseline by the end of 24 hours. Simulations for humans also follow the similar pattern.
14 Corresponding comparison of maternal and fetal output in rabbits (i.e., comparing blood to
15 blood, thyroid to thyroid) shows that the maternal is higher for the MeI profiles whereas the fetal
16 is higher for the iodide profiles.
17

18 **II.A.6. Summary**

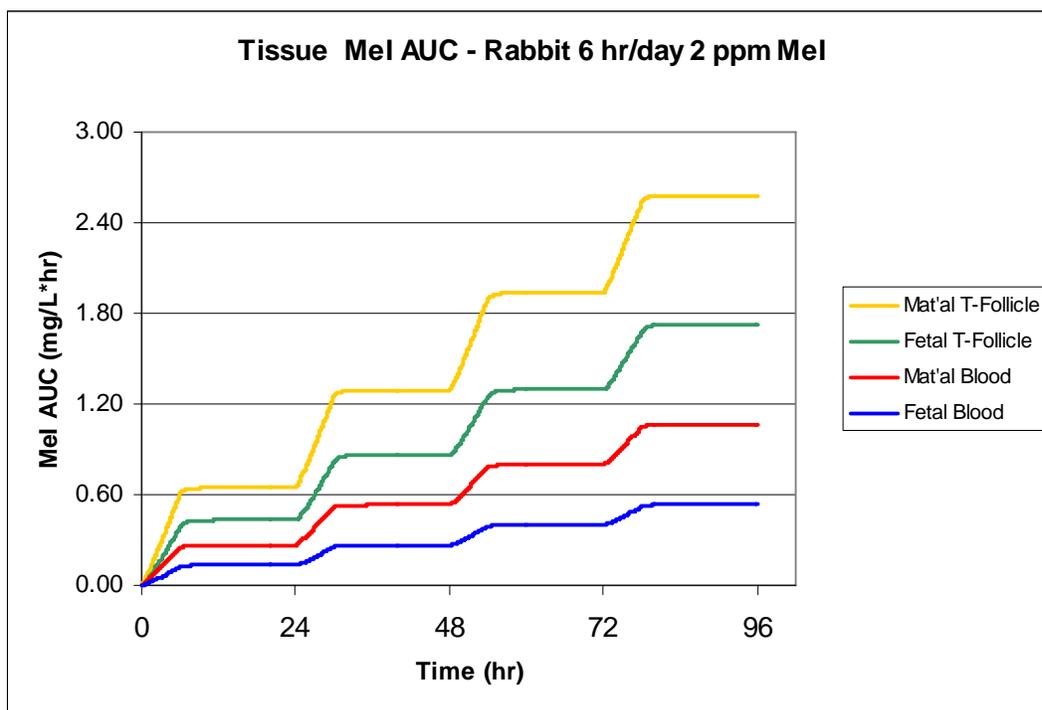
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20 Available data for adjusting the input variables are limited, with experimental data only available
21 at approximately 10-fold above the modeled 2 ppm and with high variability. The fundamental
22 issue concerning modeling fetal death based on surviving fetal data remains unresolved. When
23 compared to available experimental data, the model output shows some discrepancy within the
24 first 24 hours of exposure and to a greater extent beyond the one-day period. In general, the
25 model output shows greater iodide in rabbit fetal serum relative to the maternal level than
26 experimentally reported. This may indicate a greater uncertainty for using rabbit fetal serum
27 iodide as dose metric for HECs. Other questions remain for some biological considerations (e.g.,
28 fetal stages) and simulation outcomes (e.g., extremely high fetal thyroid iodide level). The dose
29 metric selection is discussed in the subsequent section.

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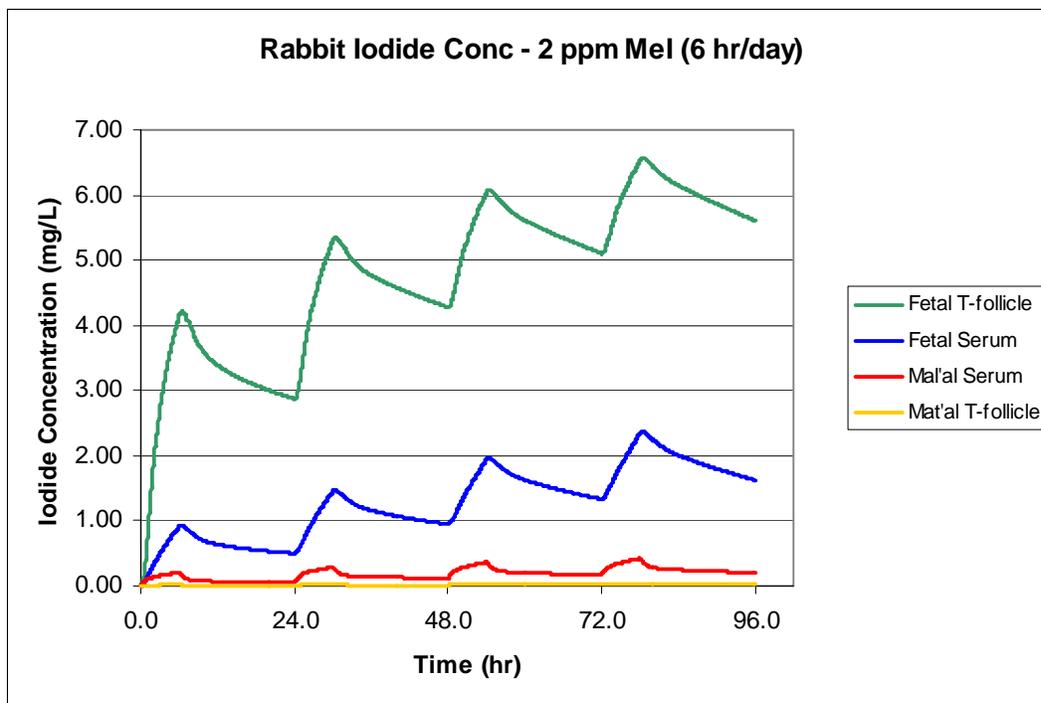


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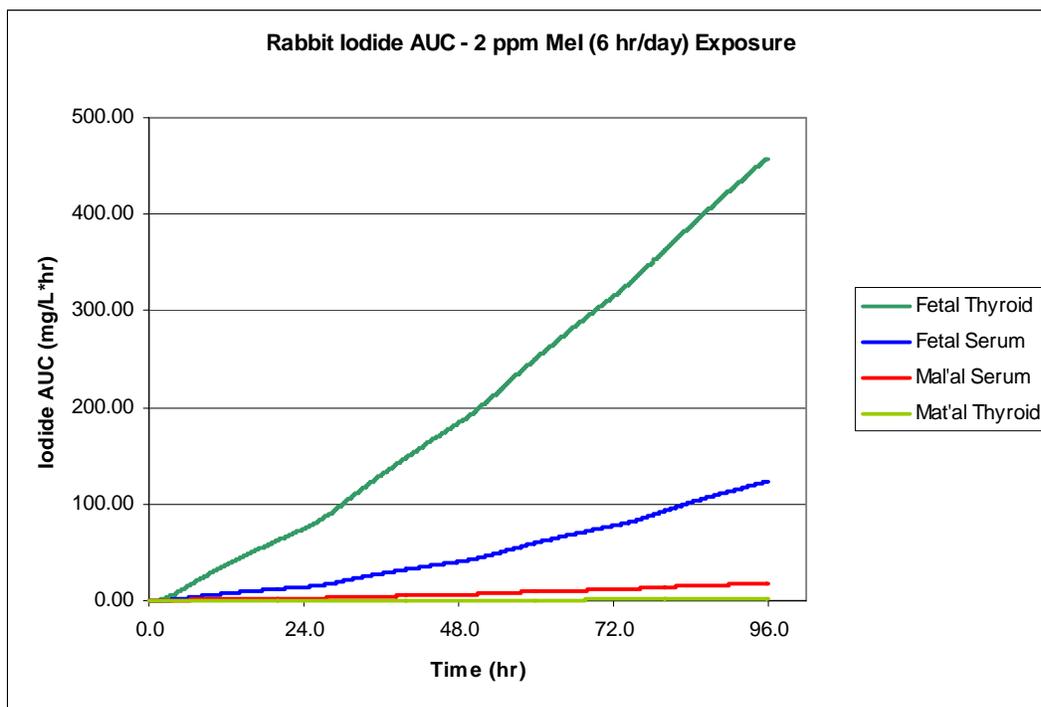


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Figure A-7. Modeled rabbit MeI concentrations and AUC (area under the curve) from 2 ppm MeI exposure, 6 hours/day. Simulated at the lower QAC of 12 L-hr/kg^{3/4}. Data from Mileson *et al.* (2007). “T-follicle”: Thyroid follicle.



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Figure A-8. Modeled rabbit iodide concentrations and AUC (area under the curve) from 2 ppm MeI exposure, 6 hrs/day. Simulated at the lower QAC of 12 L-hr/kg^{3/4}. Data from Mileson *et al.* (2007). “T-follicle”: Thyroid follicle.

1
2 **II.B. Dose Metric**

3
4 Appropriate selection of dose metric(s) is essential to the application of a PBPK model for
5 establishing the HEC. Considerations for the dose metric determination for the fetal death
6 endpoint include the exposure scenario associated with the NOEL and the model output
7 parameter(s) that best reflect the pattern of human exposure without tending toward
8 underestimation. No candidate target tissue marker beyond blood level of MeI or iodide can be
9 identified without a clearly supported MOA, especially for immediately after the second 6 hr/day
10 exposure (i.e., hour 30).

11
12 **II.B.1. Single Day 2 ppm NOEL**

13
14 One key question in modeling the HEC for fetal death is how to derive a single-day HEC based
15 on the 2 ppm NOEL established in a study when pregnant rabbits received MeI exposure during
16 GD6-28. The two possible assumptions for the NOEL are: 1) a single- day exposure, and 2) a
17 single-day incremental exposure. The first assumption was used by USEPA to model HEC at a
18 NOEL of 10 ppm (Barton, 2007). The second assumption is proposed by Mileson *et al.* (2007)
19 for modeling the HEC at the 2 ppm NOEL, i.e., the one-day increment of the area under curve
20 (AUC) for fetal serum iodide after its steady state is achieved on day 13 of repeated exposure
21 (i.e., $AUC_{day14} - AUC_{day13}$). On the human side of the equation, the AUC is extended over 96
22 hours to accommodate the iodide clearance subsequent to a 24-hour exposure (i.e., AUC_{day0-4}).
23 Thus, this second assumption can be expressed as “human $AUC_{day0-4} = rabbit [AUC_{day14} -$
24 $AUC_{day13}]$ ”.

25
26 In this review, several aspects of MeI toxicity data are considered for determining the most
27 appropriate frequency of exposure for modeling the HEC based on the 2 ppm NOEL. The
28 dilemma is due to the lack of data to determine the dose-response relationship for less than the
29 23 days (GD6-28) of exposure from which the current 2 ppm NOEL is established. There are no
30 data for estimating what might be the NOEL had pregnant rabbits been exposed to MeI for only
31 a few days. However, it has been demonstrated that an 8 – 9 days of 20 ppm MeI exposure prior
32 to GD22 (i.e., GD6-14 or GD15-22) did not result in pre-natal fetal death (Table 55 in Volume
33 I). Thus, there is no support for modeling HEC based on 14 days of MeI exposure (i.e., rabbit
34 $[AUC_{day14} - AUC_{day13}]$). It has also been demonstrated that during GD23-26, fetal death is
35 evident at hour 30, immediately after the second 6-hour daily exposure to 20 - 25 ppm MeI
36 (Tables 55, 56, and 57 in Volume I). Although the incidence was not statistically significant, it
37 is unequivocally recognized as biologically significant for identify the window of vulnerability.
38 Thus, it is reasonable to model the HEC based on a single- day exposure.

39
40 There are also no data for assessing the dose-response relation for 1 - 2 days of MeI exposure
41 and establishing a NOEL other than the current 2 ppm benchmark. The only studies within this
42 duration are conducted at a single MeI concentration 10- to 13-fold higher than 2 ppm. These
43 studies, in which test animals are killed right after the second day of exposure, would also not be
44 sufficient for characterizing the full magnitude of response because enough time has not been
45 given for the manifestation of fetal effects.

1 Given the lack of data, DPR follows the conventional default for assessing developmental effects
2 and assumes that these effects can occur as a result of a single exposure event within a specific
3 window of vulnerability corresponding to a specific vulnerable developmental stage (USEPA,
4 1991). This guideline was also acknowledged and followed in Arysta's risk assessment (Miles
5 *et al.*, 2009). In addition to the support from fetal death immediately after the second 6 hours of
6 MeI exposure, support for the single-day exposure assumption is also provided by the profiles on
7 GSH depletion as presented in Section IV.A.1.a. of Volume I (including Table 59 and Figure 5).
8 Significant GSH depletion in fetal blood was detected as early as after one 6-hour 20-ppm
9 exposure. There is no clear evidence that the level of GSH at 62% of controls is further reduced
10 significantly with additional repeated exposure, at least within the available measurement time
11 point, i.e., Table 59 in Volume I which shows a range of 55 to 72% of controls after 2- to 4-day
12 of exposure. Moreover, *in vitro* study with neural cell cultures showed a very quick decline of
13 GSH that reaches the maximum depletion 15 minutes after a 5-minute exposure to MeI
14 (Chamberlain *et al.*, 1999) while cell death did not begin until 6 hours after the exposure, near
15 the time for full GSH recovery. Thus, for a possible MOA that involves oxidative stress and
16 with delayed onset of cytotoxicity and cell death, a single-day exposure would also be reasonable
17 for HEC determination.

18
19 In summary, with insufficient support for a single predominant MOA within the time frame of 30
20 or less hours, it is prudent to model the HEC at the 2 ppm NOEL based on a single-day exposure
21 for both rabbits and humans.

22 23 **II.B.2. HEC Dose Metric**

24
25 The 8 possible dose metrics are the permutations of maternal or fetal blood levels of MeI or
26 iodide at their peak (or steady state) concentration or area under the curve (AUC).

27
28 For the fetal compartment, fetal circulating MeI can be a possible dose metric because its
29 presence is supported by the detection of S-methylcysteine hemoglobin adducts in the fetal
30 blood. However, no experimental data are available for model validation. Fetal circulating
31 iodide is a viable candidate dose metric because experimental data in rabbits are available.
32 However, the use of this dose metric should be viewed with caution for several reasons. First, all
33 the experimental measurements used for model validation are from fetuses that survived the MeI
34 exposure, a direct opposite outcome to the endpoint targeted for modeling. Secondly, the model
35 predicted iodide F/M (fetal-to-maternal) ratios are generally higher than those experimentally
36 measured in rabbits (Section II.A.2.). The proportionally higher simulated distribution to the
37 rabbit fetal blood may result in underestimation of risk by setting a higher benchmark for
38 modeling the HEC than can be supported. Moreover, the 0.9 - 1.3 cord-to-maternal ratios from
39 the survey by Rayburn *et al.* (2007) (see: Table A-3) has been cited as support for lower fetal
40 iodide load in humans than in rabbits (Miles *et al.*, 2007). However, the range of human cord-
41 to-maternal ratio is wide with 12 of the 121 sets at or above 2 (the highest ratio of 5.4),
42 significantly overlapping the average F/M ratio in rabbits. An earlier study by Cottino *et al.*
43 (1972) also showed a wide blood ratio (0.5 - 3.4) among 18 women who received
44 iodomethylsparteine for 15 minutes to 18 hours at termed delivery. Moreover, the issue of
45 appropriate human fetal stage for modeling the HEC also brought out the question of the
46 applicability of Rayburn study data. While this remains a question of interest, it should be

1 remembered that a significantly higher fetal body weight model input parameter would have a
2 much greater impact on the predicted human iodide levels in the fetal than maternal serum, thus
3 proportionally raising the HEC based on fetal serum iodide dose metric. Finally, the baselines
4 for the data on F/M ratio between rabbits and humans are dissimilar. The maternal levels
5 reported in the Rayburn study (2007) are from subjects with no known excess iodide exposure,
6 with the plasma iodide ranging from 0.003 to 0.05 mg/L (or, 0.3 to 5.6 µg/dL as reported).
7 Whereas, the rabbit maternal iodide concentration from MeI exposure is 460 – 4,700 fold higher,
8 ranging from 14 to 26 mg/L (Table 56 and 57 in Volume I).

9
10 Additional discussion on dynamic changes in the F/M ratio has been presented in Section II.A.2.
11 No other data, including fetal iodide distribution in rats, are available for supporting the
12 argument of wide interspecies sensitivity to excess iodide. Thus, while species specific
13 distribution of iodide to fetus remains a valid pharmacokinetic consideration, fetal serum iodide
14 should not be the definitive dose metric for HEC, especially when it yields higher HECs than all
15 other valid dose metrics and presumes on a MOA that cannot be sufficiently supported.

16
17 The use of the maternal MeI or iodide dose metric has the advantage of focusing more on the
18 total internal dose of exposure without the additional uncertainties of further modeling to the
19 fetal distribution level. They are more suitable dose metrics when no single MOA can be
20 supported. The potential disadvantage of the maternal MeI dose metric is that no measurement
21 data are available for model validation. Moreover, its level is only a small fraction of iodide due
22 to its rapid transformation and thus can be potentially more subject to accuracy concerns for
23 reflecting the pattern of total MeI exposure.

24
25 In contrast, USEPA (2007) agreed with Arysta's proposed MOA that fetal thyroid perturbation
26 from excess iodide is the definitive MOA for rabbit fetal death (see: Section IV.A.1.a. of Volume
27 I). However, maternal instead of fetal serum iodide was initially chosen by USEPA as the dose
28 metric due to the inadequacy of fetal versus maternal iodide data in humans. Following the
29 completion of a study by Rayburn *et al.* (2007) that surveyed iodide levels in human maternal
30 and cord blood, USEPA determined that the data on human maternal-to-fetal iodide distribution
31 was sufficient for changing the HEC dose metric from maternal to fetal iodide (Barton, 2007).

32
33 The choice of peak concentration versus AUC is an important consideration, especially because
34 the NOEL determined in rabbits consists of only 6 hours of exposure while both the general
35 public and workers are expected to be exposed for 24 hours. Although workers associated with
36 the use of MeI may only receive 8 hours of exposure during work, if they also live within the
37 exposed community, they can be expected to receive further MeI exposure at the ambient level
38 for the remaining 16 hours. The cumulative dose from 6- versus 24-hour MeI exposure durations
39 between rabbits and humans can be accounted for by the AUC dose metric but not by the peak
40 concentration, especially if the steady state of the selected dose metric is reached before the end
41 of the specified exposure duration or the protracted decline after the exposure is to be accounted
42 for.

43
44 In conclusion, the overall evidence presented in this and previous sections indicate that maternal
45 iodide dose metric is more reliable compared to the fetal iodide picture for reflecting the
46 maternal MeI exposure status on which the rabbit NOEL was based. Maternal dose metrics are

1 also more reliable than fetal dose metric for interspecies comparisons without contending with
2 the uncertainties of an exclusive MOA based fetal thyroid perturbation from excess iodide, and
3 the apparent higher simulated fetal to maternal serum iodide ratio in rabbits. Finally, the
4 decision for using maternal serum iodide AUC dose metric is also supported by the overall
5 conclusion by Sweeney *et al.* (2009). Although coming from somewhat different points of
6 consideration, the model authors stated that the "... confidence in the PBPK model predictions
7 for the reproductive/development effects of iodide in rabbits is considered moderate using fetal
8 iodide and high using maternal iodide...".

9
10 The HEC should be based on the equivalence AUC between a single 6-hour 2 ppm MeI exposure
11 in rabbits and a single 24-hour MeI exposure in humans (i.e., referred to by Arysta model output
12 as "bystanders"). Workers are expected to continue receiving exposure at the MeI level as a
13 member of the general public after receiving occupational exposure during work hours.

14 15 **II.C. HECs**

16
17 The rabbit model uses meidr2.csl and meidr2cmd files provided by Arysta (2007). Three sets
18 of HEC simulation runs were conducted in 2008. These include: 1) output for the general
19 population (Arysta's "bystander's") HECs (Arysta, 2008a, b) and their subsequent correction
20 (Arysta, 2008c); 2) output for occupational (Arysta's "worker's") exposure HECs (Arysta,
21 2008d); and 3) output for using higher rabbit QAC reflective of the GD23-26 window of
22 vulnerability (Arysta, 2008e). HECs are modeled for a single day of exposure to the 2 ppm (6
23 hours/day) NOEL in rabbits based on fetal death endpoint.

24 25 **II.C.1. General Population HEC**

26
27 Although maternal iodide AUC is selected as the dose metric for HEC determination, HECs
28 based on all 8 dose metrics (i.e., permutation of peak concentration or AUC of MeI or iodide in
29 maternal or fetal blood) are presented below for demonstrating their overall impact to the HEC.

30
31 The HEC is determined by matching the rabbit and human values of a given dose metric. When
32 the dose metric is based on the peak concentrations, it is taken from immediately after the
33 cessation of exposure (i.e., hour 6 for rabbits, hour 24 for humans) and before their decline
34 thereafter (Figure A-7 and A-8). When the dose metric is based on AUCs, the duration coverage
35 is 24 hours for rabbits and 96 hours for humans to account for the elimination time. Thus, the
36 rabbit 24-hour AUC from a 6-hour exposure is matched to the human 96-hour AUC from a 24-
37 hour exposure. The corresponding graphic depictions are presented later, in Figures A-9 in
38 conjunction with presenting the selected HEC.

39
40 The initial sets of HECs were modeled based on a rabbit QAC of 12 L-hr/kg^{3/4}. Subsequent to
41 DPR's consideration regarding the biological uncertainties in using model input parameters that
42 are not reflective of the GD23-26 window of vulnerability, Arysta re-submitted a new set of
43 HEC model runs for a single MeI exposure using a QAC of 20 L-hr/kg^{3/4} and the same maternal
44 body weight of 4.1 kg, and fetal weight of 0.046 kg (Arysta, 2008e). The final sets of HECs are
45 presented in Table A-4. The earlier set of HECs based on the low rabbit QAC are included in
46 strikethrough form to demonstrate the impact of the 1.7-fold increase in QAC. The HECs based

1 on iodide profile are proportionally increased while the change is much less based on the MeI
 2 profile. The lower sensitivity of MeI output parameters is likely due to the rapid equilibration
 3 with tissues (Arysta, 2009). This strengthens the previous conclusion of modeling HEC based on
 4 maternal serum iodide instead of the maternal MeI profile.
 5
 6
 7
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 9

10
 11
 12 Table A-4. List of 24-hour HECs for rabbit fetal death endpoint^a

Dose metric	Maternal MeI	Fetal MeI	Maternal Iodide	Fetal Iodide
Peak	2.8 2.9 ppm	3.4 4.1 ppm	0.38 0.58 ppm	1.5 2.4 ppm
AUC	0.7 0.73 ppm	0.86 1.0 ppm	0.15 0.24 ppm	0.78 1.3 ppm

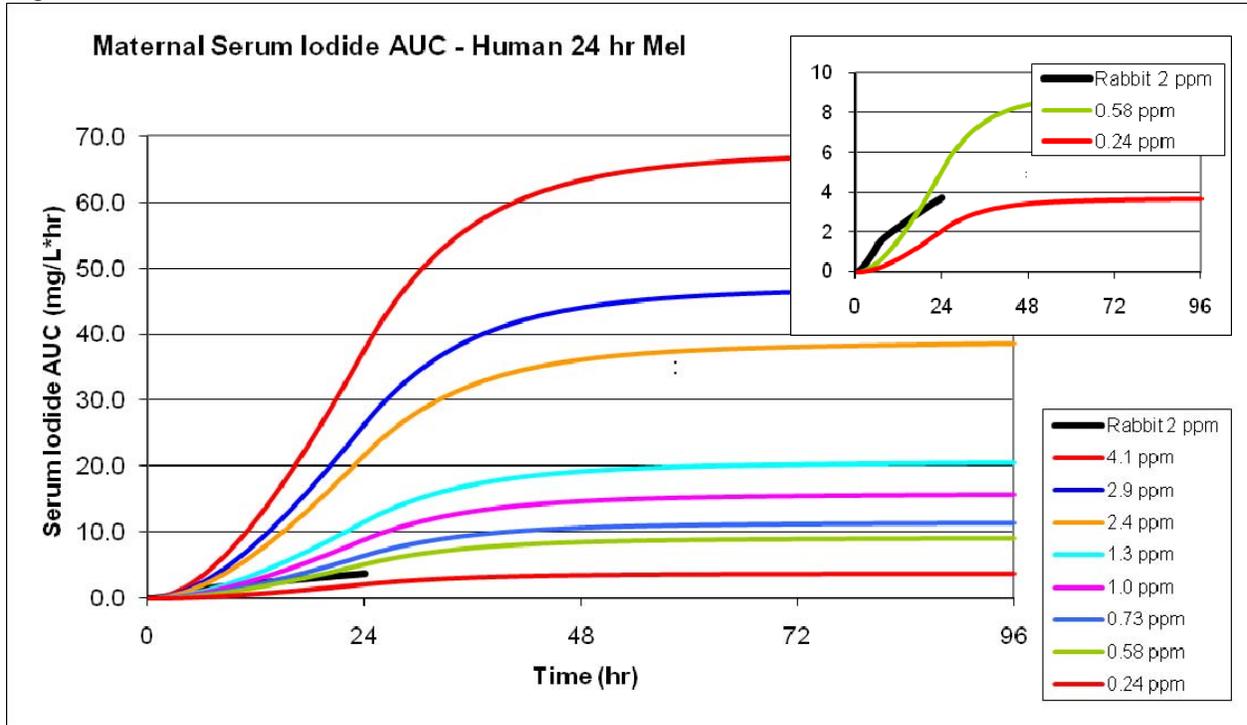
13 ^{a/} The HEC is modeled for the NOEL of 2 ppm (6 hr/day) MeI, using the QAC of 20 L-hr/kg^{3/4}
 14 for rabbit late stage pregnancy. The strike-through HECs are modeled for early pregnancy at
 15 QAC of 12 L-hr/kg^{3/4}, given only for illustration purposes.
 16
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23 Table A-4 shows that within the same output parameters (i.e., serum MeI or iodide), the HECs
 24 are generally lower based on maternal than fetal dose metrics. The greatest difference is in
 25 modeling for maternal rather than fetal serum iodide. The model input that resulted in a much
 26 greater accumulation of iodide from maternal to fetal blood for rabbit than humans contributes
 27 significantly to this overall 4- to 5-fold higher HEC. The generally lower HECs based on AUC
 28 than peak concentration is reflective of the 6- versus 24-hour exposure between rabbits and
 29 humans.
 30

31 The determination of HEC through matching rabbit and human simulation results can be
 32 illustrated in Figure A-9 for two maternal serum iodide dose metrics; i.e., AUC and peak
 33 concentration. All the 24-hour MeI levels listed in Table A-4 are included in Figure A-9. In
 34 Figure A-9a for maternal serum iodide AUC, the 0.24 ppm HEC is based on the equivalent AUC
 35 level between the 96-hour human AUC (at 3.66 mg/L*hr) after a 24- hour exposure to 0.24 ppm
 36 MeI (the lowest simulation curve) and the 24-hour rabbit AUC (at 3.72 mg/L*hr) after a 6-hour
 37 exposure to 2 ppm MeI (thick black curve). Similarly in Figure A-9b for maternal serum iodide
 38 peak concentration, the 0.58 ppm HEC is based on the equivalent peak level between human
 39 peak at hour 24 (0.31 mg/L) and rabbit peak at hour 6 (0.31 mg/L).
 40

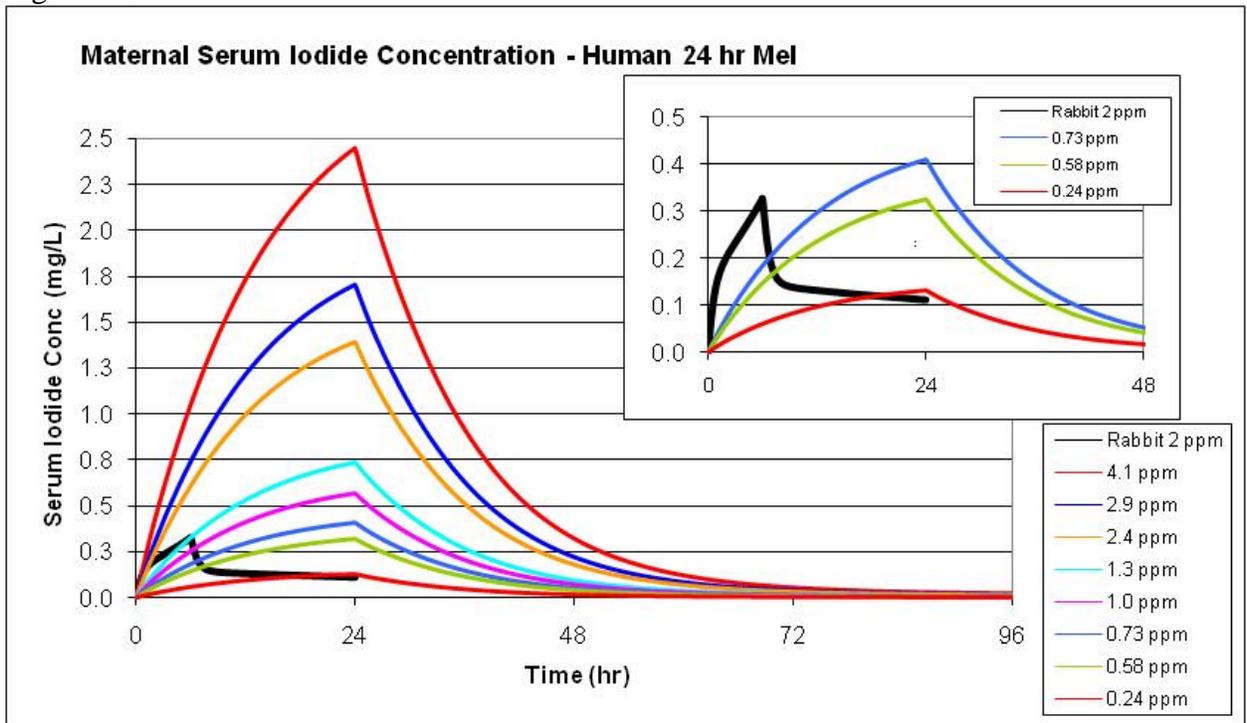
41 An interesting overarching observation regarding the implication of rabbit fetal iodide
 42 accumulation on the final HEC for fetal death endpoint is noted here. This apparently unique
 43 feature in rabbit fetus versus rats and humans was repeatedly cited by Arysta (Arysta, 2007;

1 Figure A-9a



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Figure A-9b



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Figure A-9. The 24-hour HEC based on maternal serum iodide dose metrics. Rabbit NOEL for late gestation period (thick black line) is compared to the 24-hour HECs at: a) 0.24 ppm HEC based on AUC, b) 0.58 ppm HEC based on peak concentration. Data from Arysta (2008e). Areas of interest are enlarged in the insets.

1 Myleson *et al.*, 2009; Kirman *et al.*, 2009) as support for their fetal thyroid perturbation MOA
2 due to excess iodide from MeI exposure, for presuming greater sensitivity of rabbit than human
3 fetuses to MeI, and consequently for supporting the use of the fetal serum iodide dose metric for
4 establishing HEC. However, these implications bring out many issues for which data are
5 unavailable to resolve. First of all, Myleson *et al.* (2009) characterized the normal rabbit fetal
6 iodide accumulation as 9- to 11- fold higher than the maternal. This was based on serum iodide
7 data from the control groups in the MeI study by Slotter (2005b) (see also Table 43 of Volume I).
8 With MeI exposure, this F/M ratio is reduced to approximately 2-fold (Slotter, 2005b; Myleson *et al.*
9 *et al.*, 2009). The physiological significance for this dramatic change to rabbit fetal thyroid at the
10 MeI NOEL is unclear. As to the implication of greater rabbit sensitivity than humans, it is noted
11 that the physiological range of fetal blood iodide is 0.12 - 0.22 mg/L in rabbits (Table 43,
12 Volume I) and 0.014 - 0.017 mg/L in humans (Rayburn *et al.*, 2007). This approximately 8- to
13 16- fold higher rabbit level would indicate a higher requirement for iodide or greater tolerance
14 for its excess, but in itself offers no support that rabbits are thereby “more sensitive” to excess
15 fetal iodide from MeI. If anything, the higher baseline in rabbits might suggest less sensitivity
16 at a given amount of iodide increase from MeI. In this regard, the modeled peak rabbit fetal
17 iodide is 1.4 mg/L at the end of 6-hour exposure to 2 ppm MeI, a 6- to 12-fold above the baseline
18 for rabbit fetuses, but nearly 100-fold above the baseline human cord blood level. On the other
19 hand, at the HEC of 0.24 ppm (Table A-4; based on DPR’s maternal iodide dose metric) the
20 modeled peak fetal iodide of 0.15 mg/L is 10-fold higher than the human baseline. This is within
21 the same ratio of increase over baseline in rabbit fetuses at the NOEL of 2 ppm. If equal
22 multiplier over baseline is of biological significance, this observation could provide additional
23 support for the 0.24 ppm HEC derived from maternal serum iodide dose metric (see Table A-4).

24
25 MeI at 0.24 ppm represents the HEC at the most pertinent dose metric and is the final 24-hour
26 HEC for assessing the risk of the general public. An ideal portrayal of the total amount of
27 maternal exposure to MeI would include also the portion of MeI that is not yet converted to
28 iodide. However, the MeI level is relatively insignificant since the rate of conversion to iodide is
29 rapid such that the peak level of MeI is 35-fold below the peak iodide level at the end of the 24
30 hours of exposure.

31 32 **II.C.2. Occupational HEC**

33
34 As stated under Section II.A.1, a 567 L/hr (or minute volume of 9.45 L/min) sedentary (or
35 resting) breathing rate is used for modeling the HEC for the general public presented in the
36 previous section. For worker’s occupational exposure, a 1.47-fold higher DPR default breathing
37 rate of 833 L/hr is used to model the 8-hour occupational HEC. This is achieved by Arysta
38 through changing the tidal volume (TVol) from 630 to 925 ml/breath while keeping the same 15
39 breath/minute.

40
41 Based on the same selected HEC dose metric as for the 0.24 ppm 24-hour HEC, the 8-hour
42 occupational HEC provided by Arysta is 0.22 ppm. The relationships between the 8-hour
43 occupational HECs, the rabbit 2 ppm NOEL, and the 24-hour HECs for the general public are
44 presented in Figure A-10a. An additional day of the 8-hour exposure cycle is included to
45 illustrate the pattern within two 24-hour cycles. The 8-hour occupational HEC curve
46 approximates the curve for the 24-hour HEC shortly beyond hour 24. This indicates that a

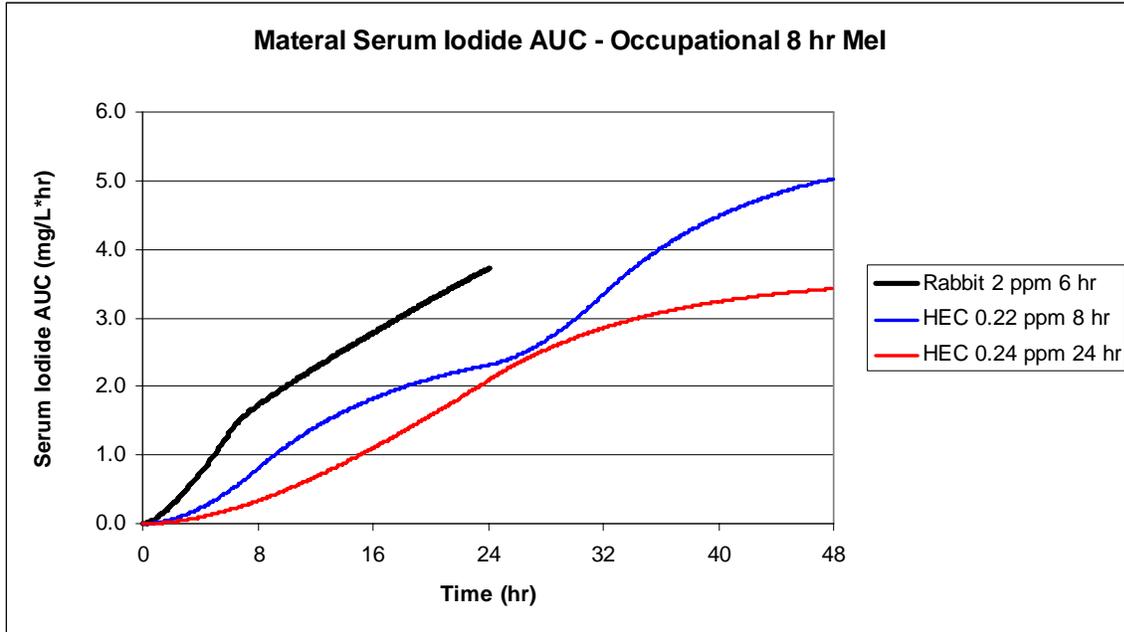
1 single-day modeling of AUC can be adequate for the 8-hour HEC determination. Alternatively,
2 Rodriguez (2009) noted that without the additional 16 hours exposure for the worker as a
3 member of the general public the 8-hour HEC is 0.5 ppm.

4
5 Although the peak maternal serum iodide concentration is not a chosen dose metric for the HEC,
6 a question may be raised regarding the sufficiency of a single-day simulation for such a scenario.
7 Simulation over multiple 8-hour exposure days showed that the peak concentration increases
8 only by 2% from the second to the third day of exposure (data not shown). Thus, had the peak
9 concentration been selected as the final HEC dose metric, it would be more appropriate to match
10 the peak rabbit iodide concentration to the peak on the second-day peak human 8-hour exposure.
11 As shown in Figure A-10b, this second-day peak was considered in establishing the HEC of 0.35
12 ppm based on maternal peak serum iodide concentration.

13 14 **II.C.3. Summary**

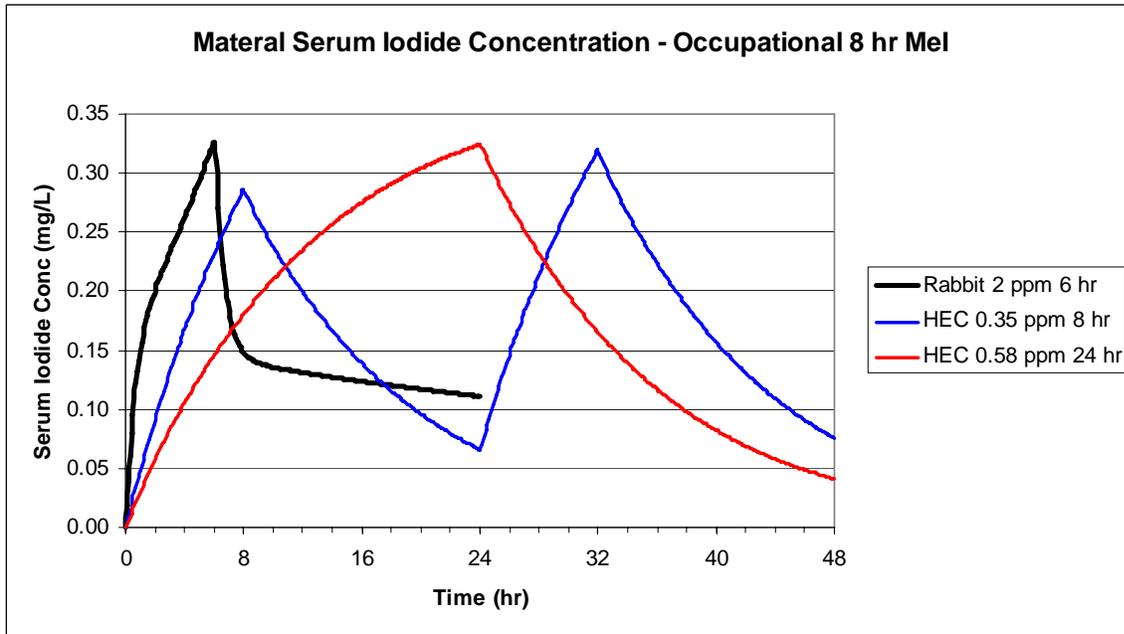
15
16 USEPA derived a 24-hour HEC at 7.4 ppm and an 8-hour occupational HEC at 23 ppm. These
17 are based on the NOEL of 10 ppm (6 hr/day) in rabbits, the dose metric of fetal serum iodide
18 AUC, and sedentary breathing rate of 567 L/hr. DPR's 24-hour HEC is 0.24 ppm and 8-hour
19 occupational HEC is 0.22 ppm. These are based on the NOEL of 2 ppm (6 hr/day) in rabbits, the
20 dose metric of maternal serum iodide AUC, and DPR's default breathing rate of 833 L/hr (i.e.,
21 83% of USEPA's recommended "light activity" rate) for occupational exposures. It is noted that
22 for workers, an additional 16 hours of MeI exposure as members of the general public (or
23 "resident") would increase the maternal serum iodide AUC and exceed the maternal serum
24 iodide benchmark in rabbits at the NOEL of 2 ppm.

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Figure A-10b



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Figure A-10. The 8-hour occupational HEC based on maternal serum iodide dose metrics. Rabbit NOEL for late gestation period (thick black line) is compared to the HECs at: a) 0.22 ppm HEC based on AUC, b) 0.35 ppm HEC based on peak concentration. Data from Arysta (2008e).

1 III. NASAL EFFECTS

2
3 This section presents the HECs for nasal effects observed in rats. The Arysta's nasal model has
4 been reviewed by USEPA (Barton, 2007; USEPA, 2007) for establishing the HECs based on
5 GSH depletion in the olfactory epithelium. The sources for model information are provided in
6 the introductory section of this review. The basic model diagram is presented in Figure A-1.
7 This section provides only a very brief description of the Arysta mei3 model² as a backdrop for
8 focusing on some key issues that could significantly impact the modeling outcome. Compared to
9 USEPA, DPR differs on the threshold GSH level for the HEC dose metrics and this difference
10 results in lower HECs. The overall support for GSH depletion as the MOA for the nasal effects
11 was discussed by Kirman *et al.* (2009). Based on the qualitative and quantitative evaluations, the
12 authors concluded that the confidence for this MOA was only medium. Nevertheless, DPR's use
13 of GSH depletion as the dose metric is not dependent on this endpoint as a definitive MOA for
14 toxicity but as an early marker for the protection of olfactory epithelial cells and is consistent
15 with the nasal toxicity observations that define a NOEL at 21 ppm.

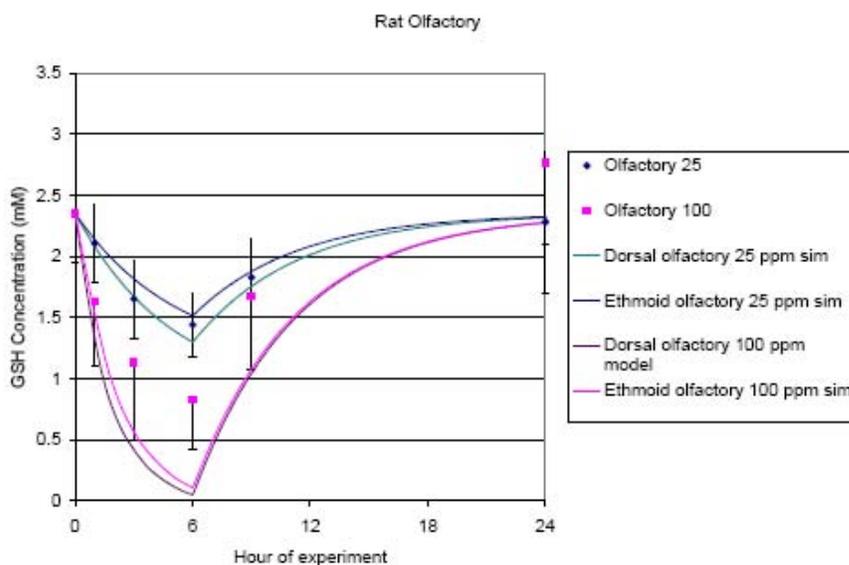
16 III.A. Model and Parameters

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18 Instead of a detailed tissue structure, the nasal olfactory architecture in the MeI model is
19 simplified into a descriptive structure of 4 layers each for the dorsal meatus or ethmoid regions.
20 The model parameter for the width of the olfactory epithelium is designated as WOE. The width
21 of the next layer, the olfactory exchange membrane with lamina propria, is WOX. The values
22 for the WOE and WOX in the HEC model are: 0.008 and 0.005 cm for rats, 0.006 and 0.05 cm
23 for children, and 0.008 and 0.134 cm for adults. The cardiac output in the mei3 model for rat
24 nose and brain HEC simulations (see Section IV) is 2/3 of the minute volume (MINVol, or
25 "breathing rate").
26

27
28 Model validation through comparing simulation output to the measured data in rats by
29 Himmelstein (2004) at 25 and 100 ppm MeI was provided by Arysta (2007). Input parameter
30 adjustments were made to achieve adequate fit to the experimental data, e.g., using lower
31 ventilation rate than measured by DeLorme (2004). Some of these documented adjustments are
32 extensive, e.g., using only 1.5% of the *in vitro* measured GSH conjugation rate for simulating
33 kidney GSH changes and increasing the nasal GSH turnover rate from 0.016/hr measured by
34 Poet and Wu (2004) to 0.19/hr (Arysta, 2007). The graphic presentations of the final output
35 from the Arysta model documentation are reproduced in Figure A-11a (from Figure 9c of
36 Mileson *et al.*, 2007) for the nasal olfactory region, and in Figure A-11b (from Figure 8 of
37 Mileson *et al.*, 2007) for serum iodide levels. The simulation on nasal GSH depletion tracks the
38 experimental data sufficiently at 25 ppm but not at 100 ppm (Figure A-11a). However,
39 compared to the measured data, the model underestimates the peak serum iodide concentration at
40 25 ppm (Figure A-11b). This is mainly attributed to the higher model input of rat body weight
41 (0.376 kg) than the lower weight (0.207 kg) of rats used in the Himmelstein study. This issue is
42 pertinent to systemic endpoints and is further discussed in Section IV.A.
43

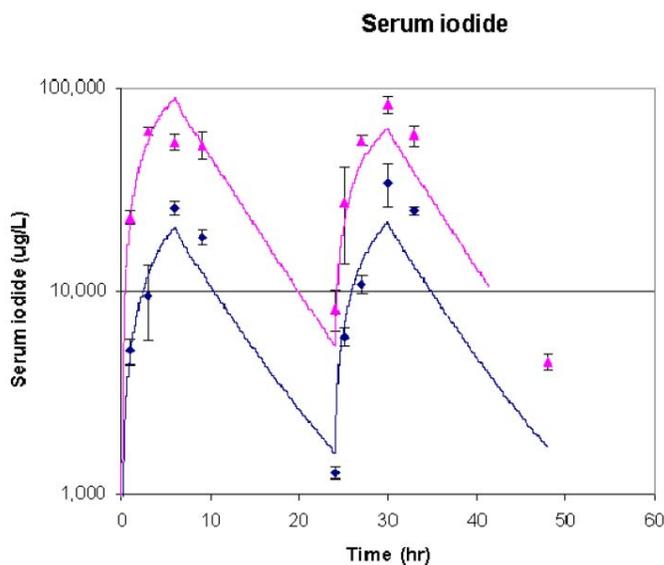
² The basic model "mei3" was provided to DPR in July 26, 2007. It is understood that this model remains the same for the model output subsequently provided by Arysta in 2008.

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Figure A-11b



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8 Figure A-11. Modeled versus measured data in rats. a) GSH concentrations at dorsal meatus
9 and ethmoid olfactory regions (from Mileson *et al.*, 2007, Figure 9c); b) Blood
10 iodide concentrations (from Mileson *et al.*, 2007, Figure 8). Lines: simulations;
11 Symbols: experimental data from Himmelstein, 2004 with 6 hr/day exposure at 25
12 and 100 ppm MeI.

1 **III.B. Dose Metric**
2

3 Based on the apparent relationship between GSH depletion and cellular degeneration in the
4 olfactory epithelium as presented in Section IV.A.1.b of Volume I, DPR concluded that GSH
5 depletion is a likely early event for the nasal effect and agreed with USEPA that the depletion at
6 the dorsal olfactory epithelium can be the dose metric for modeling the nasal effect HECs.
7

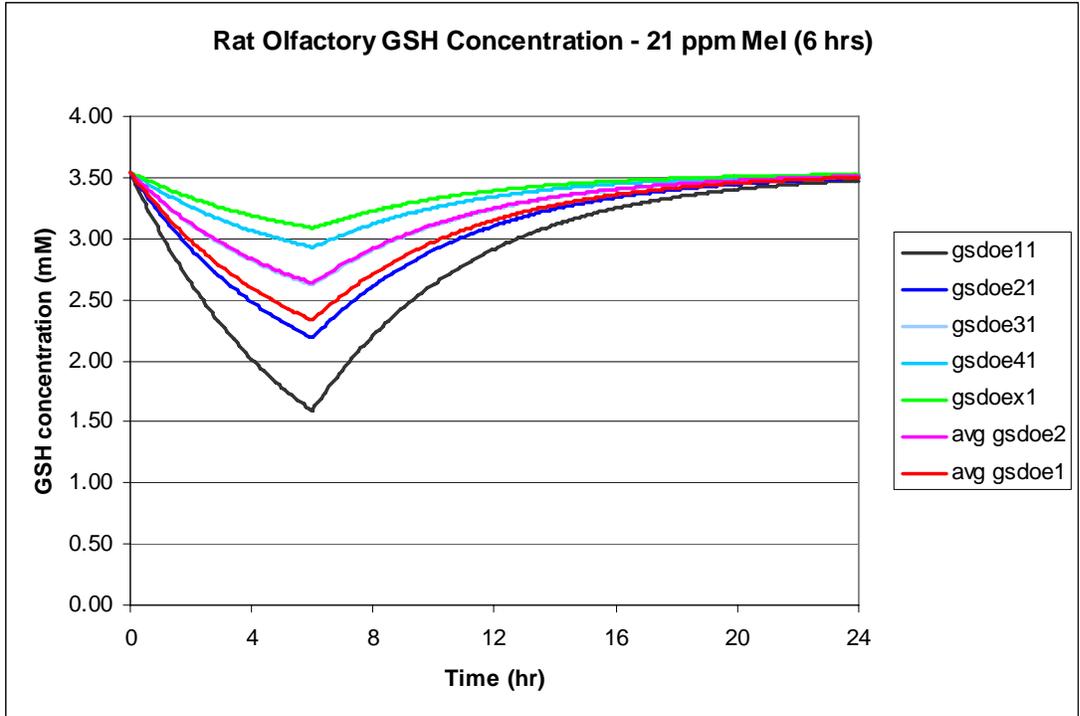
8 **III.B.1. Regional Olfactory GSH**
9

10 Since the experimental measurements in rats did not differentiate the tissue layers, HEC
11 modeling is limited to interspecies comparison based on the average regional GSH
12 concentrations. The averaging should consist of only the 4 layers of each meatus or ethmoid
13 region and not the innermost blood exchange layer because the interspecies WOX (values given
14 in previous section) are quite different between rats and humans and between human age groups
15 (Barton, 2007). Due to the relatively greater thickness of the basement exchange layer in
16 humans, including this layer in the human HEC model would largely reflect the GSH level at this
17 layer and not at the four outer architectural olfactory epithelial layers that are in closer contact
18 with MeI and that have greater GSH depletion. Figure A-12 shows the modeled GSH level for
19 each of the 4 layers in the dorsal meatus (“gsdoe11, gsdoe 21, gsdoe31, gsdoe41), the basement
20 exchange layer (“gsdoex1”), and the regional 4-layer average for both meatus (“ave gsdoe1”) and
21 ethmoid (“ave gsdoe2”) regions for rats at the NOEL of 21 ppm exposure for 6 hours
22 (Kirkpatrick, 2002b). Because of the interspecies anatomical differences (i.e., no rat “ethmoid”
23 equivalence in humans), it is reasonable that the GSH dose metric in humans is matched to the
24 dorsal meatus region in rats (i.e., “ave gsdoe1”) for the HEC simulation (USEPA, 2007).
25

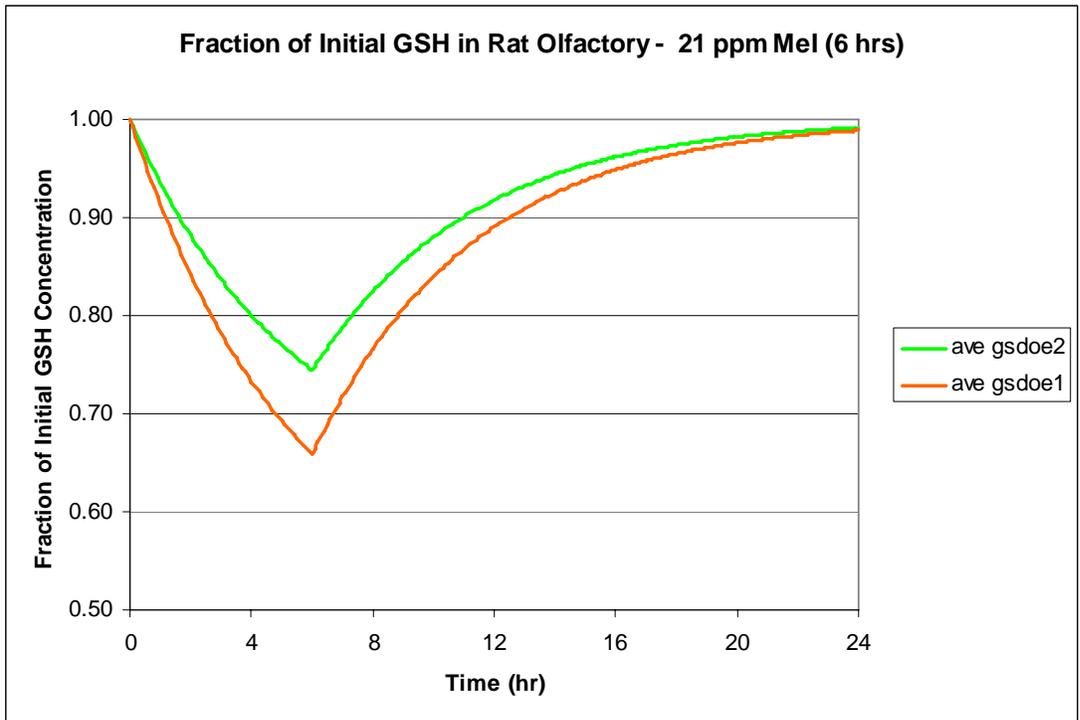
26 **III.B.2. Threshold GSH Depletion**
27

28 The key issue for the HEC dose metric based on nasal effects is the benchmark level of GSH
29 depletion. Without elaboration, USEPA (2007) modeled the HEC based on a 50% depletion
30 benchmark, the same level as proposed by Arysta (Sweeney *et al.*, 2005; Sweeney and Gargas,
31 2005; Arysta, 2006, 2007). In contrast, this DPR review concludes that a benchmark at 25%
32 depletion can better represent a level of no effects. The issue exists because no available study
33 with MeI exposure includes both the measurement of GSH levels and side-by-side
34 histopathological observations at or near the NOEL.
35

36 The support provided by Arysta (Sweeney *et al.*, 2005; Arysta, 2006, 2007) for the 50%
37 benchmark as equivalent to “no effect level” is mainly based on data for other chemicals and in
38 other target tissues. These data generally include chemicals that require metabolic activation
39 (e.g., esterase activity for ethyl acrylate by Frederick *et al.*, 1992; cytochrome P450 activity for
40 naphthalene by Plopper *et al.*, 2001 and Phimister *et al.*, 2004; Lin *et al.*, 2006); observations in
41 cells other than the olfactory epithelium (Clara cells by Plopper *et al.*, 2001; Phimister *et al.*,
42 2004); cellular effects that may not be directly indicated by non-protein sulfhydryl depletion
43 (ethyl acrylate by Frederick *et al.*, 1992), and toxicity endpoints beyond the initial cellular



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Figure A-12. Modeled rat olfactory GSH level from 21 ppm (6 hr) MeI exposure. Top: GSH level. Bottom: Fraction of initial GSH. The “gsdoe11”, “gsdoe21”, “gsdoe31”, and “gsdoe41” were the 4 meatus layers, the “ave gsdoe1” was their average. The “gsdoex1” was the basement exchange layer. The “ave gsdoe2” was the average of the ethmoid layers. Model output from Arysta (2008c).

1 degeneration and are associated with tumor formation (cell proliferation by propylene oxide by
2 Rios-Blanco *et al.*, 2003; Lee *et al.*, 2005).

3
4 In addition, three studies were specifically cited in Sweeney *et al.* (2005) as providing the
5 support for the 50% benchmark for MeI. The first citation was a report by Biaglow *et al.* (1986)
6 that investigated the enhancement of therapeutic response of tumor tissues to nitro radiation or
7 chemotherapeutic drugs, i.e., misomidazole and SR-2508. The report mentioned that only 10-
8 20% GSH depletion can cause liver damage but “*spontaneous peroxidative damage... can occur*
9 *with other³ normal tissue when GSH reaches 50% of control*”. The second citation was a report
10 by Frederick *et al.* (1992) regarding the application of a PBPK/PD model to oral dosing of ethyl
11 acrylate for estimating its delivery dose associated with forestomach tumorigenicity in rats.
12 Nevertheless, the nasal tissue was not among the 14 sites for which measured metabolic binding
13 of ethyl acrylate to thiol was available for the model. In addition, a pattern of GSH circadian
14 rhythm was attributed to this report. However, no data were presented. The third citation was a
15 report by Plopper *et al.* (2001) which referred to a threshold of 75% depletion of intracellular
16 GSH pool for irreversible organelle changes in mouse Clara cells at the distal conducting airway
17 through conjugation of reactive metabolites of naphthalene after i.v. injection.

18
19 DPR concluded that none of these 3 reports provided substantive support for the 50% benchmark
20 in nasal olfactory epithelium. At best, the aforementioned statement by Biaglow *et al.* (1986)
21 would indicate that the 50% depletion is not a clear “no effect” level but a level of “beginning to
22 show effects”, i.e., close to a “low-effect” level. A diurnal variation of GSH as much as 50% in
23 some tissues was mentioned as support for the 50% benchmark. However, if this wide diurnal
24 fluctuation is indeed reflective of the baseline pattern of GSH levels in the olfactory epithelium,
25 it can arguably support a modeling benchmark substantially below 50% to account for the
26 possible heightened vulnerability during the low GSH state within a 24-hour period.

27
28 More importantly, the evidence for inadequate health protectiveness of 50% GSH depletion as
29 benchmark for establishing the HEC can be found within the MeI database. Three MeI datasets
30 are available to bridge the observation of histopathological tissue damage at 100 ppm to an
31 estimated GSH depletion bordering 50%. The 100 ppm is above the LOEL of 70 ppm from
32 which the 21 ppm NOEL used in nasal HEC modeling was established (Kirkpatrick, 2002b).
33 The first dataset by Himmelstein (2004) provides time-course GSH measurements from 2 days
34 of exposure while the remaining two datasets by Chamberlain *et al.* (1998a) and Reed *et al.*
35 (1995) provide the time-to-effects at 100 ppm.

- 36
37
- 38 • Data on nasal GSH levels from the Himmelstein study are summarized in Table A-5.
39 Note that the percentage given in this table is relative to the corresponding controls which
40 fluctuate with time. Thus, they may not reflect the level of changes in GSH
41 concentration from one time point to the next. At 100 ppm, olfactory GSH depletion at
42 hour 1 was 48% on day 1 of exposure and merely 8% on day 2 of exposure. Peak
43 depletion at hour 6 was 74% on day 1 and 56% on day 2.
 - 44 • The Chamberlain *et al.* (1998a) study showed that slight olfactory epithelium
45 degeneration was evident within 24 hours of a 2-hour exposure (Table 10 in Volume I).

³ specified as non-liver tissues (Biaglow *et al.*, 1986)

1 Marked degeneration with various degrees of exfoliation occurred with a 4-hour
2 exposure. The authors reported that the non-protein sulfhydryls in the olfactory
3 epithelium and the lung were reduced by approximately 60% one hour after the MeI
4 exposure and remained at this level for the 6 hours of exposure. However, graphic
5 interpretation appeared to show a little less reduction at hour 1 than hour 6.
6

- 7 • The Reed *et al.* (1995) study with Wistar-derived albino rats showed undulated
8 appearance at as early as hour 0.5, vacuolation and early degenerative changes at hour 1,
9 clear evidence of destruction and exfoliation at hour 2, degenerated cells attached to
10 damaged epithelium at hour 3, and marked degeneration and damage to transitional
11 epithelium at hour 6 (Table 10 in Volume I). The GSH depletion at the earlier time
12 points may be estimated by interpolating the first day data from the Himmelstein study
13 shown in Table A-5; i.e., approximately 24% depletion at hour 0.5 (between 0% and 48%
14 GSH depletion), 48% at hour 1 as reported, and approximately 60% at hour 2 (between
15 48% and 72%).
16

17 Overall, these data show a high degree of consistency. Even excluding the undulated appearance
18 at hour 0.5 with an estimated 22% GSH depletion, and excluding also the generally lower GSH
19 depletion from the second day data from Himmelstein study, data at hour one showing
20 vacuolation and early degenerative cellular changes can be associated with as low as 48% GSH
21 depletion. Considering the variation at the average of 48% depletion (i.e., or $52.4 \pm 18.3\%$ of
22 controls), the 50% depletion cannot be taken as representing a “no-effect” benchmark.
23

24 Thus, a reasonable approach to establish a “no-effect” benchmark for HECs is simply by
25 estimating the GSH depletion at the NOEL of 21 ppm. Two sets of data are available for this
26 approach. One is from the data reported by Himmelstein (2004) as given in Table A-5. The
27 other is from modeling the GSH level at the NOEL. Table A-5 shows that at 25 ppm MeI, a
28 level slightly above the 21 ppm NOEL, the peak olfactory epithelial GSH depletion at hour 6 is
29 35 - 42% (i.e., or $65.1 \pm 14.0\%$ of the controls for day 1, and $57.8 \pm 14.3\%$ for day 2 of MeI
30 exposure). Thus, the expected GSH depletion at 21 ppm would be lower than 35% even without
31 considering its variability. The model output at the 21 ppm NOEL as presented in Figure A-12
32 shows a 34% average GSH depletion at the meatus region and 25% average depletion at the
33 ethmoid region. Given that the model may slightly underestimate the GSH concentration at the
34 dorsal olfactory region (Figure A-11a), 25% GSH depletion is reasonably close to the upper limit
35 of “no-effect” benchmark.
36

1 Table A-5. Average level of GSH in rat nasal epithelium.^a

Hour	Olfactory Epithelium - % of initial		Respiratory Epithelium - % of initial	
	25 ppm MeI	100 ppm MeI	25 ppm MeI	100 ppm MeI
0(1st dose)	100.0 (0%)	100.0 (0%)	100 (0%)	100.0 (0%)
1	84.8 (15%)	52.4 (48%)	90.6 (9%)	68.6 (31%)
3	63.4 (37%)	27.6 (72%)	48.9 (51%)	17.2 (82%)
6	65.1 (35%)	24.2 (74%)	52.0 (48%)	14.3 (86%)
9	85.6 (14%)	64.1 (36%)	86.8 (13%)	57.0 (43%)
24(2nd dose)	86.9 (13%)	114.3 (-14%)	120.0 (-20%)	157.8 (-58%)
25	102.5 (-3%)	92.3 (8%)	96.6 (3%)	93.1 (7%)
27	63.0 (37%)	55.5 (44%)	51.2 (49%)	54.6 (45%)
30	57.8 (42%)	44.4 (56%)	57.1 (43%)	43.2 (57%)
33	69.2 (31%)	74.6 (25%)	70.8 (29%)	77.4 (23%)
48	125.4 (-25%)	143.6 (-44%)	95.5 (4%)	129.1 (-29%)

2 ^{a/} Data from Himmelstein, 2004. Rats were exposed to MeI for 6 hours per day for two days.
3 Data presented as average % of the controls. Data expressed as % depletion is given in the
4 parenthesis. Note that the percentage given in this table is relative to the corresponding
5 controls which fluctuate with time. Thus, they may not reflect the level of changes in GSH
6 concentration from one time point to the next.

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15 Two additional observations can be made from data in Table A-5 regarding the pattern of GSH
16 recovery after MeI exposure. First, the on-going GSH replenishment appears to play a
17 significant role in the rapid return to its background level after the end of exposure. This process
18 often surpasses the initial GSH level (as indicated by the negative % of depletion) by hour 24
19 after a 6-hour exposure. This pattern provides further support for the use of a NOEL established
20 from the repeated dosing study by Kirkpatrick (2002b) to address the risk of acute exposure
21 scenarios. Second, as was pointed out in the review by Sweeney and Gargas (2005), cellular
22 damage through GSH depletion tends to be time-dependent. Thus, considering the prolonged
23 GSH depletion in human 24-hour exposure scenario and the lack of time to recover from day to
24 day, repeated days of exposure may result in a greater severity of cellular damage for which an
25 HEC based on a single day exposure at 25% GSH depletion may not be adequate to protect.
26

1 **III.C. HECs**
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3 The rat model uses mei3.csl and mei3cmd files submitted to DPR by Arysta (2007). Three sets
4 of HEC simulation runs were conducted by Arysta in 2008. These include: 1) output for the
5 general population (Arysta's "bystanders") and occupational (Arysta's "worker's") HECs based
6 on both 25% and 50% GSH depletion (Arysta, 2008b) and their subsequent correction (Arysta,
7 2008c); 2) output for occupational (Arysta's "worker's") exposure HECs that applied the higher
8 DPR default breathing rate of 833 L/hr but assumed a 40% oral breathing (i.e., only 500 L/hr
9 passes through the nose) (Arysta, 2008d); and 3) repeating output #2 but assumed 0% oral
10 breathing (Arysta, 2008f). HECs are modeled for a single 24-hour day of exposure for the
11 general population and at 8 hours for occupational exposure.
12

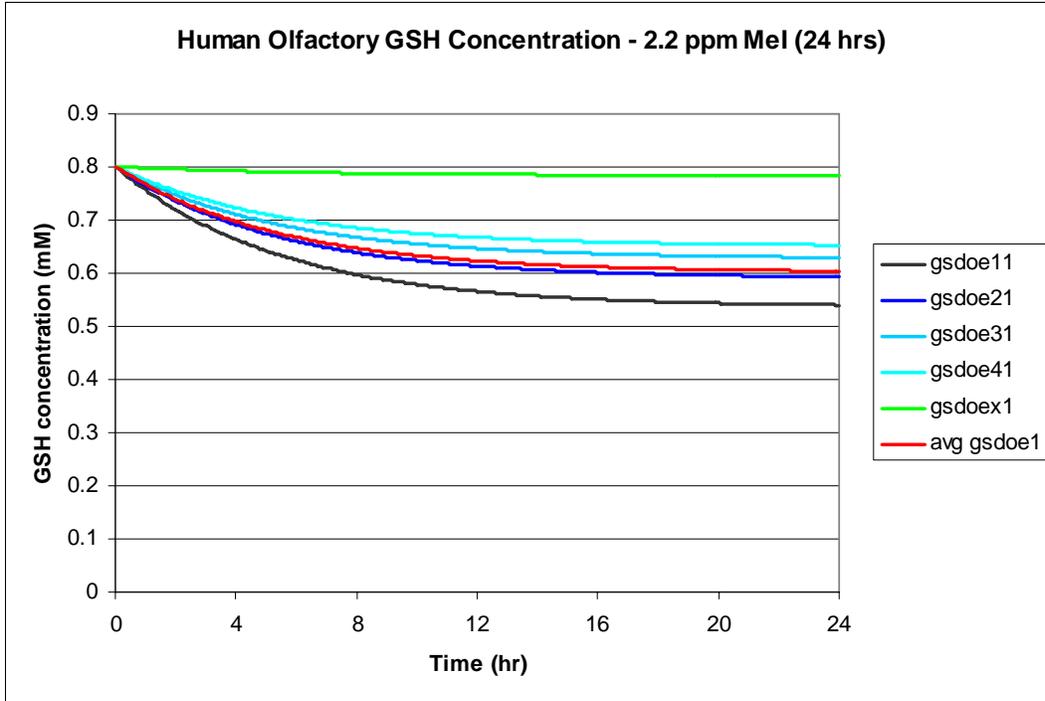
13 **III.C.1. General Population HEC**
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15 Based on a 25% olfactory GSH depletion, the HEC is 2.2 ppm for a 24-hour exposure. Using the
16 same model, USEPA (2007) reported that applying input parameters for children at ages of 3
17 month-old infants, children at 1, 5, 10, and 15 years old did not result in different HECs than for
18 the adults. The simulations for children were reported as using age appropriate body weight and
19 nasal, and ventilation parameters (values not specified in USEPA report). A same WOE
20 thickness of 0.006 cm was used for all ages, but a slightly lower WOX thickness at 0.05 cm was
21 used for infants and young children, while 0.08 cm was used for older children and adults.
22 Arysta came to the same conclusion of no age differences in HEC by assuming a constant
23 TVol/BWt ratio in age-specific model runs (Milesen *et al.*, 2009).
24

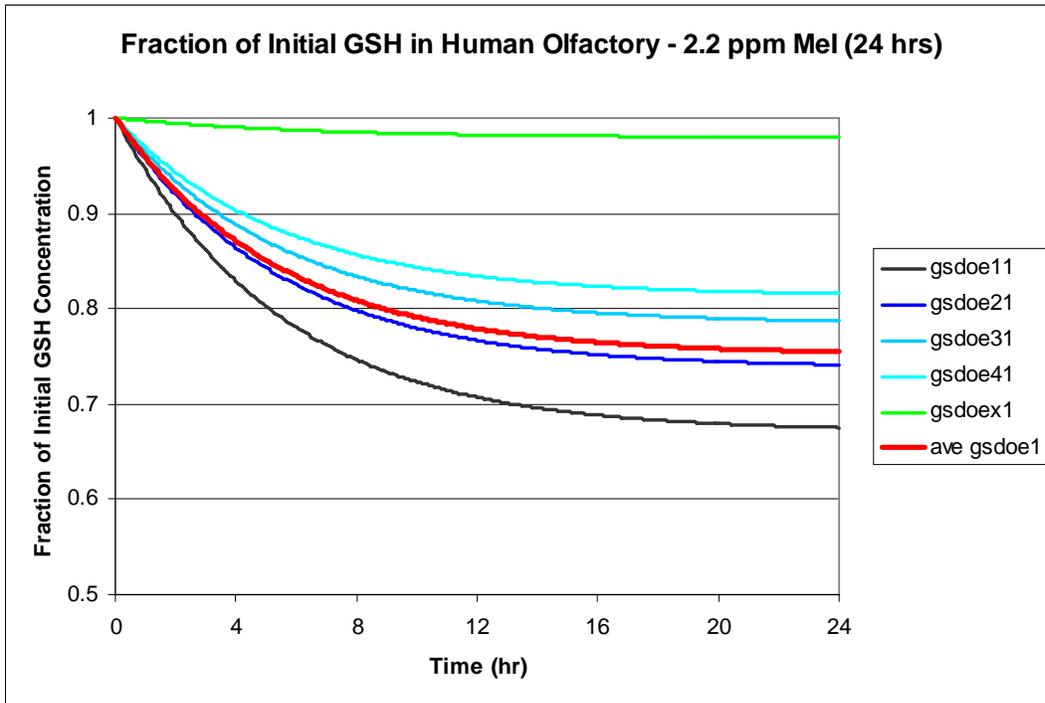
25 The corresponding pattern of GSH depletion is presented in Figure A-13. The highest level of
26 GSH depletion at the outermost olfactory layer gsdoe11 is 32% (or at a fraction of 0.675) of the
27 initial GSH concentration. The level stays below the 35 – 42% GSH depletion reported in rats at
28 25 ppm, slightly above the NOEL of 21 ppm. The time to a steady state depletion with less than
29 0.5% change in the GSH level is not reached until beyond hour 14 of exposure. This indicates
30 the importance of the time factor in the overall risk assessment for this endpoint, i.e., increase in
31 exposure duration is expected to result in greater GSH depletion before a steady state depletion is
32 reached.
33

34 **III.C.2. Occupational HEC**
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36 In the nasal HEC model performed by Arysta, DPR's default ventilation rate of 833 L/hr (0.833
37 m³/hr) was entered as 925 ml/breath at the same resting 15 breath/min rate. This yields a minute
38 volume of 13.88 L/min, or the target breathing rate of 833 L/hr (versus the 1.5-fold lower resting
39 rate of 9.45 L/min or 567 L/hr). The initial HEC modeling assumes only 60% nasal contribution
40 to the total ventilation at this light activity level (Arysta, 2008d). The resultant 500 L/hr air
41 intake through the nose is lower than the 567 L/hr used for the general population HEC
42 simulation with a 100% nasal contribution.



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Figure A-13. The 24-hour HEC of 2.2 ppm based on 25% olfactory GSH depletion. Include 4 meatus layers (gsdoe11, gsdoe21, gsdoe31, gsdoe41; with gsdoe11 as the outmost layer), basement exchange layer (gsdoex1), and the 4-layer average in meatus (ave gsdoe1). Data from Arysta (2008b, c).

1 A study by Wheatley *et al.* (1991) was cited as basis for the 40% oral contribution assumption.
2 However, the associated data for the 5 subjects in this study are not pertinent for the current MeI
3 model because their lowest initial inspiratory flow of 1 L/s (or 60 L/min; 3,600 L/hr) is already
4 substantially higher than the 833 L/hr. Moreover, the authors reported that the interindividual
5 variability was great, showing one of the 5 subjects had 70% nasal contribution at 120 L/min
6 (7,200 L/hr), an inspiratory level more than 8-fold above the DPR rate for the MeI model input.
7 The study concluded that the oronasal partitioning is related to the ventilation rate and the 60%
8 nasal air flow was attributed to a 1940 publication which only designated the condition as “on
9 exercise”.

10
11 More recently, Bennett *et al.* (2003) reported the average nasal contribution among 11 males and
12 11 females as 79% in females at 23.5 L/min (1,400 L/hr). The DPR’s default of 833 L/hr is still
13 lower than the “20% of maximum physical work level” in this study which showed 80-100%
14 nasal contribution in female subjects. DPR default rate is actually much lower than the USEPA
15 EFH’s recommended average light activity rate of 1,300 L/hr for outdoor workers (USEPA,
16 1997). Thus, a more appropriate adjustment for oral contribution should be closer to 0 - 10%.
17 This issue was not considered in the USEPA’s model review for the HECs (USEPA, 2007).
18 Within the nasal model construct, the breathing rate alone did not significantly impact the
19 simulated olfactory GSH level. However, in general, physiological accuracy remains to be
20 desirable in PBPK modeling, especially since the same model is used for the next set of HEC
21 based on systemic uptake of MeI.

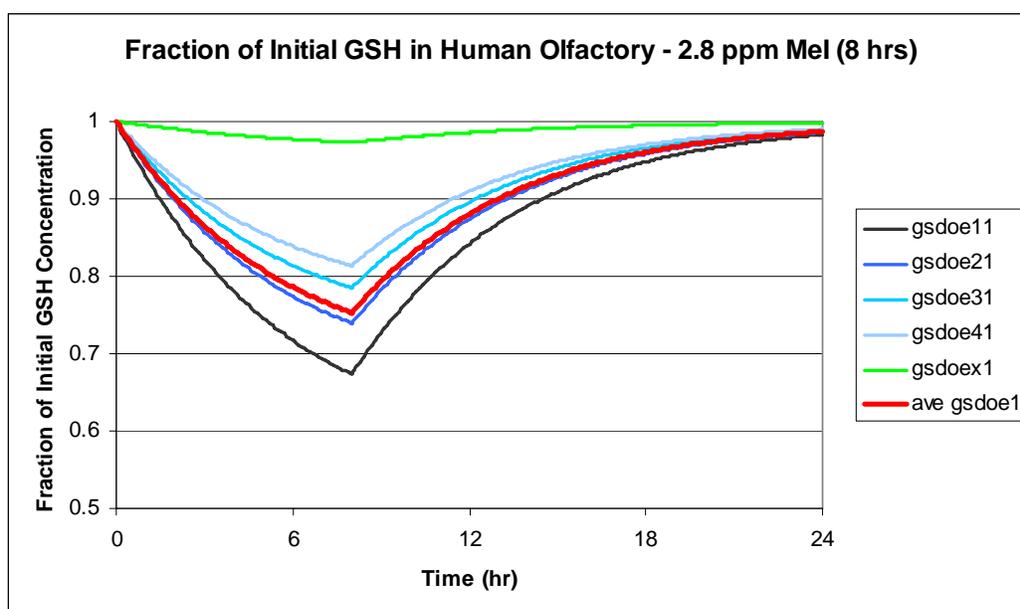
22
23 Subsequent model simulation using 100% nasal breathing resulted in an 8-hour occupational
24 HEC of 2.8 ppm (Arysta, 2008f). The GSH profile at this HEC is illustrated in Figure A-14.
25 The modeled recovery after the 8-hour exposure is near completion at the end of a 24-hour cycle.
26 However, because the GSH decline has not reached a plateau by the end of 8 hours, greater
27 depletion can be expected from longer exposure at this MeI level. This HEC also does not
28 account for the remaining 16 hours of exposure at the level of the general population.
29 Nevertheless, because of its similarity to the 24-hour HEC of 2.2 ppm, and the ongoing GSH
30 replenishing, the additional 16-hour exposure after work may not significantly impact this
31 occupational HEC.

32 33 **III.C.3. Summary**

34
35 The USEPA-derived 24-hour HEC is 4.5 ppm and 8-hour occupational HEC is 5.8 ppm. These
36 are based on 50% average GSH depletion from the 4 architectural layers of the dorsal meatus in
37 the olfactory region. By using the benchmark GSH depletion at 25% instead of 50%, the DPR
38 24-hour HEC is 2.2 ppm. DPR’s 8-hour occupational HEC is 2.8 ppm using DPR’s default
39 breathing rate of 833 L/hr (i.e., 83% of USEPA’s recommended “light activity” rate) for
40 occupational activities, and assuming 100% nasal breathing.

41
42 Several uncertainties are noted. First, the 25% benchmark GSH depletion does not fully account
43 for the data variability in animal studies from which it is established. Furthermore, the HEC is
44 based on the average GSH depletion over 4 olfactory epithelial modeling structures,
45 underestimating the greater depletion at the outermost cell layer that is in immediate contact with
46 MeI. Finally, the GSH depletion has not reached a plateau at the end of an 8-hour occupational

1 exposure such that further depletion exceeding the 25% no-effect benchmark is expected if the
2 occupational exposure is extended beyond 8 hours at the 2.8 ppm HEC.
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14
15 Figure A-14. The 8-hour occupational HEC of 2.8 ppm based on 25% olfactory GSH depletion.
16 During working hours, the breathing rate was 833 L/hr with 0% oral breathing.
17 Include 4 meatus layers (gsdoe11, gsdoe21, gsdoe31, gsdoe41; with gsdoe11 as the
18 outmost layer), basement exchange layer (gsdoex1), and the 4-layer average in
19 meatus (ave gsdoe1). Data from Arysta (2008f).

1 IV. NEUROTOXICITY

2
3 This section presents the establishment of HECs for neurotoxicity following the same format as
4 the nasal effect HEC section. However, the coverage is less extensive due to a general
5 agreement between DPR and USEPA on the selection of the critical NOEL of 27 ppm (Schaefer
6 2002 and 2003), the limited availability of data on the possible MOA, and the use of same
7 aforementioned rat nose model for HEC simulation. The key difference between the HECs
8 established by DPR and USEPA is in the dose metric selection that resulted in lower HECs. The
9 lack of data to support any possible MOA for neurotoxicity was discussed by Kirman *et al.*
10 (2009). It should be noted that the authors concluded that the confidence is low for supporting
11 the use of peak brain MeI concentration as dose metric for PBPK modeling.
12

13 IV.A. Model and Parameters

14
15 The same PBPK model used for the HEC for nasal effects in rats is used for establishing the
16 neurotoxicity HEC. Model behavior pertinent to the HEC determination is discussed in this
17 section.
18

19 As discussed in Section III. A., within the model construct, simulation for serum iodide level in
20 rats is affected by the input rat body weight. A supplementary model run using a lower rat body
21 weight was provided by Arysta for illustrating its impact on model outcome (Arysta, 2008f).
22 The comparative analysis showed that the MeI profiles in the blood and brain are not
23 significantly different between input body weights of 0.207 kg (closer resembling the
24 “Himmelstein rat”) and 0.376 kg (used in rat model). This is likely due to the rapid metabolism
25 of MeI after uptake. However, the iodide profiles in the serum and brain are inversely
26 proportional to the two input body weights; i.e., the 1.8-fold lower body weight (i.e., $0.376/0.207$
27 $= 1.8$) resulted in 1.8-fold higher iodide concentrations. On the other hand, the 2.5-fold blood-to-
28 brain iodide ratio remained the same.
29

30 A more striking difference in the iodide profile is the 5.5-fold increase in the serum and brain
31 iodide peak concentrations when the 6-hour MeI exposure was increased by 1.3-fold, from 21 to
32 27 ppm. The 0.226 kg for male rat at the 27 ppm dose group from the Schaefer (2002 and 2003)
33 study was used for the HEC simulation. However, this additional 1.66-fold difference in the
34 body weight parameter (i.e., $0.376/0.226 = 1.66$) could not proportionally account for the marked
35 increase in the iodide profile. The exact reason for this model behavior cannot be deciphered
36 merely based on the output from these two simulations. This unresolved uncertainty within the
37 model output provided by Arysta further deters the use of iodide profiles for the HEC
38 determination at the NOEL of 27 ppm.
39

40 IV.B. Dose Metric

41
42 USEPA agreed with Arysta’s proposal to use the peak concentration of MeI in the brain as dose
43 metric for neurotoxicity HEC. The argument for the relevance of peak concentration was the
44 assumption that MeI neurotoxicity is similar to the sedative effects of many volatile solvents.
45 However, based on the time lapse between MeI exposure and the changes in neurobehavioral
46 measurements in the Schaefer studies, USEPA cautioned that this assumption could not be

1 substantiated (USEPA, 2007). In reviewing the March 2009 draft of this document, USEPA
2 agreed that the AUC is a more appropriate HEC dose metric (Rodriguez, 2009).
3

4 Several limitations for the choice of dose metric associated with the 27 ppm NOEL are noted.
5 First, there are no data to show that the 3 hour time point for administering the battery of
6 neurobehavioral tests represents the time to peak effects. There is also no assurance that the
7 severity of neurotoxicity would not increase had the exposure in rats been extended past 6 hours
8 in the study. Neither is there assurance that the NOEL would remain the same had the rats been
9 exposed for 24 hours.

10
11 The model output generally shows that the brain MeI concentration is proportional to the
12 concentration in the blood. By choosing the brain concentration dose metric, USEPA
13 demonstrated that it is also proportional to the exposure between the NOEL (27 ppm) and the
14 LOEL (93 ppm). However, DPR's concerns remain about their use of brain MeI concentration
15 instead of its AUC for the HEC dose metric. Since the simulated steady state brain MeI
16 concentration is reached within 30 minutes of exposure, substantial uncertainties exist with the
17 use of peak blood MeI concentration, i.e., without accounting for the longer duration of sustained
18 MeI in human brain. Furthermore, the peak concentration dose metric is inconsistent with the
19 suggested MOA regarding similarity to the anesthetic or sedative effects of chemical solvents.
20 For these effects, it is necessary that the time-dose factor should be accounted for, instead of the
21 dose factor alone. Interestingly, while peak MeI concentration in the brain was used by USEPA
22 as basis for modeling the HEC, it was stated in USEPA's MeI risk assessment that time-dose
23 relationship as in the "Haber's law" (i.e., $C^n \times t = K$) should be assumed for all systemic effects
24 (USEPA, 2007). The same "Haber's law" was also mentioned in the published MeI risk
25 assessment by Arysta (Milesion *et al.*, 2009) as applicable to all systemic effects and yet peak
26 MeI concentration instead of AUC was used for their HEC derivation.
27

28 Given that the MOA is unknown (Section IV.A.1.c. in Volume I), the AUC of MeI in the brain
29 instead of the MeI peak concentration was used by DPR as the dose metric to account for the
30 time-dose consideration. However, the contribution of iodide to neurotoxicity of MeI cannot be
31 ruled out. Nevertheless, given the aforementioned (Section IV.C.1) modeling uncertainties in its
32 disproportionate increase in rats with increased MeI exposure levels around the NOEL, the dose
33 metric of brain iodide AUC simulated by the model is not suitable here for HEC determination.
34

35 **IV.C. HECs**

36
37 Simulation outputs for a single day of exposure at 24 hours for the general population as well as
38 for 8 hours for occupational exposure were provided by Arysta (2008f). However, these
39 modeling data for HECs are generated based on the brain MeI peak concentration dose metric.
40 No simulation of HEC based on the AUC of brain MeI was provided. Thus, the HECs based on
41 the latter dose metric are extrapolated from the existing modeling datasets, including those
42 simulated for establishing nasal HEC, since the same model is used for both endpoints. The
43 rationale for extrapolation is included in the following presentation of HECs.
44

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2 **IV.C.1. General Population HEC**
3

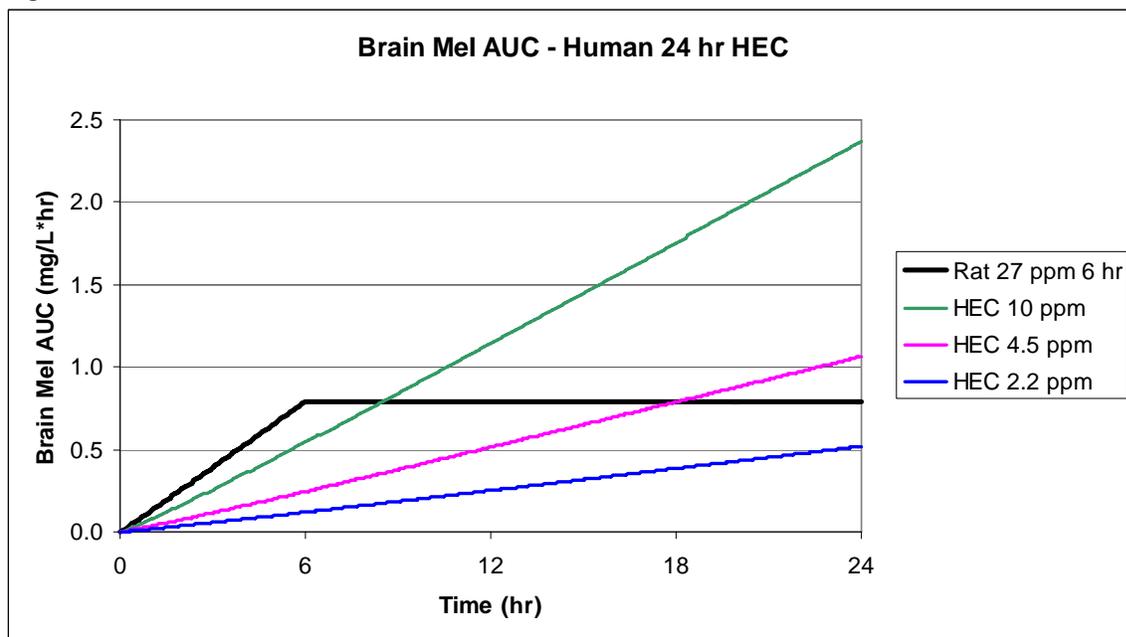
4 A 24-hour HEC simulation was only provided for 10 ppm MeI based on USEPA’s dose metric of
5 peak brain MeI concentration (Arysta, 2008f). Model outputs from rat nasal HEC simulations
6 are additionally used in estimating the HEC based on brain MeI AUC. The 24-hour MeI AUC in
7 the brain at 2.2, 4.5, and 10 ppm are presented in Table A-6.
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16 Table A-6. Modeled brain MeI AUC of human exposures at 2.2 to 10 ppm for 24 hours

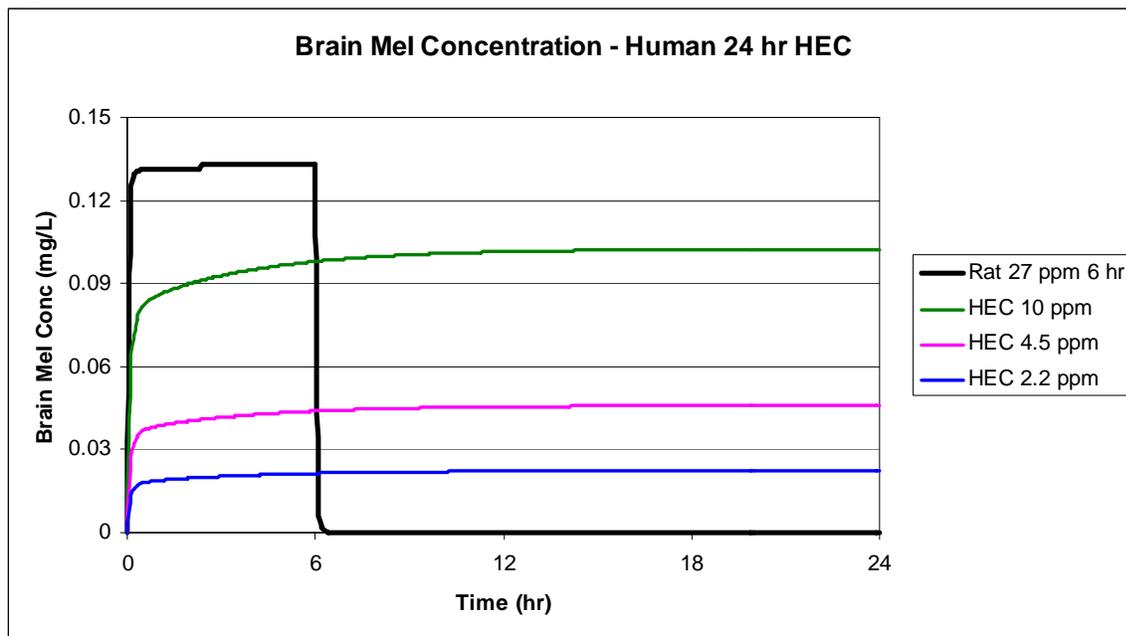
Simulation Condition	Brain MeI AUC (mg/L* hr)	Reference
Rat; NOEL 27 ppm 6-hour	0.794	Arysta, 2008f
Human; 2.2 ppm 24-hour	0.519	Arysta, 2008b, c
Human; 4.5 ppm 24-hour	1.062	Arysta, 2008b, c
Human; 10 ppm 24-hour	2.370	Arysta, 2008f

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25 These model outputs show a linear relationship between the brain MeI AUC and the MeI air
26 concentration, with the intercept at -0.00167 and the slope at 0.2365. Thus, a 24-hour HEC of
27 3.4 ppm would yield a brain MeI AUC of 0.794 mg/L*hr, the same AUC determined for the rat
28 in 24 hours from a 6 hour exposure at the NOEL of 27 ppm. Graphic presentations of these
29 simulations are shown in Figure A-15 for both the AUC and peak concentration of brain MeI. It
30 should be noted that the 0.133 mg/L peak MeI concentration in this simulation from Arysta is
31 30% higher than the 0.1 mg/L presented by USEPA (Barton, 2007; USEPA, 2007). The exact
32 reason for the difference between the two model simulations is unclear. Using the lower peak
33 MeI concentration from USEPA’s rat model, the HEC would be lower. This was confirmed by a
34 model run by Rodriguez (2009) showing the HEC at 2.8 ppm, approximately 20% lower than 3.4
35 ppm. Nevertheless, since the reasons for the difference between Arysta and USEPA’s model
36 output remain unknown, the 3.4 ppm is used in DPR risk assessment for the acute neurotoxicity
37 endpoint based on Arysta’s data submission accompanied by a set of modeling information.

1 Figure A-15a



2
3
4 Figure A-15b



5
6 Figure A-15. Modeled 24-hour HEC based on brain MeI AUC. Presented are brain MeI levels
7 of a) AUC, and b) peak concentration. The HEC of 3.4 ppm can be extrapolated
8 from the modeled AUC. Data from Arysta (2008c, f).

1 The HEC simulations are based on the parameters for a 70 kg adult with breathing rate of 567
2 L/hr. It was stated by Sweeney (2008) that based on their sensitivity analysis the HEC for a 6 kg
3 child would be similar to the HEC for a 70 kg adult. According to a later publication by
4 Sweeney *et al.* (2009), the same ratio of tidal volume (TVol) to body weight was used for adults
5 and children (Sweeney *et al.*, 2009).
6
7

8 **IV.C.2. Occupational HEC** 9

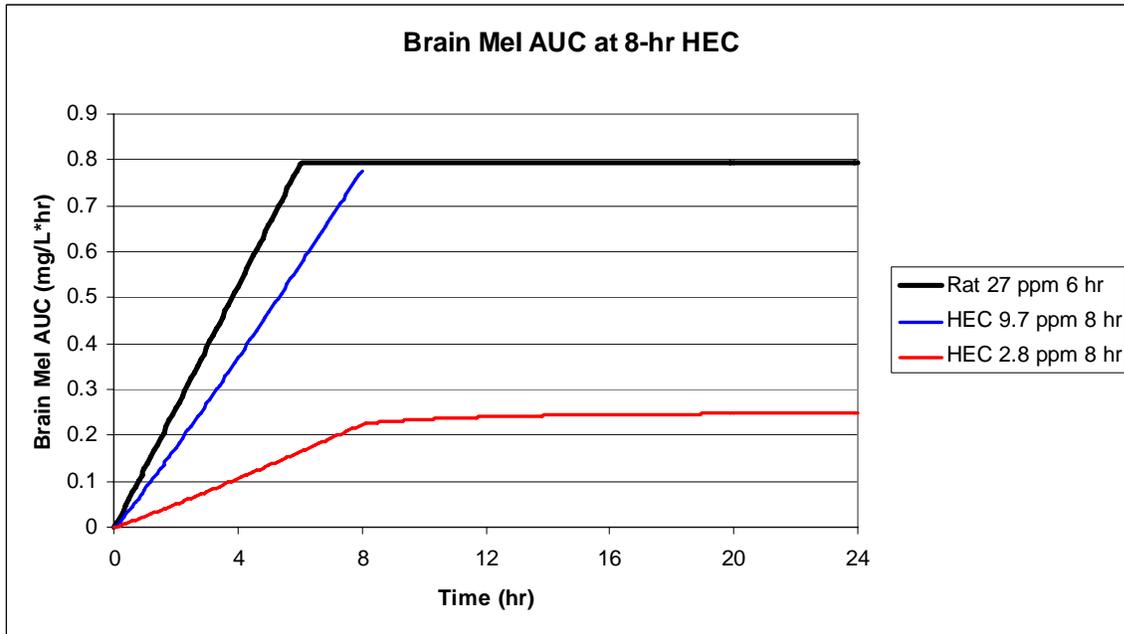
10 An 8-hour HEC simulation was provided for 9.7 ppm MeI (Arysta, 2008f) based on DPR's
11 default breathing rate of 833 L/hr, but with no additional 16-hour exposure after work. Similar
12 to the derivation of 24-hour HEC described in the previous section (Section IV.C.1), a
13 comparison can be made to the available modeling results from other Arysta model outputs at
14 different MeI concentrations. Although this HEC was only modeled for an 8-hour period (Figure
15 A-16), a simulation extended over 24 hours also showed that MeI rapidly declined after the
16 cessation of exposure.
17

18 The HEC based on brain MeI AUC for only 8 hours of exposure is 9.7 ppm. This is
19 approximately 3-fold higher than the 24-hour HEC of 3.4 ppm presented in Section IV.C.1,
20 although the latter was modeled at a lower breathing rate of 567 L/hr. Rodriguez (2009) noted
21 that based on USEPA's lower simulated brain MeI profile, the 8-hour HEC would be 7.5 ppm.
22 However, the "8-hour only" HEC of 9.7 ppm from Arysta and 7.5 ppm from USEPA do not take
23 into account the additional 16-hour exposure after work. Thus, it is reasonable to set the
24 worker's 8-hour HEC at 3.4 ppm, the same level for the 24-hour HEC for the general public.
25 This is also approximately one-third of the 9.7 ppm assuming that the 8 hour of exposure is
26 evenly spread out over 24 hours. No other simulations were submitted for further evaluation.
27

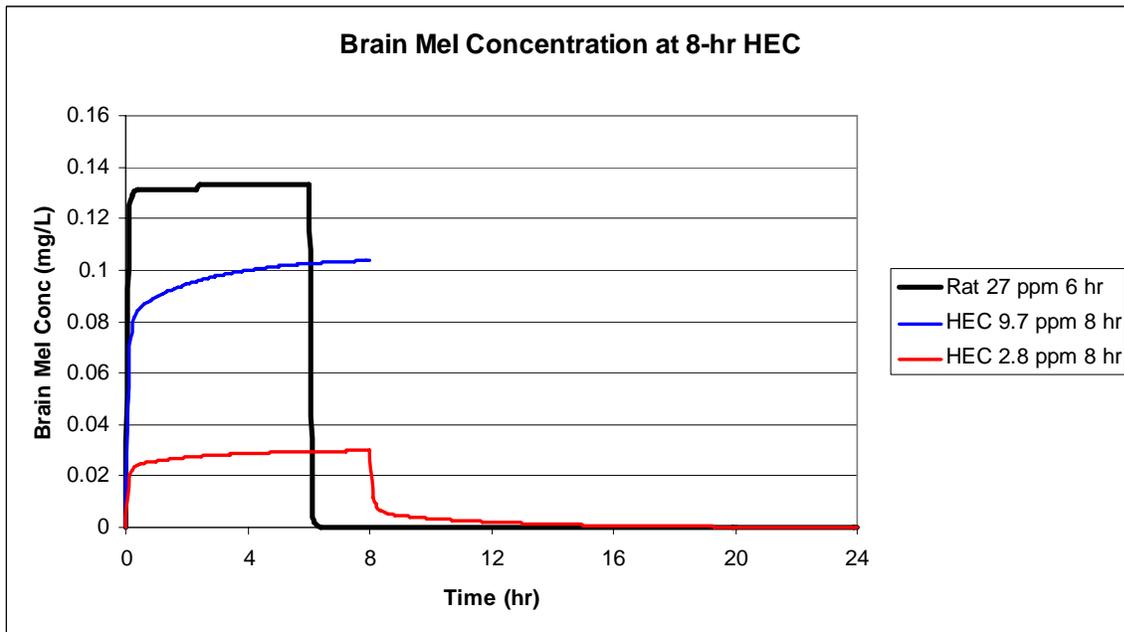
28 **IV.C.3. Summary** 29

30 The HEC derived by USEPA is 10 ppm for both 24-hour and 8-hour exposures. This is based on
31 the peak concentration of MeI in the brain. Since the peak is reached within 30 minutes of
32 exposure, the difference in the duration of exposure did not impact the USEPA's HEC. By using
33 the brain MeI AUC as dose metric, DPR's HEC for both 24-hour and 8-hour occupational
34 exposure is 3.4 ppm. It is noted that the simulated peak rat brain MeI concentration from
35 Arysta's simulation is 30% higher than the level reported for the USEPA simulation. Using the
36 lower level from the latter would result in a lower 24-hour HEC of 2.8 ppm.
37

1 Figure A-16a



2
3
4 Figure A-16b



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6 Figure A-16. The 8-hour-only HEC of 9.7 ppm based on brain MeI AUC. Presented are brain
7 MeI levels of a) AUC, and b) peak concentration. Data from the 24-hour
8 simulation of 8-hour exposure at 2.8 ppm MeI (nasal HEC simulation) based on the
9 same breathing rate of 833 L/hr are included for comparison. Data from Arysta
10 (2008f).

V. Summary of All Acute HECs

A summary of MeI HECs established from Section II through IV are presented in Table A-7. These values are provided for calculating the margin of exposure (MOE).

In using toxicity endpoints identified in animal studies, the current approach in health risk assessment takes into account the pharmacokinetic (PK) and pharmacodynamic (PD) differences between species (i.e., PK_{animal}, PD_{animal}) and the variation within human population (i.e., PK_{human}, PD_{human}). The PK_{animal} is accounted for in the PBPK modeling presented in this review. Default values for the remaining 3 factors (i.e., PD_{animal}, PK_{human}, PD_{human}) are then used for setting the health-protective benchmark MOE.

Because MeI perturbs thyroid functions, additional considerations should be given for protecting against neurodevelopmental effects from pre- and post-natal exposures for which toxicity data are lacking (Section V.C.1. of Volume I). Moreover, because MeI is rapidly converted to iodide, the toxicity of excess iodide from MeI should also be considered. Thus, although the lowest 24-hour HEC of 0.24 ppm is only applicable for assessing the risk of exposure for women of child-bearing age, care should be taken in establishing MeI reference concentrations (RfCs) based on the HECs listed in Table A-7 to ensure that the excess iodide from MeI does not exceed health-based standards for all age groups, not limited to women of child-bearing age. The consideration for iodide toxicity also applies in the derivation of RfCs for subchronic and chronic scenarios.

Table A-7. Acute HECs for MeI based on fetal death, nasal effects, and neurotoxicity

Endpoints	Rabbit Fetal Death	Rat Nasal Effect	Rat Neurotoxicity
24-hour HEC ^a	0.24 ppm	2.2 ppm	3.4 ppm
8-hour HEC ^b	0.22 ppm ^c	2.8 ppm ^c	3.4 ppm

a/ The 24-hour HEC used resting breathing rate (BR) of 567 L/min, 1.4x lower than DPR default BR of 833 L/hr for occupational work that is also used for the general public. The 24-hour HEC of 0.24 ppm and 3.4 ppm, but not the nasal HEC of 2.2 ppm, would be lower when DPR’s default BR is used.

b/ The 8-hour HEC include the 8-hour exposure during work time and a remaining 16-hour exposure as a member of the general public

c/ The 8-hour HEC does not include 16 hours of “ambient air” exposure. No model runs are available to assess its impact. However, since the 8-hour and 24-hour HECs are within the same range, the 0.22 ppm can be used for both scenarios.

d/ The 8-hour HEC does not include 16 hours of “ambient air” exposure. However, adding another 16 hours is not likely to significantly affect the HEC.

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Appendix B. Calculations

1. Equation for the conversion of NOEL (ppm) to amortized daily dose (mg/kg/day) for comparison of study NOELs (Table B-1):

$$\text{ppm} \times \frac{\text{MeI molecular weight}}{\text{Molar volume}} \times \text{Breathing Rate} \times \frac{\text{Exposure hours/day}}{24 \text{ hours}} \times \frac{\text{Exposure days/week}}{7 \text{ days}} \times \text{AF}$$

Table B-1. Calculation of mg/kg/day for inhalation toxicity studies.

Studies	Species	Endpoint	NOEL ppm	NOEL mg/L ^a	BR ^b L/kg/day	hours/day	days/week	NOEL mg/kg/day
Acute Exposure								
Schaefer, 2002	Rat	Neurotoxicity	27	0.15	960	6/24	NA	37
Kirkpatrick, 2002b	Rat	Nasal effect	21	0.12	960	6/24	NA	28
Himmelstein, 2004	Rat	Nasal and thyroid effects	25	0.14	1890 ^c	6/24	NA	67
Nemec, 2002c	Rat	Maternal weight effect	60	0.34	960	6/24	NA	81
Nemec, 2002d	Rabbit	Fetal death	2	0.011	540	6/24	NA	1.5
Nemec, 2003	Rabbit	Fetal death	25	0.14	540	6/24	NA	19
Sloter, 2005a	Rabbit	Fetal death, thyroid effect	25	0.14	540	6/24	NA	19
Sloter, 2005b	Rabbit	Fetal death, thyroid effect	20	0.11	540	6/24	NA	15
Subchronic Exposure								
Kirkpatrick 2002b	Rat	Body and liver weight effects	21	0.12	960	6/24	5/7	20
Nemec, 2004	Rat	Systemic, reproductive effects	25	0.14	960	6/24	7/7	34
	Rat	systemic effects	25	0.14	960	6/24	5/7	24
Nemec, 2002a	Rat	Reproductive effects	20	0.11	960	6/24	7/7	27
	Rat	Reproductive effects	5	0.03	960	6/24	7/7	7
Nemec, 2002c	Rat	Maternal body weight effect	20	0.11	960	6/24	7/7	27
Nemec, 2002d	Rabbit	Maternal body weight effect	10	0.057	540	6/24	7/7	8
Chronic Exposure								
Kirkpatrick, 2005	Rat	Salivary gland metaplasia	5	0.03	960	6/24	5/7	5
	Rat	Nasal and thyroid effects	20	0.11	960	6/24	5/7	19

^a/ molar volume= 0.0056 mg/L (21°C). Inhalation absorption factor (AF) is assumed at 100% (Sved *et al.*, 2002).

^b/ Default breathing rates (BR) of 960 L/kg/day (rats), and 540 L/kg/day (rabbits) (Zielhuis and van der Kreek, 1979).

^c/ BR was experimentally determined.

1 **2. HEC and RfC calculations (Table B-2)**

2
3 Equation for HEC, when not determined by PBPK modeling, is:

4
5
$$\text{HEC} = \text{NOEL} \times \frac{\text{Animal Breathing Rate}}{\text{Human Breathing Rate}} \times \frac{\text{Animal Exposure hours/day}}{\text{Human Exposure hours/day}} \times \frac{\text{Animal Exposure days/week}}{\text{Human Exposure days/week}} \times \frac{1}{\text{PK}_{\text{animal}}}$$

6
7 where $\text{PK}_{\text{animal}}$ = default factor of $10^{0.5}$ (actual value used 3.16).

8
9
10 Equation for RfC is:

11
$$\text{RfC} = \text{HEC} \times \frac{1}{\text{PD}_{\text{animal}}} \times \frac{1}{\text{PK}_{\text{human}} \times \text{PD}_{\text{human}}}$$

12
13 where $\text{PD}_{\text{animal}}$ = default factor of $10^{0.5}$ (rounded to 3), and $\text{PK}_{\text{human}} \times \text{PD}_{\text{human}}$ = total default
14 uncertainty factor of 10. If an additional uncertainty factor of 10 is applied, the RfCs will be 10-
15 fold lower.

16
17 **3. Margin of Exposure:**

18
19
$$\text{MOE} = \frac{\text{HEC}}{\text{Human Exposure}}$$

20
21
22 **4. Iodide levels from MeI exposure:**

23
24
25
$$\text{Additional Iodide in MeI (ug/day)} = \text{RfC (ppb)} \times \frac{5.65 \text{ ug/m}^3}{\text{ppb}} \times \text{BR (m}^3/\text{day)} \times \frac{127}{142}$$

26
27 When,

28 $1 \text{ ppb} = 5.65 \text{ ug/m}^3$

29 BR: age specific breathing rate (8.3 m³/day for 1-3 years old, 10 m³/day for 4 - 8 years
30 old; 15 m³/day for 9 - 13 years old, 17 m³/day for 14 - 18 years old, and pregnant and
31 lactating females; and 15.2 m³/day for 19+ years (USEPA, 1997)

32 (127/142): mol. wt ratio of iodide to MeI

1 **Table B-2. Calculation of HECs and RfCs for MeI.**

Duration/endpoint	NOEL (ppm)	BR ratio ^a	Hours/Day ratio ^b	Days/week ratio ^c	PK factor ^d	HEC (ppm)	RfC UF=30 ^e (ppb)
Acute Exposure							
Development effect (Nemec, 2002d)	2	PBPK modeling (maternal plasma iodide AUC)				0.22 (workers)	7
						0.24 (adults, general)	8
Nasal effect in rats (Kirkpatrick, 2002b)	21	PBPK modeling (25% GSH depletion in olfactory epithelium)				2.8 (workers)	93
						2.2 (general population)	73
Neurotoxicity in rats (Schaefer, 2002)	37	PBPK modeling (brain methyl iodide AUC)				3.4 (all groups)	113
Subchronic Exposure							
Reproductive effects in rats (Nemec, 2002a)	5	0.96/0.28	6/8	7/7	10 ^{0.5}	4.1 (workers)	136
		0.96/0.28	6/24	7/7	10 ^{0.5}	1.4 (non-worker adults)	45
Systemic effects in rats (Nemec, 2002a)	20	0.96/0.28	6/8	7/7	10 ^{0.5}	16.3 (workers)	542
		0.96/0.28	6/24	7/7	10 ^{0.5}	5.4 (non-worker adults)	181
		0.96/0.45	6/24	7/7	10 ^{0.5}	3.4 (children)	100
		0.96/0.59	6/24	7/7	10 ^{0.5}	2.6 (infants)	86
Systemic effects in rats (Kirkpatrick, 2002b)	21	0.96/0.28	6/8	5/5	10 ^{0.5}	17.1 (workers)	569
		0.96/0.28	6/24	5/7	10 ^{0.5}	4.1 (non-worker adults)	136
		0.96/0.45	6/24	5/7	10 ^{0.5}	2.4 (children)	81
		0.96/0.59	6/24	5/7	10 ^{0.5}	1.9 (infants)	64
Chronic Exposure							
Salivary gland metaplasia in rats (Kirkpatrick, 2005)	5	0.96/0.28	6/8	5/5	10 ^{0.5}	4.1 (workers)	136
		0.96/0.28	6/24	5/7	10 ^{0.5}	1.0 (non-worker adults)	32
		0.96/0.45	6/24	5/7	10 ^{0.5}	0.6 (children)	19
		0.96/0.59	6/24	5/7	10 ^{0.5}	0.5 (infants)	15
Lifetime Exposure							
Thyroid tumors (Kirkpatrick, 2005)	20	0.96/0.28	6/8	5/5	10 ^{0.5}	16.3 (workers)	542
		0.96/0.28	6/24	5/7	10 ^{0.5}	3.9 (non-worker adults)	129

2 a/ For DPR methodology, default breathing rates are: 0.96 m³/kg/day for rats and 0.54 m³/kg/day for rabbits (Zielhuis and van der
3 Kreek, 1979); 0.28 m³/kg/day for adult, 0.45 m³/kg/day for children 3-5 years old, and 0.59 m³/kg/day for infants (Andrews
4 and Patterson, 2000).

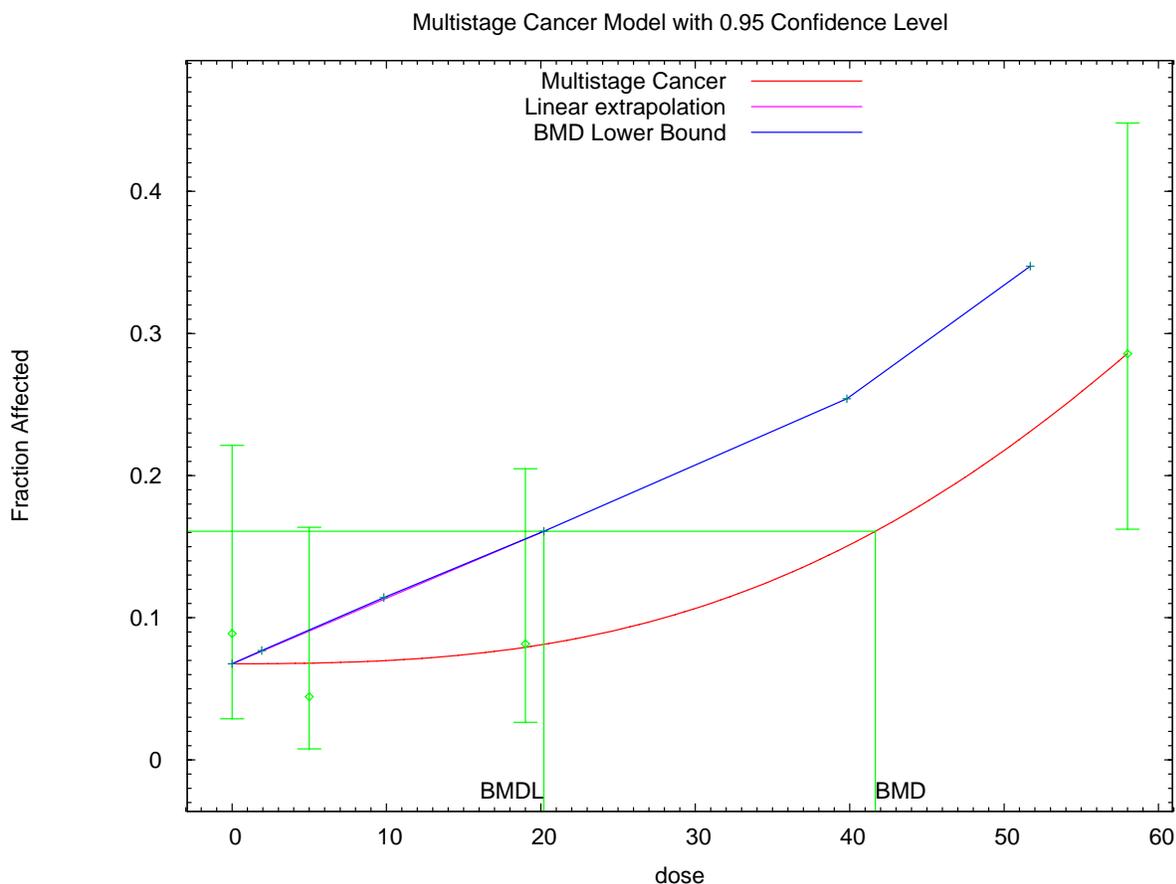
5 b/ Workers and non-workers are assumed to be exposed for 8 hours/day and 24 hours/day, respectively.

6 c/ Workers and non-workers are assumed to be exposed daily. For experiments conducted with exposures for 5 days/week, the
7 HECs are reduced (i.e., by a 5/7 factor) because it is reasonable to assume a lower HEC for daily repeated exposure.

8 d/ PK_{animal} factor=3.16

9 e/ UF of 30 =3 (pharmacodynamic factor PD_{animal}) x 10 (intraspecies factor PD_{human} x PK_{human}). Note that the total UF for acute
10 RfC is 30 because the interspecies PK difference is accounted for by PBPK modeling. The factor of 3 for PD_{animal} is an
11 approximation of 10^{0.5}, or 3.16. Thus, the total UF for subchronic, chronic, and lifetime RfCs is 100 if calculated from the
12 NOEL because it includes the default interspecies PK difference (PK_{animal}) of 10^{0.5}, or 3.16-fold.

1 **5. BMD multistage cancer model output for thyroid tumors in male rats (Table 22,**
 2 **Kirkpatrick, 2005)**
 3



```

4 10:08 05/18 2009
5 =====
6 Multistage Cancer Model. (Version: 1.7; Date: 05/16/2008)
7 Input Data File: C:\USEPA\BMDS2\Temp\tmp13.(d)
8 Gnuplot Plotting File: C:\USEPA\BMDS2\Temp\tmp13.plt
9                               Mon May 18 10:08:18 2009
10 =====
11 BMDS Model Run
12 ~~~~~
13 The form of the probability function is:
14
15 P[response] = background + (1-background)*[1-EXP(
16               -beta1*dose^1-beta2*dose^2-beta3*dose^3)]
17
18 The parameter betas are restricted to be positive
19
20 Dependent variable = affected
21 Independent variable = DOSE
22
23 Total number of observations = 4
24 Total number of records with missing values = 0
25 Total number of parameters in model = 4
26 Total number of specified parameters = 0
27 Degree of polynomial = 3
28
29
    
```

External Panel Review Draft MeI RCD Appendices to Volume I- August 10, 2009

1 Maximum number of iterations = 250
 2 Relative Function Convergence has been set to: 2.22045e-016
 3 Parameter Convergence has been set to: 1.49012e-008
 4

5 **** We are sorry but Relative Function and Parameter Convergence are currently
 6 unavailable in this model. Please keep checking the web sight for model updates which
 7 will eventually incorporate these convergence criterion. Default values used. ****
 8

9 Default Initial Parameter Values

10 Background = 0.0625262
 11 Beta(1) = 0
 12 Beta(2) = 8.05112e-005
 13 Beta(3) = 0
 14

15 Asymptotic Correlation Matrix of Parameter Estimates

16 (*** The model parameter(s) -Beta(1) have been estimated at a boundary point, or
 17 have been specified by the user, and do not appear in the correlation matrix)
 18

	Background	Beta(2)	Beta(3)
Background	1	-0.62	0.59
Beta(2)	-0.62	1	-1
Beta(3)	0.59	-1	1

19 Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval	
			Lower Conf. Limit	Upper Conf. Limit
Background	0.0675944	*	*	*
Beta(1)	0	*	*	*
Beta(2)	1.32052e-005	*	*	*
Beta(3)	1.14016e-006	*	*	*

20 * - Indicates that this value is not calculated.
 21
 22
 23
 24

25 Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-60.6616	4			
Fitted model	-61.0351	3	0.746884	1	0.3875
Reduced model	-66.9693	1	12.6153	3	0.005547

26 AIC: 128.07
 27
 28
 29
 30
 31

32 Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0676	3.042	4.000	45	0.569
5.0000	0.0680	3.062	2.000	45	-0.628
19.0000	0.0793	3.884	4.000	49	0.062
58.0000	0.2860	12.012	12.000	42	-0.004

33 Chi^2 = 0.72 d.f. = 1 P-value = 0.3953
 34
 35
 36
 37
 38
 39

40 Benchmark Dose Computation

41 Specified effect = 0.1
 42 Risk Type = Extra risk
 43 Confidence level = 0.95
 44 BMD = 41.6607
 45 **BMDL = 20.1955**
 46 BMDU = 55.3514
 47
 48
 49
 50

51 Taken together, (20.1955, 55.3514) is a 90% two-sided confidence interval for the BMD
 52
 53
 54
 55
 56
 57

58 **Multistage Cancer Slope Factor = 0.00495161**
 59
 60
 61
 62
 63

1 **Appendix C. U.S. Environmental Protection Agency Risk Assessment**

2
3 This section is a brief comparison between this RCD and the USEPA risk assessment
4 (USEPA, 2007).

5
6 **1. Human Equivalent Concentration**

7
8 For acute exposure, DPR and USEPA both use PBPK modeling to derive the HECs.
9 However there are differences in the selection of the acute fetal death NOEL, MOA, and the dose
10 metrics for PBPK modeling. These differences have been discussed under **IV.A.1. Acute**
11 **Inhalation Toxicity** and Appendix A. As a result, DPR determined HECs are lower than those
12 of the USEPA. A comparison of the HECs is presented in Table C-1.

13
14 For fetal death, the USEPA HECs are 23 ppm (worker 8 hours) and 7.4 ppm (bystander
15 24 hours) based on a NOEL of 10 ppm (Nemec, 2002d) and fetal serum iodide AUC after a
16 single day of exposure from PBPK modeling. In comparison, DPR establishes a lower of NOEL
17 at 2 ppm and uses the dose metric of maternal serum iodide AUC after a single day of exposure
18 to derive much lower HECs of 0.22 ppm, and 0.24 ppm, for 8 hours and 24 hours respectively, of
19 adult exposures.

20
21 For rat olfactory epithelium degeneration (Kirkpatrick, 2002b), both DPR and USEPA
22 establish the same NOEL for the study, but the difference lies in the selection of dose metric.
23 USEPA considers a regional average of 50% GSH depletion as the dose metric, and the HECs
24 were 5.8 ppm (workers) and 4.5 ppm (bystander all ages). In comparison, DPR sets the regional
25 average of 25% GSH depletion, resulting in HECs of 2.8 ppm (workers) and 2.2 ppm (bystander
26 and residents).

27
28 For both DPR and USEPA, the NOEL and the dose metric for acute neurotoxicity in rats
29 (Schaefer, 2002) are the same at 27 ppm. The difference is the dose metric with peak brain MeI
30 concentration by USEPA and the AUC of brain MeI by DPR, to establish the HECs. The
31 USEPA HEC is 10 ppm (workers and bystanders), while the DPR HEC is 3.4 ppm (all groups).

32
33 For the calculation of HECs of systemic effects after repeated MeI exposure, USEPA
34 uses a default RGDR of 1, the ratio of the blood:gas partition coefficient of the chemical for the
35 test species to humans ($H_{b/g \text{ animal}} / H_{b/g \text{ human}}$), to account for the pharmacokinetic differences
36 between species (USEPA, 2007 and 1994). An UF of 3 is then applied to account for the PD
37 differences since the interspecies PK differences have presumably been included in the RGDR,
38 as it is an approximation of the PBPK model. DPR has not adopted the use of the USEPA
39 methodology because of the uncertainty involved. In the case of a default RGDR of 1, no
40 quantitative adjustment for interspecies PK from animals to humans has been made.
41 Alternatively, DPR's methodology seeks to make interspecies exposure adjustment only for the
42 "intake" portion of the exposure scheme, and not the "uptake and tissue distribution" to the target
43 site. For this approach, the "intake" is calculated based on the breathing rate (air "intake") on a
44 per body weight basis (as is the common expression for exposure or dose). This calculation is
45 similar to the estimation of exposure through the diet while the "intake" is the amount of food
46 consumed instead of the air breathed in. DPR recognizes that sufficient data and experience are

1 not yet available for a subsequent adjustment down to the "uptake and tissue distribution" portion
 2 of the dose estimation that enables an adequate account for all PK aspects of the interspecies
 3 difference in a simple dosimetric equation. Thus, DPR maintains the PK factor of $10^{0.5}$ (Table
 4 B-2). Both USEPA and DPR apply a factor of $10^{0.5}$ for interspecies PD differences and a total
 5 10-fold factor for interindividual PK and PD differences in the human population. As shown in
 6 Table C-1 for subchronic and chronic exposures, when the test species is the rat, there are only
 7 slight differences between these two approaches in the HECs for adults. It is because
 8 mathematically, the total PK correction as the product of breathing rate ratio (0.96
 9 $m^3/kg/day_{rat}/0.28 m^3/kg/day_{human}$) and PK uncertainty factor of 3 equals to 1, the same as the
 10 USEPA RGDR default ratio of 1. However, this is not the case for the children and infant HECs.
 11 The DPR calculations show much lower values for these groups than for adults. USEPA did not
 12 calculate HECs for exposure of young children to MeI.

13
 14 **Table C-1. Comparison of HECs between USEPA and DPR.^a**

Study	USEPA HEC (ppm)		DPR HEC (ppm)				NOEL and Dose metric comparisons between USEPA and DPR
	Worker	By-stander	Worker	Bystander			
				Adult	Child	Infant	
Acute Toxicity							
Fetal death in rabbits (Nemec, 2002d)	23	7.4	0.22	0.24	NA	NA	<u>NOEL:</u> USEPA-10 ppm DPR-2 ppm <u>Dose metric:</u> USEPA-fetal iodide, single day DPR-maternal iodide, single day
Acute nasal effect in rats (Kirkpatrick, 2002b)	5.8	4.5	2.8	2.2	2.2	2.2	<u>NOEL:</u> 21 ppm (same) <u>Dose metric:</u> GSH depletion USEPA-50% DPR- 25%
Neurotoxicity in rats (Schaefer, 2002)	10	10	3.4	3.4	3.4	3.4	<u>NOEL:</u> 27 ppm (same) <u>Dose metric:</u> brain MeI USEPA-peak concentration DPR- AUC
Subchronic Toxicity							
Reproductive and developmental effect (Nemec, 2002a)	3.75	1.25	4.1	1.4	NA	NA	<u>NOEL:</u> 5 ppm (same)
Systemic effects (Kirkpatrick, 2002b)	15.75	3.75	17.1	4.1	2.4	1.9	<u>NOEL:</u> 21 ppm (same)
Chronic Toxicity							
Salivary gland effect (Kirkpatrick, 2005)	3.75	0.89	4.1	1.0	0.6	0.5	<u>NOEL:</u> 5 ppm (same)

15 ^{a/} Bolded values are used in the calculation of margins of exposure by DPR. USEPA did not calculate MOEs for repeated
 16 exposures; the HECs are included only as a comparison of the RfC methodology.

1 For MeI oncogenicity, DPR determines that both a genotoxic and a non-genotoxic mode
 2 of action may be involved in the formation of thyroid tumors in rats. Thus, both a threshold
 3 (using MOE) and a nonthreshold (using potency factor) are used to assess human exposure.
 4 While USEPA concludes that a genotoxic mechanism can not be excluded, the USEPA considers
 5 the formation of this tumor type as a threshold effect with the rat as the most sensitive species.

6
 7 **2. Exposure Assessment**
 8

9 A comparison of DPR's MeI exposure estimates for workers, bystanders, and residents
 10 with those in the USEPA risk assessment is provided in Volume II. Both DPR and USEPA
 11 estimate acute exposures, but only DPR provides repeated exposure values in the risk
 12 assessment. For occupational acute exposures, among the differences are: replicate samplers
 13 were considered as a single replicate (DPR) or as two values (USEPA), measured air
 14 concentrations were adjusted (DPR) or not (USEPA) for maximum application rate, and
 15 exposure was based on upper-bound value (DPR) versus maximum measured value (USEPA).
 16 The end result is that DPR estimates are similar to USEPA for applicators and hole punchers for
 17 drip irrigation, but higher values, as much as 3.4-fold, for other workers as shown for tarp
 18 monitor for shank injection (Table C-2).
 19

20 **Table C-2. Comparison of acute exposures between USEPA and DPR.^a**

Scenarios	DPR ppm	USEPA ppm
Workers (No PPE)		
Shallow shank-tarped soil fumigation (broadcast and bedded)		
Applicators (using shanks, 10-12")	1.51	1.03
Shovelmen and Shovelers	1.09	0.76
Tarp Monitors	3.75	1.11
Tarp Hole punchers, cutters, and removers	0.16	0.07
Planters	0.01	0.007
Drip irrigation fumigation (tarped-bed)		
Applicator	0.25	0.24
Hole Puncher	0.02	0.02
Planter	0.01	0.007
Bystanders^b	ppm at 30 meters from field	ppm at 25 meters from field
Drip irrigation	0.6	0.24
Shank injection, raised bed	0.3	0.32
Shank injection, flat fume	0.4	0.23

21 ^{a/} Values from **Volume II.**

22 ^{b/} 24-hour TWA air concentration.
 23
 24
 25

1 For bystander exposures, the difference in MeI air concentrations arises from the use of
2 different models and modeling assumptions, and selection of field studies. USEPA uses both the
3 ISCST3 model and the Probabilistic Exposure and Risk model for Fumigants (PERFUM) to
4 evaluate distributional bystander exposure from data derived from fumigation studies conducted
5 in California, Florida, and Michigan, and to estimate the buffer zone distances (USEPA, 2007).
6 DPR estimates the air concentrations using the ISCST3 model using only California data. In
7 modeling, USEPA adopts the whole field, probabilistic approach, while DPR applied the
8 maximum direction approach. A comparison of 24-hour time-weighted average air
9 concentrations (at 30 meters for DPR and 25 meters for USEPA values) for a 40 acre field,
10 shows similar values for raised bed shank injection, but 2 to 3 fold higher for flat fume shank
11 injection and drip irrigation, respectively (Table C-2).
12

13 Both USEPA and DPR conclude that MeI would not be expected to contaminate the
14 ground or surface water. USEPA conducts a qualitative drinking water assessment because MeI
15 is water soluble, and may be found in ground water and surface water if the treated soil is
16 exposed when there is rain (USEPA, 2007). Tier II PRZM/EXAMS for surface water and Tier I
17 SCIGROW for ground water are used to estimate MeI concentration in the drinking water.
18 While no residue levels were provided, USEPA concludes that MeI would not be expected to
19 “adversely impact ground water or surface water.” The DPR evaluation is presented in **Volume**
20 **III**. An additional concern for iodide in drinking water is included in the assessment.
21

22 **3. Risk Characterization**

23

24 The differences in HECs and exposure estimates result in DPR and USEPA reaching
25 different conclusions regarding the potential risk with MeI acute exposure to workers and
26 bystanders. Using a benchmark of 30 for acceptable risk, the USEPA concludes that MeI
27 registration can be approved with some restrictions on the application rate and field size, and
28 requirements (USEPA, 2007 and 2008). DPR reaches the opposite conclusion with a benchmark
29 of 300 for acute exposure and fetal death endpoint, and a benchmark of 30 for other endpoints
30 and durations.
31

32 A more important difference is that DPR recommends a more thorough investigation of
33 the potential pre- and post-natal developmental neurotoxicity. In the absence of sufficient
34 information, the application of an additional uncertainty factor of 10-fold is necessary because of
35 concerns about inadequacy of toxicity testing on young animals and the potential toxicity from
36 additional iodide from MeI exposure. This factor should be applied toward the MOE
37 benchmark, resulting in a higher benchmark of 300 as well as proportionally lower calculated
38 reference concentrations. Under the section for uncertainty factors, USEPA states that MeI is a
39 non-food use pesticide and consequently, it was not subjected to the Food Quality Protection Act
40 (1996) and the 10x FQPA factor did not apply (USEPA, 2007).
41

42 With iodide, DPR is concerned with increased body burden from iodide in the drinking
43 water and after MeI inhalation exposure. While iodide contamination of surface water is
44 unlikely, a screening evaluation estimates an upper-bound level of 18 ppm iodide in the ground
45 water. Iodide levels from MeI inhalation exposure are calculated from the RfCs of the acute
46 toxicity endpoints. From both water and air, the calculated iodide intakes under most cases are

1 higher than established health standards for iodide. Thus, the recommended MeI RfCs for any
2 duration should be much lower, at levels not to exceed 1 ppb, for the protection of young
3 children. On the other hand, the USEPA is apparently only concerned with iodide in the air, as a
4 result of MeI degradation after application. This level was considered to be “lower than those
5 expected to cause toxic effects,” but the data to support this statement were not provided in their
6 risk assessment (USEPA, 2007). If an UF of 30 is applied to the USEPA HEC, the RfCs will
7 result in excess iodide exposure much higher than any established health standards (as discussed
8 in Section V.C. of Volume I). For example for the USEPA 24-hr HEC of 7.4 ppm for fetal death
9 endpoint, the RfC is 247 ppb with a corresponding excess iodide body burden of 10,400 µg/day
10 for young children⁴. For the 4.5 ppm 24-hr HEC for nasal effects, the hypothetical RfC is 150
11 ppb with the corresponding excess iodide for young children at 6,300 µg/day. The NAS
12 tolerable upper limit (2000) and the ATSDR MRL (2004) are 200-300 µg/day, and 113-153
13 µg/day, respectively, for 1-3 year old.

⁴ Total iodide exposure=RfC (ppb) x 5.65 (µg/m³)/ppb x BR (8.3 m³/day for 1-3 year old) x 127/142. The ratio of molecular weight of iodide (127) to MeI (142) is used to account for the weight of iodide in MeI, assuming 100% absorption of MeI and conversion to iodide. BR=breathing rate from USEPA (1997).