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

draft
informal
deliberative

dpr
Mary-Ann Warmerdam
Director

Department of Pesticide Regulation

Arnold Schwarzenegger
Governor

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, OEHHA, and DPR-MT are compared with a focus on the derivation of reference concentrations for systemic effects by gases[1]. 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 $H_{blood/gas}$ 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.

$$RGD = (\dot{V}_E)(\dot{Q}_T)H_{blood/gas}$$

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

$$RGDR = (RGD)_{Animal} \div (RGD)_{Human}$$

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

$$RGDR = (H_{blood/gas})_{Animal} \div (H_{blood/gas})_{Human}$$

where RGDR value is 1 if $(H_{blood/gas})_{Animal}$ is greater than $(H_{blood/gas})_{Human}$ 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.

The DPR draft regulation for MeI is based on proposed target levels of 96 ppb and 32 ppb for workers and bystanders with 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 2 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 MeI 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 MeI human exposure, this 10-fold factor is considered insufficient by MT scientists. The MeI RCD emphasized the need for an additional uncertainty factor of 10-fold for developmental and postnatal neurotoxicity with MeI 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[2] (Table 4.4.2; OEHHA, 2008). The differences in the PK factor between infants and adults were: UF PK is $\leq 10^{0.5}$ 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 MeI 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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[2] PK and Chemicals are: $\leq 10^{0.5}$ (furan, perchloroethylene, naphthalene/naphthalene oxides, carbon tetrachloride, chloroform, arsenic and metabolites, ethylbenzene, 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, m-xylene, toluene/xylene 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:

OEHHA, 2008. Technical Support Document for the Derivation of Noncancer Reference Exposure Levels. Air Toxic Hot Spots Risk Assessment Guidelines. (Approved by the AB 1807 Scientific Review Panel, June 18, 2008). Air Toxicology and Epidemiology Branch, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA

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USEPA, 1994. Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F; October 1994). Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC.

USEPA, 2006. Methyl Bromide: Phase 5 Health Effects Division (HED) Human Health Risk Assessment For Commodity Uses. Memorandum from J.L Dawson and E. Mendez to S. Weiss (March 10, 2006). Office of Prevention, Pesticides and Toxic Substances, U.S. Environmental Protection Agency, Washington, D.C.

Table 1. Default methodology comparison

Methodology	POD	Intake	Time extrapolation *Shorter to longer duration*		Interspecies Extrapolation: Lab animal to Human		Intraspecies Extrapolation: Human inter-individual differences		Additional UF
			Hours/ Day ratio	Days/ week ratio	PK factor	PD factor	PK factor	PD factor	
USEPA	NOEL or BMDL	No	Yes	Yes	RGDR=1	$10^{0.5}$	$10^{0.5}$	$10^{0.5}$	≤10
OEHHA	NOEL or BMDL	No	Yes	Yes	RGDR=1 and UF =2[a]	$10^{0.5}$	$10^{0.5}$ (some data) 10 (no PK data)	$10^{0.5}$ (human adult studies, no ↑children sensitivity concern) 10 (evidence of ↑children sensitivity, no DNT data)	
DPR-MT	NOEL or BMDL	Breathing rate ratio	Yes	Yes	$10^{0.5}$	$10^{0.5}$	$10^{0.5}$	$10^{0.5}$	≤10
PBPK Modeling									
General	NOEL or BMDL	PBPK determined HEC				$10^{0.5}$	$10^{0.5}$	$10^{0.5}$	≤10

a/ 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.

Sources	NOEL or LED	Intake BR ratio[a]	Time Extrap. Hours/ Day ratio	Time Extrap. Days/ week ratio	Interspecies Extrapolation: Lab animal to Human — PK factor	Interspecies Extrapolation: Lab animal to Human — PD factor	Intraspecies Extrapolation: Human inter-individual differences — PK factor	Intraspecies Extrapolation: Human inter-individual differences — PD factor	Add. UF	Rfc ppb
Fetal death endpoint										
MedTox (2010 MeI RCD)	0.5 ppm (LED_{01})	0.54/0.28 0.54/0.28	6/8 6/24	7/7 7/7	$10^{0.5}$ $10^{0.5}$	$10^{0.5}$ $10^{0.5}$	$10^{0.5}$ $10^{0.5}$	$10^{0.5}$ $10^{0.5}$	10 10	0.8 (worker) 0.3 (bystander)
MedTox method and NOEL= 2ppm	2.0 ppm	0.54/0.28 0.54/0.28	6/8 6/24	7/7 7/7	$10^{0.5}$ $10^{0.5}$	$10^{0.5}$ $10^{0.5}$	$10^{0.5}$ $10^{0.5}$	$10^{0.5}$ $10^{0.5}$	10 10	3.2 (worker) 1.2 (bystander)
USEPA RfC method[a] and NOEL=2 ppm	2.0 ppm	NA	6/8 6/24	5/5 5/7	RGDR=1 RGDR=1	$10^{0.5}$ $10^{0.5}$	$10^{0.5}$ $10^{0.5}$	$10^{0.5}$ $10^{0.5}$	1 1	48 (worker) 11 (bystander)
OEHHA –REL method and NOEL= 2ppm	2.0 ppm	NA	6/8[b] 6/24[b]	5/5[b] 5/7[b]	RGDR=1,UF=2 RGDR=1,UF=2	$10^{0.5}$ $10^{0.5}$	$10^{0.5}$ $10^{0.5}$	$10^{0.5}$ $10^{0.5}$	10[c] 10[c]	2.4 (worker) 0.6 (bystander)
DPR draft regulation	2.0 ppm	0.54/0.28 0.54/0.28	6/8 6/24	7/7 7/7	RGDR=1 RGDR=1	$10^{0.5}$ $10^{0.5}$	$10^{0.5}$ $10^{0.5}$	$10^{0.5}$ $10^{0.5}$	1 1	96 (worker) 32 (bystander)
USEPA RfCs using PBPK modeling (2008 RED)										
Fetal death	10 ppm	Workers HEC=23 Bystanders HEC=7.4				$10^{0.5}$ $10^{0.5}$	$10^{0.5}$ $10^{0.5}$	$10^{0.5}$ $10^{0.5}$	1 1	767 (worker) 247 (bystander)
Nasal effect	21 ppm	Workers HEC=5.8 Bystanders HEC=4.5				$10^{0.5}$ $10^{0.5}$	$10^{0.5}$ $10^{0.5}$	$10^{0.5}$ $10^{0.5}$	1 1	193 (worker) 150 (bystander)

a/ Using USEPA calculation method for methyl bromide developmental toxicity endpoint (USEPA, 2006).
b/ It is unclear from the OEHHA TSD whether time extrapolation factors would be applied.
c/ OEHHA has expressed concern about increased children sensitivity to developmental neurotoxicity.