**On-line Supplementary Material for**

**Advances in Inhalation Dosimetry Models and Methods for Occupational Risk Assessment and Exposure Limit Derivation,” by Eileen D. Kuempel, PhD; Lisa M. Sweeney, PhD, DABT; John B. Morris, PhD; and Annie M. Jarabek, BS**

**S-1. Examples of Proposed Occupational Exposure Limits (OELs) and Guidance Values using PBPK Modeling**

Other proposed occupational exposure limits (OEL) or guidance values have been developed using PBPK modeling which do not have the same authority as the OSHA PEL for methylene chloride (described in the main manuscript, “PBPK Model for Systemic Effects of Category 3 Gases: Example of Methylene Chloride”), but nonetheless demonstrate how internal dosimetry can be used to characterize the risks from occupational inhalation exposure. Examples of proposed occupational exposure limits published in the peer reviewed literature are described for the acute effects of trichloroethylene (TCE), developmental toxicity of glycol ethers, and three possible acute effects of iodomethane (methyl iodide). These examples demonstrate the use of PBPK modeling to extrapolate from one population effect level to another (TCE), for interspecies extrapolation and uncertainty factor refinement (glycol ethers), and discriminating among multiple potential “key” effects under different exposure scenarios (iodomethane).

**S-1.1 Acute inhalation guidance value for trichloroethylene (TCE)**

Drowsiness, an acute effect of TCE, was identified as the endpoint of occupational concern by Simon (1997). Based on the expectation that both the parent compound TCE and metabolite trichloroethanol (TCOH) (a known sedative) could contribute to the effect of concern, the dose surrogate for acute effects of TCE was the sum of the blood TCE and TCOH concentrations. Given the focus on this dosimeter, the desired model structure was intermediate in complexity as compared to contemporary human PBPK models for TCE which accounted for fewer or more metabolic pathways and metabolites (e.g., Fisher and Allen, 1993; Clewell et al., 1995). Simon (1997) used parameter distributions based on literature data for physiological/anatomical parameters, partition coefficients, and some metabolic parameters. Additional metabolic parameters were estimated by optimization of fit to three human data sets and the composite distribution (developed from the three optimized distributions) was used as in input for validation of the model by comparison to a fourth data set. The model was then used to derive internal dosimetry estimates corresponding to the population in a study where 60% of subjects reported feeling “sleepy” during 7 hr exposures to 200 ppm TCE. The 40th percentile value of this distribution, generated using Monte Carlo methods, was identified as an acceptable internal exposure to TCE and TCOH (i.e., the 40th percentile individual was the person with the highest internal exposure who remained unaffected). An acceptable 7 hr TWA exposure to TCE was then identified by lowering the TCE exposure and determining the TCE concentrations which would yield 95th and 99th percentile individuals with internal exposure to TCE and TCOH that was equivalent to the 40th percentile individual in the key toxicity study. The values derived by Simon (1997) indicate that the contemporary American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) of 50 ppm would protect 95 percent of workers, but not 99%. Simon (1997) further determined that, after 15 minutes exposure to the ACGIH short term exposure limit (STEL) of 200 ppm, individuals would need 2.5 hrs exposure to fresh air prior to resuming exposures at the TLV, in order to adequately reduce the level of TCE +TCOH in blood.

**S-1.2 Glycol ethers OELs**

OELs for 2-methoxyethanol (ethylene glycol monomethylether, EGME), 2-ethyoxyethanol (ethylene glycol monoethyl ether, EGEE) and ethoxyethanol acetate (EGEEA), proposed by Sweeney et al. (2001), were derived using PBPK modeling for interspecies extrapolation and estimation of intraspecies pharmacokinetic variability/uncertainty. These glycol ether compounds have been identified as developmental toxicants in laboratory animals with a mode of action related to internal concentrations of alkoxyacetic acid metabolites. Using previously developed PBPK models (Gargas et al., 2000a, b), the average daily area under the maternal blood alkoxyacetic acid concentration vs. time curve (maternal blood alkoxyacetic acid AUC) was calculated for rats exposed to the NOAEL concentration of EGEE or EGME for 6 hrs/day on GD 6-15. Human PBPK model simulations using average parameter values were then conducted to identify EGEEA, EGEE, and EGME concentrations which would yield internal doses in pregnant human workers that would be equivalent to those determined for the animal NOAELs, termed human no adverse effect levels (NAELs). Sensitivity analyses were then conducted at the NAELs to determine how much the dose metric of interest, daily average human maternal blood alkoxyacetic acid concentration, would change if the values of the input parameters changed. It was determined that the dose metric was sensitive to a limited subset of the model parameters, including inhalation rate, body weight, alkoxyacetic acid formation rate, and alkoxyacetic acid excretion rate. Monte Carlo simulations with parameter distributions of sensitive parameters were then conducted at the NAEL to identify the 50th, 95th, and 99th percentile values of the dose metric for a population of pregnant workers. The ratio of the 95th and 50th percentile values (1.8 for EGEEA and EGEE, 1.7 for EGME) was used as a chemical-specific adjustment factor for intraspecies (human) variability in pharmacokinetics. Default values were used for uncertainty factors for inter- and intra-species pharmacodynamic uncertainty. The NAELs were divided by the composite uncertainty/adjustment factors to calculate the proposed inhalation OELs for these glycol ethers, in the absence of significant dermal exposure.

**S-1.3 Iodomethane (methyl iodide)**

Iodomethane is an agricultural soil fumigant, and therefore health concerns pertain to both bystanders and occupationally exposed individuals (e.g., applicators) (Mileson et al., 2009). PBPK models were used to extrapolate from findings in test animals to estimate acceptable exposure levels for iodomethane for both bystanders (one day, for 24 hrs) and workers (8 hrs/day, 5 days/week) (Sweeney et al., 2009). Three effects identified in animals were considered to be potential concerns with respect to acute exposure: nasal effects and neurotoxicity, identified in rats, and developmental toxicity, identified in rabbits. PBPK models for rats, rabbits and humans were therefore developed which described the inhalation of iodomethane, its conjugation with glutathione (GSH), and the distribution and elimination of the iodide that is liberated when iodomethane is conjugated with GSH. Mode of action evaluations (Kirman et al., 2009) led to the conclusion that each of three potential acute effects was most appropriately attributed to a different dose metric—minimum level of GSH in the nasal olfactory epithelium for the rat nasal effects, maximum iodomethane concentration in the brain for rat neurotoxicity, and fetal blood iodide AUC for developmental effects in the rabbit. Because of the different modes of action for the endpoints and the different schedules for bystanders vs. workers, different endpoints yield the lowest (most health protective) HECs for the two different groups (i.e., developmental toxicity is the most sensitive endpoint for bystanders, vs. neurotoxicity for workers) (Table S-1). This example highlights the importance of considering studies which may not have the lowest NOAEL, when incorporating dosimetric adjustments

**Table S-1. Insterspecies extrapolation for iodomethane Sweeney, L.M., C.R. Kirman, S.A. Gannon, K.D. Thrall, M.L. Gargas, J.H. Kinzell: Development of a physiologically based pharmacokinetic (PBPK) model for methyl iodide in rats, rabbits, and humans. Inhal Toxicol. 21(6):552-582, copyright © (2009) Informa Healthcare]. Reproduced with permission of Informa Healthcare.**

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| --- | --- | --- | --- |
| **Endpoint** | **Animal NOAEL** | **Bystander HEC** | **Occupational HEC** |
| Transient neurotoxicity | 27 ppm | 10 ppm | 10 ppm |
| Nasal toxicity | 21 ppm | 36 ppm | 50 ppm |
| Developmental toxicity | 10 ppm | 7.4 ppm | 23 ppm |

**S-2 Route-to-Route Extrapolation: PBPK Modeling Approaches**

Guidance for deciding when to use route-to-route-extrapolation for OEL derivation was provided in the main part of the manuscript along with (“Route-to-Route Extrapolation (to Derive OELs for Inhaled Substances)”). In a PBPK modeling based approach to route-to-route extrapolation, a NOAEL, LOAEL, or BMDL exposure level by the test route will typically be simulated using a validated model and the corresponding dose metric will be calculated. If applicable, uncertainty factors may be applied to the internal dose prior to or after extrapolations. The adjusted or unadjusted internal dose for the test route will then serve as the target value for further dosimetry simulations corresponding to the inhalation route. The inhalation simulations can either be done using a model for human workers (preferred) or for the test species. In the latter case, adjustment factors for interspecies extrapolations, including interspecies kinetic differences, will need to be applied.

**S-2.1 Example of route-to-route extrapolation in OELs derived for pharmaceuticals**

To develop worker inhalation OELs for active pharmaceutical ingredients, manufacturers may extrapolate from effect s evaluated by more commonly tested clinical routes (e.g., oral) to routes of greater occupational concern, e.g., inhalation. However, rather than conduct additional kinetic or toxicity studies by the inhalation route, it is typically easier and less expensive to conduct studies by intratracheal or intranasal instillation (Naumann et al., 2009). In order to account for distribution differences between inhalation studies and studies conducted by intranasal or intratracheal instillation, Naumann et al. (2009) incorporated inhalation deposition fractions in the upper airway and lower respiratory tract for aerosols of differing particle sizes into the calculation of data-derived bioavailability correction factors. They also used a preliminary pharmacokinetic model for disposition after intravenous, intratracheal, intranasal and oral dosing and extrapolated to inhalation dosimetry, which also could be used to predict inhalation uptake.

**S-2.2 Example of route-to-route extrapolation for OEL n-methyl pyrroliodone**

An illustration of how internal dosimetry from exposure by the dermal and oral routes was considered in the context of a worker OEL may be found in the quantitative assessment of n-methyl pyrrolidone (NMP) of Poet et al. (2010). In their evaluation, Poet et al. (2010) developed PBPK models for rats and humans exposed to NMP via the oral route (rats only), dermal exposure, or inhalation. The 24 hr AUC and peak blood concentrations of NMP at the NOAELs and LOAELs of in five rat developmental toxicity studies (one by gavage, one in feed, one by dermal exposure, and two by inhalation) were compared. The two studies with the lowest AUCs were further evaluated using benchmark dose modeling to identify a rodent internal dose point of departure, which was then converted to a HEC for human dermal and inhalation (combined) exposure for workers (8 hrs/day, 5 days/week). This HEC was then compared to existing OELs, and the margin of exposure noted, but no specific OEL was recommended by the authors.

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