From: Lori Lim
To: Schreider, Jay
CC: Patterson, Gary
Date: 4/28/2010 10:12 AM
Subject: revised draft Mel memo
Attachments: Mel memo to gary with LL notes2.doc

Attached is the revised draft memo incorporating yours and Joyce's comments.
Lori

[Handwritten note: Internal Declarative]
MEMORANDUM

TO: Gary Patterson, Ph.D.
    Supervising Toxicologist
    Medical Toxicology Branch

FROM: Jay Schreider, Ph.D. (DRAFT)
    Primary State Toxicologist

DATE: April 28, 2010

SUBJECT: POTENTIAL MISINTERPRETATION OF METHYL IODIDE RISK ASSESSMENT

I understand that the Health Assessment Section in Medical Toxicology is responsible only for risk assessments and risk assessment decisions. Risk management decisions are not in our purview and should not be part of the risk assessment. Correspondingly, risk assessment decisions should not be made as part of the risk management process. This separation of risk assessment and risk management is fundamental to a credible and transparent process. I am, however, puzzled by some of the numbers cited in the draft regulation on methyl iodide (MeI) for inhalation exposure. They appear to have been extracted from different MeI risk assessment methodologies that are not interchangeable. Each approach is made up of a series of interrelated values and assumptions: one value or assumption is predicated on the preceding one. It is not scientifically credible to select a value or assumption from one and combine it with a value or assumption from another.

Reference concentration (RfC) methodologies are applied when laboratory animal toxicity data, represented by a point of departure value (POD, such as NOEL or BMDL), are used to calculate the reference concentrations in human health risk assessment. These are default methodologies in the absence of human data or sufficient data for PBPK modeling.

For this discussion related to MeI, the RfC methodologies from USEPA, OEHHAA, and DPR-MT are compared with a focus on the derivation of reference concentrations for systemic effects by gases. The methodologies have the following components with the key differences for the intake adjustment and interspecies pharmacokinetic (PK) extrapolation (Table 1).

(a) Intake differences reflecting the breathing rate differences between species
(b) Time extrapolation to account for the difference in the duration of exposure in the laboratory animal studies compared to human exposure to the chemical of concern.
(c) Interspecies differences in the PK and pharmacodynamic (PD) processes between laboratory animals and humans

1 Types of inhaled material are particles and gases (USEPA, 1994). Categories for gases are: 1 (do not penetrate to blood, e.g., highly water soluble/rapidly reactive), 2: water soluble/blood accumulation, and 3: water insoluble/perfusion limited.
(d) Intraspecies differences in PK and PD between individuals in the human population 
(e) Other concerns such as increased sensitivity of infants and children.

In the USEPA RfC methodology, potential species difference in intake is considered in the pharmacokinetic adjustment expressed as the Regional Gas Dose (RGD) where \( V_e \) is minute volume, \( Q_T \) is cardiac output, and \( H_{\text{blood/gas}} \) is partition coefficient between blood and gas (p. 4-57; USEPA, 1994). The RGD estimates the steady state concentration in the arterial blood after exposure.

\[
\text{RGD} = (V_e)(Q_T)H_{\text{blood/gas}}
\]

For extrapolation of animal data to humans, the Regional Gas Dose Ratio is expressed as:

\[
\text{RGDR} = \frac{(\text{RGD})_{\text{Animal}}}{(\text{RGD})_{\text{Human}}}
\]

Through a series of assumptions (discussed in Appendix J of USEPA, 1994), the equation is reduced to the following:

\[
\text{RGDR} = \frac{(H_{\text{blood/gas}})_{\text{Animal}}}{(H_{\text{blood/gas}})_{\text{Human}}}
\]

where RGDR value is 1 if \((H_{\text{blood/gas}})_{\text{Animal}}\) is greater than \((H_{\text{blood/gas}})_{\text{Human}}\) or if the partition coefficient values are not known. Since the RGD for most chemicals are unknown, the PK factor is often a value of 1 in the RfC calculation.

OEHHA scientists previously have used the USEPA RfC methodology in the development of the reference effect level (REL) for the Hot Spots program. In their recent revision of the technical document, they modified their approach because the RGDR addresses only respiratory regional exposure and deposition of the parent compound (OEHHA, 2008). A PK factor of 2 is now added to account for any differences in the other pharmacokinetic processes, metabolism and elimination, between species (p. 61; OEHHA, 2008).

DPR-Medical Toxicology (MT) scientists have not adopted the USEPA RfC methodology because they do not consider the use of RGDR ratio sufficient to address PK differences. Further, the default value of 1 is not health protective because it results in an assumption of no interspecies differences in the absence of data. The current DPR-MT methodology is to use a breathing rate ratio to adjust for the known species differences in the breathing rates for the intake portion of the exposure. In the absence of PK data, any potential PK difference is addressed using a default UF of \(10^{0.5}\). We have not reviewed the current OEHHA methodology.
Gary Patterson  
April 28, 2010  
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The DPR draft regulation for Mel is based on proposed target levels of 96 ppb and 32 ppb for 8 hours and 24 hours of exposure, respectively. Based on the brief description in the draft regulation, the levels appear to be derived using a higher POD of 12 ppm, instead of 0.5 ppm; retaining the breathing rate ratio for intake from the DPR-MT method but reducing the interspecies PK factor to 1 and excluding the recommended additional uncertainty factor (Table 2). These "non-Risk Characterization Document (RCD)" calculated target levels cannot be supported by MT scientists. As discussed already, each of the RfC methodologies has different underlying assumptions. If the starting point of the RfC calculation is the DPR-MT method using the breathing rate ratio, then the interspecies PK factor cannot be set at 1 using the USEPA's rationale for the default RGDR value. The RGDR already includes intake considerations between species. The differences in the outcome between the methods using Mel endpoints and PODs are indicated in Table 2. While it is useful to demonstrate the numerical outcome, the selection of a methodology must be science based. Furthermore, it is unclear why the interspecies PK factor is referred to as an additional uncertainty factor in the draft regulation. The RCD designated that factor for the need to address developmental and postnatal neurotoxicity concerns.

Another issue with the draft regulation is how sensitive individuals in a population are addressed in the calculation of the regulatory level. The total intraspecies UF of 10 was stated to include sensitive individuals and no additional uncertainty factor was applied. In the absence of sufficient data for PBPK modeling, an intraspecies UF of 10-fold (10^0.5 each for PK and PD difference) is traditionally used to account for variability within the human population. This factor is intended to account for the greater susceptibility to chemicals of various sensitive subpopulations, including infants and children (p. 63; OEHHA, 2008). However, in the case of Mel human exposure, this 10-fold factor is considered insufficient by MT scientists. The Mel RCD emphasized the need for an additional uncertainty factor of 10-fold for developmental and postnatal neurotoxicity with Mel exposure. In the current REL technical support document, OEHHA increases the intraspecies default PK factor from 10^0.5 to 10 for systemic effects after exposure to gases and particles to protect neonates and young infants from potential adverse effects of airborne toxicants (p. 65; OEHHA, 2008). This was based on PBPK modeling to derive PK UF values for 25 chemicals (Table 4.42; OEHHA, 2008). The differences in the PK factor between infants and adults were: UF PK is ≤10^0.5 for 12 chemicals, >10^0.5 to 9.9 for 8 chemicals, and ≥ 10 for 5 chemicals. Thus, the default total intraspecies UF is 30 with a factor of 10 for PK and 10^0.5 for PD differences.

The Mel RCD has been vetted in a transparent manner, has undergone a rigorous external peer review, and we stand by our methodology. If the risk management decision is to be made

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1 PK and Chemicals are: ≤10^0.5 (furan, perchloroethylene, naphthalene/naphthalene oxides, carbon tetrachloride, chloroform, arsenic and metabolites, ethylene, benzene, 1,1-dichloroethylene, benzene, bromochloromethane, methyl chloroform, and diethyl ether), >10^0.5 to 9.9 (MTBE, styrene/styrene oxide, ethylene/ethylene oxide, vinyl chloride, toluene, xylenes, toluene/xylenes mixtures, and isopropanol), ≥10 (butadiene/butadiene monoxide/diepoxybutane, dichloromethane, TCE and metabolites, and benzo[a]pyrene).
predicated on another approach, that approach should be selected in a transparent and credible manner. We may not agree with that decision, but that is management's prerogative. However, the presentation of the risk management decision should not imply that the DPR risk assessment is the basis for that decision or that the apparent "mix and match" approach provides a scientifically credible basis for the decision.
References:


<table>
<thead>
<tr>
<th>Methodology</th>
<th>POD</th>
<th>Intake</th>
<th>Time extrapolation</th>
<th>Interspecies Extrapolation: Lab animal to Human</th>
<th>Intraspecies Extrapolation: Human inter-individual differences</th>
<th>Additional UF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>&quot;Shorter to longer duration&quot;</td>
<td>RGDR=1</td>
<td>10^{0.3}</td>
<td>10^{0.3}</td>
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<tr>
<td>USEPA</td>
<td>NOEL or BMDL</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>10^{0.3}</td>
<td>10^{0.3}</td>
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<tr>
<td>OEHHA</td>
<td>NOEL or BMDL</td>
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<td>Yes</td>
<td>Yes</td>
<td>10^{0.3}</td>
<td>10^{0.3}</td>
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<tr>
<td>DPR-MT</td>
<td>NOEL or BMDL</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>10^{0.3}</td>
<td>10^{0.3}</td>
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<td>PBPK Modeling</td>
<td>NOEL or BMDL</td>
<td>PBPK determined HEC</td>
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<td>10^{0.3}</td>
<td>10^{0.3}</td>
<td>≤10</td>
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</table>

* OEHHA finds the USEPA RfC methodology using RGDR ratio as insufficient to account for PK differences. So a factor of 2 is applied to the RfC methodology.
Table 2. Comparison of RfC calculation for MeI.

<table>
<thead>
<tr>
<th>Sources</th>
<th>NOEL or LED</th>
<th>Intake BR ratio</th>
<th>Time Extrapolation: Hours/Day ratio</th>
<th>Days/week ratio</th>
<th>Interspecies Extrapolation: Lab animal to Human</th>
<th>Intraspecies Extrapolation: Human inter-individual differences</th>
<th>Add. UF</th>
<th>Rfc ppb</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>PK factor</td>
<td>PD factor</td>
<td>PK factor</td>
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<tr>
<td>Fetal death endpoint</td>
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<tr>
<td>MedTox (2010 Mel RCD)</td>
<td>0.5 ppm (LED&lt;sub&gt;10&lt;/sub&gt;)</td>
<td>0.54/0.28</td>
<td>6/8</td>
<td>7/7</td>
<td>10&lt;sup&gt;6.5&lt;/sup&gt;</td>
<td>10&lt;sup&gt;4.5&lt;/sup&gt;</td>
<td>10&lt;sup&gt;5.5&lt;/sup&gt;</td>
<td>10&lt;sup&gt;6.5&lt;/sup&gt;</td>
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<tr>
<td>MedTox method and NOEL = 2ppm</td>
<td>2.0 ppm</td>
<td>0.54/0.28</td>
<td>6/8</td>
<td>7/7</td>
<td>10&lt;sup&gt;6.5&lt;/sup&gt;</td>
<td>10&lt;sup&gt;4.5&lt;/sup&gt;</td>
<td>10&lt;sup&gt;5.5&lt;/sup&gt;</td>
<td>10&lt;sup&gt;6.5&lt;/sup&gt;</td>
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<tr>
<td>USEPA RfC method&lt;sup&gt;a&lt;/sup&gt; and NOEL = 2ppm</td>
<td>2.0 ppm</td>
<td>NA</td>
<td>6/8</td>
<td>5/5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>RGDR=1</td>
<td>10&lt;sup&gt;4.5&lt;/sup&gt;</td>
<td>10&lt;sup&gt;6.5&lt;/sup&gt;</td>
<td>10&lt;sup&gt;5.5&lt;/sup&gt;</td>
</tr>
<tr>
<td>USEPA RfC using PBPK modeling (2006 RED)</td>
<td>2.0 ppm</td>
<td>NA</td>
<td>6/8&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5/5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>RGDR=1&lt;sub&gt;1,UF=2&lt;/sub&gt;</td>
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<td>0.54/0.28</td>
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<td>RGDR=1</td>
<td>10&lt;sup&gt;4.5&lt;/sup&gt;</td>
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<td>10&lt;sup&gt;5.5&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Using USEPA calculation method for methyl bromide developmental toxicity endpoint (USEPA, 2006).

<sup>b</sup> It is unclear from the OEHHA TSD whether time extrapolation factors would be applied.

<sup>c</sup> OEHHA has expressed concern about increased children sensitivity to developmental neurotoxicity.