Appendix E. Application of Toxicokinetic Modeling and Analysis of Toxicokinetic Differences by Age at Exposure.

E.1 Applications of Toxicokinetic Analysis and PBPK Modeling

Physiologically based pharmacokinetic (PBPK) models consist of a series of equations representing bodily compartments (e.g., liver, lung, highly perfused tissues, less perfused tissues), fluid flows, and biotransformation reactions that represent real biological tissues and physiological processes in the body. The models simulate the time course of absorption, distribution, metabolism, and excretion (ADME) of chemicals that enter the body.

PBPK models may also provide a scientific methodology for determining duration adjustments, and for making interspecies extrapolations, while evaluating additional uncertainty related to interspecies differences and intraspecies variability. PBPK modeling can be used to support route-to-route extrapolation, as in the situation where it is necessary to predict the toxicity of a substance from an inhaled dose from the results of an experiment in which a test species was exposed by the oral route in order to develop an inhalation REL**.**

A range of modeling approaches can be used to characterize exposures and resulting delivered doses to target tissues. The dose of the parent compound or of a toxic metabolite at a target tissue, rather than the applied dose, may provide a better basis for determining a NOAEL or point of departure (POD) in a benchmark dose assessment, especially where toxicokinetic features such as saturation of metabolism complicate and obscure the underlying toxicodynamic dose-response relationship. The relevance of a specific modeling approach depends on the physical and chemical characteristics of the material (e.g., stable or reactive gases, particulate matter, lipophilic or water-soluble compounds), the method and route of exposure or delivery, and the toxicities under consideration (e.g., contact site or systemic toxic effects) (U.S.EPA, 1994a; Andersen and Jarabek, 2001; Overton et al., 2001; U.S.EPA, 2004). All of these approaches attempt to improve the understanding of the dose-response relationship by describing and estimating the dose delivered to the relevant areas of the body, and can provide a reduction in uncertainty and an improved scientific basis for the risk value.

In the ideal case, where sufficient data are available, OEHHA will apply PBPK modeling to the dose-response assessment, instead of the default application of the pharmacokinetic portions of the intraspecies and interspecies uncertainty factors, and in preference to the default human equivalent concentration (HEC) procedure for applying interspecies dosimetric adjustments, as described in section 4 of this document. However, it must be recognized that in most cases sufficient data are not available to allow PBPK modeling to be used in developing a REL. Even when pharmacokinetic models for a compound and route of interest are identified it may not always be advisable to rely on these, for example, when independent data separate from those used to calibrate a model are not available to check that model's predictive validity.

OEHHA has explored PBPK modeling to evaluate the adequacy of default uncertainty factors, in particular the previously applied default of 10 for intraspecies variability, i.e. interindividual variability in the human population. We have used PBPK modeling to gain insight into the range of interindividual variability, focusing on the differences among infants, children and adults. Such information is useful in determining whether risk assessment procedures are sufficiently protective of infants and children. We also review available studies that have examined kinetic differences at age of exposure using information on pharmaceuticals. (For ethical reasons studies of kinetics in children are largely confined to pharmaceuticals, where the subjects may

receive some benefit from the exposure to the drug.) These studies demonstrate differences in clearance of chemicals by age, which in several cases exceed the previously used default factor of √10 for toxicokinetic variability in the human population.

The purposes of this appendix are:

1. To document published literature, and present our investigations using modeling approaches, which inform the selection of a default value for the intraspecies toxicokinetic uncertainty factor ($UF_{H\text{-}k}$) which is reasonably protective of members of the general population, specifically including infants and children.

2. To explore the use of toxicokinetic models for interspecies extrapolation, when sufficient data are available to use this approach as an alternative to the existing HEC adjustment for dosimetry (US EPA, 1994) and/or the application of an uncertainty factor ($UF_{A\text{-}k}$) to allow for the uncertainty in interspecies extrapolation of toxicokinetics.

3. To explore and present various toxicokinetic models as examples which may be useful in REL development in those cases where sufficient data are available to use this approach rather than merely applying assumed (default) uncertainty factors. Detailed results and model codes are presented to facilitate the application of these examples.

E.2 Published Summaries of Age-Dependent Toxicokinetics

OEHHA has reviewed published pharmacokinetic analyses which may be of interest in illustrating the applicability of these methods to specific problems in risk assessment identified in the main part of this document, and in particular to the question of how different the kinetics of toxicants may be in infants and children relative to adults (e.g., Renwick and Lazarus, 1998; Dorne et al., 2001). This is a subset of the larger question of how extensive is the inter-individual variability in kinetics for the human population as a whole, but one which is of particular concern in relation to the mandate under SB 25 to determine whether existing risk assessment practices (which have previously focused primarily on effects in adults) are sufficiently protective of the young. The objectives of this literature review were both to identify examples of successful analyses relevant to noncancer risk assessment, and secondly to assess whether a sufficient number and range of examples have been studied to inform the selection of uncertainty factor values in the general case where compound-specific and age-specific information or kinetic models are not available.

E.2.1 Age-dependent Toxicokinetic Parameters.

The following tables show published values, excerpted from kinetic studies of pharmaceuticals, of a variety of kinetic parameters where age-dependent differences have been observed. The examples in the literature of analyses of the effects of age on disposition of chemicals deal with drugs; ethical concerns generally rule out clinical studies of the effect of toxic pollutants or industrial chemicals on juvenile subjects. But the pharmacokinetics of drugs are studied as part of the requirements for registration by the US FDA (and similar regulatory authorities in other countries). In addition, the use of drugs in pediatrics has resulted in information on their disposition in younger patients. These data provide a foundation for evaluating chemical disposition by age at exposure for airborne toxicants as well as drugs, since the metabolic pathways responsible for activation and clearance of these toxicants are in general the same as those responsible for handling drugs. Some discussion of these data and age-specific characteristics of the underlying processes of absorption, distribution, metabolism and excretion appears in Section 3.1 of the main document. The principal pharmacokinetic terms used are: clearance (CL) the quantity of blood from which the chemical has been removed or cleared per unit body weight or surface area per unit time; the half-life ($T_{1/2}$) of the chemical in the blood or the time required to reduce the chemical blood concentration by half as a result of excretion, metabolism etc.; the area under the chemical blood concentration times time curve (AUC), a measure of the duration of internal dosimetry; and the maximum chemical concentration in the blood (Cmax), a measure of the intensity of exposure. Depending on the mode of action (MOA) either duration or intensity may be more closely related to the toxic effects observed. Similar metrics may also apply to key metabolites.

TABLE E.2.1. COMPOUNDS SHOWING REDUCED ELIMINATION IN INFANTSAND/OR CHILDREN[1].

Compound	Parameter	Age	Value
Morphine	CL (mL/kg-min)	<7 d 7d – 2 mo 2 – 6 mo	8.7 ± 5.8 11.9 ± 5.1 28.0 ± 8.9
Paracetamol	CL (L/kg-hr)	< 10 d 1-12 mo	0.15 0.37
Pipecuronium	CL (mL/kg-min)	6.8 mo 4.6 yr Adult (42 yr)	1.5 2.3 2.5
Desacetylcefotaxime	$T_{1/2}$ (hr)	Neonate Infant Adult	9.4 2.1 1.6
Ganciclovir	CL (mL/kg-min)	2-50 d Adult	3.4 4.2
Alfentanil	CL (mL/kg-min)	Newborn Newborn Adult	3.2 1.5-1.7 6.0
Trichloroethanol (from chloral hydrate)	$T_{1/2}$ (hr)	Neonate Adult	35 8
Trichloroethanol glucuronide	$T_{1/2}$ (hr)	Neonate Adult	30 7
Digoxin	CL renal (mL/1.73 m^2-min)	1 week 3 mo 12 mo	32 ± 7 66 ± 30 88 ± 43

[1] Adapted from Renwick and Lazarus (1998): CL = Clearance; $T_{1/2}$ = Half life.

TABLE E.2.2. CYP1A2 MEDIATED METABOLIC PARTIAL CLEARANCES IN HEALTHY VOLUNTEERS

Drug	CYP1A2 Pathway	Number of subjects	Weighted Mean mL/kg-min	Weighted SD	CV
p.o. administration					
Caffeine	1-N-Demethylation	5	0.24	0.07	29.2
Caffeine	3-N-Demethylation	5	1.84	1.08	58.7
Caffeine	7-N-Demethylation	5	0.08	0.02	25.0
Theophylline	1-N-Demethylation	13	0.21	0.11	52.4
Theophylline	3-N-Demethylation	13	0.16	0.10	62.5
Theobromine	1-N-Demethylation	23	0.20	0.09	42.5
Paraxanthine	7-N-Demethylation	6	0.89	0.26	29.2
i.v. administration					
Theophylline	1-N-Demethylation	22	0.16	0.06	37.4
Theophylline	3-N-Demethylation	6	0.19	0.06	31.1
R-Warfarin	6-Hydroxylation	6	0.26 mL/min	0.15	59.1

[1] Adapted from Dorne et al. (2001): p.o. = oral; i.v = intravenous; SD = standard deviation; CV = coefficient of variation. Weighted SD = standard deviation weighted by coefficient of variation

TABLE E.2.3. INTER-INDIVIDUAL VARIATION IN TOXICOKINETICS OF CAFFEINE IN HEALTHY VOLUNTEERS[1].

Toxicokinetic Parameter	Number of subjects	Weighted mean	Weighted SD	CV
p.o. administration				
CL mL/kg-min	163	1.20	0.43	35.7
CL mL/min	10	142	79.1	55.7
AUC/dose ng/mL-hr	15	17,200	9,490	55.2
Cmax/dose ng/mL	67	1,780	435	24.1
i.v. administration				
CL mL/kg-min	20	1.97	0.92	46.8
AUC/dose ng/mL-hr	8	14,050	5,760	41.0

[1] Adapted from (Dorne et al., 2001). P.o. = oral; i.v. = intravenous; CL = Clearance; AUC = area under the blood concentration x time curve; Cmax = maximum blood concentration; SD = Standard Deviation; CV = Coefficient of Variation.

TABLE E.2.4. TOXICOKINETICS OF CAFFEINE: COMPARISONS BETWEEN HEALTHY ADULTS AND DIFFERENT SUBGROUPS.[1]

Toxicokinetic Parameter	Number of subjects	Weighted mean	Weighted SD	CV	Ratio S/H	Ratio CV
Smokers						
CL mL/kg-min p.o.	38	2.62	0.93	35.5	0.46	0.99
Cmax/dose ng/mL	6	1,750	610	34.9	0.98	1.43
Pregnant women						
CL mL/kg-min p.o. 36 wk	6	0.72	0.38	52.8	1.67	1.48
CL mL/kg-min p.o. 38 wk	8	0.39	0.18	46.2	3.08	1.29
Cmax/dose ng/mL	8	2,018	1,460	72.3	1.13	2.95
Elderly						
CL mL/kg-min i.v.	18	1.43	0.50	35.2	1.96	0.75
AUC/dose ng/mL-hr p.o.	8	12,400	5,920	47.9	0.78	0.90
Cmax/dose ng/mL	8	370.4	64.5	17.4	0.21	0.71
Children						
CL mL/kg-min p.o.	3	1.79	0.57	31.8	0.67	0.89
Infants						
CL mL/kg-min p.o.	4	1.00	1.04	104	1.20	2.91
Neonates						
CL mL/kg-min p.o.	5	0.127	0.023	18.1	9.45	0.51
CL mL/kg-min i.v.	31	0.14	0.06	42.2	13.9	0.90
Cmax/dose ng/mL	16	1280	1000	7.8	0.72	0.32
Liver disease						
CL mL/kg-min p.o.	81	0.62	0.61	98.9	1.96	2.77
CL mL/kg-min i.v.	45	1.00	0.48	48.3	1.96	1.03
Cmax/dose ng/mL	27	1700	283	16.6	0.96	0.68
Renal disease						
CL mL/kg-min i.v.	5	0.78	0.35	44.6	2.53	0.95

[1] Adapted from (Dorne et al., 2001): p.o. = oral; CL = Clearance; Cmax = maximum blood concentration; AUC = area under the blood concentration x time curve; SD = standard deviation; CV = coefficient of variation; Ratio S/H = ratio between subgroup and healthy volunteers; Ratio CV= ratio between the variability of the subgroup and the healthy volunteers..

TABLE E.2.5. INTERINDIVIDUAL VARIATION IN TOXICOKINETICS OF THEOPHYLLINE IN HEALTHY VOLUNTEERS[1]

Toxicokinetic Parameter	Number of subjects	Weighted mean	Weighted SD	CV
p.o. administration				
CL mL/kg-min	106	0.60	0.38	41.4
AUC/dose ng/mL-hr	22	24,300	5,790	23.8
Cmax/dose ng/mL	32	4,600	842	18.2
i.v. administration				
CL mL/kg-min	100	1.00	0.29	29.2
AUC/dose ng/mL-hr	14	51,900	9,840	19.0

[1] Adapted from (Dorne et al., 2001): p.o = oral; i.v. = intravenous; CL = clearance; AUC = area under the blood concentration x time curve; Cmax = maximum blood concentration; SD = standard deviation; CV = coefficient of variation.

TABLE E.2.6. TOXICOKINETICS OF THEOPHYLLINE: COMPARISONS BETWEEN HEALTHY ADULTS AND DIFFERENT SUBGROUPS

Toxicokinetic Parameter	Number of subjects	Weighted mean	Weighted SD	CV	Ratio S/H	Ratio CV
Smokers						
CL mL/kg-min p.o.	15	1.15	0.30	25.9	0.79	0.63
AUC/dose ng/mL-hr p.o.	6	12,200	4,850	39.8	0.50	1.67
CL mL/kg-min i.v.	8	0.72	0.17	23.6	1.39	0.81
AUC/dose ng/mL-hr i.v.	14	32,900	10,300	31.3	1.58	1.65
Pregnant women						
CL mL/kg-min p.o.	14	0.83	0.22	25.8	1.20	0.88
Elderly non-smokers						
CL mL/kg-min p.o.	19	0.73	0.11	15.0	1.24	0.36
CL mL/kg-min i.v.	41	0.72	0.32	45.2	1.39	1.55
Cmax/dose ng/mL	19	2,700	408	14.3	0.59	0.79
Children						
CL mL/kg-min p.o.	3	1.79	0.57	31.8	0.67	0.89
Infants						
CL mL/kg-min p.o.	33	1.00	0.58	58.1	0.90	1.40
Cmax ng/mL	20	2,610	990	37.9	0.57	2.08
CL mL/kg-min i.v.	43	0.46	0.17	36.1	2.16	1.24
Neonates						
CL mL/kg-min i.v.	220	0.35	0.11	31.1	2.87	0.94

TABLE E.2.6. TOXICOKINETICS OF THEOPHYLLINE: COMPARISONS BETWEEN HEALTHY ADULTS AND DIFFERENT SUBGROUPS

Toxicokinetic Parameter	Number of subjects	Weighted mean	Weighted SD	CV	Ratio S/H	Ratio CV
Liver disease						
CL mL/kg-min p.o.	35	0.38	0.16	42.7	2.36	1.03
CL mL/kg-min i.v.	68	0.52	0.40	78.4	1.94	2.69
Renal disease						
CL mL/kg-min i.v.	31	0.97	0.33	34.3	1.03	1.18

[1] Adapted from (Dorne et al., 2001): p.o = oral; i.v. intravenous; CL = clearance; AUC = area under the blood concentration x time curve; Cmax = the maximum blood concentration; SD -= standard deviation; CV = coefficient of variation; Ratio S/H = ratio between subgroup and healthy volunteers; Ratio CV = ratio between the variability of the subgroup and the healthy volunteers.

TABLE E.2.7. INTERINDIVIDUAL VARIATION IN TOXICOKINETICS OF THEOBROMINE AND PARAXANTHINE IN HEALTHY VOLUNTEERS AFTER ORAL ADMINISTRATION[1]

Toxicokinetic Parameter	Number of subjects	Weighted mean	Weighted SD	CV
Theobromine				
CL mL/kg-min	45	1.02	0.33	42.8
AUC/dose ng/mL-hr	6	12,738	5,474	43.0
Cmax/dose ng/mL	3	1,478	378	21.4
Paraxanthine				
CL mL/kg-min	6	1.71	0.30	17.6

[1] Adapted from (Dorne et al., 2001): SD = standard deviation; CV = coefficient of variation; CL = Clearance; AUC = area under the blood concentration x time curve; Cmax = maximum blood concentration.

TABLE E.2.8. PATHWAY-SPECIFIC TOXICOKINETIC UNCERTAINTY FACTORS FOR CHILDREN AFTER ORAL EXPOSURE AND NEONATES AFTER INTRAVENOUS EXPOSURE[1].

Pathway	Nc	Ns	N	LN 95%	LN97.5%	LN99%
Children						
CYP1A2	1	12	195	1.4	1.6	1.8
CYP2C19	1	1	25	5.4	6.9	9.0
CYP2D6	1	2	173	22	31	45
CYP3A4	3	3	16	1.4	1.6	1.8
Hydrolysis	3	3	43	1.5	1.7	2.0
Glucuronidation	5	13	131	1.3	1.4	1.5
Glycine conjugation	1	1	20	1.5	1.6	1.8
NAT	1	1	25	2.0	2.2	2.5
NAT	1	1	25	2.2	2.3	2.4
Renal excretion	6	9	126	1.2	1.3	1.5
Neonates						
CYP1A2	2	7	251	11	12	14
CYP3A4	2	5	35	8.1	9.7	12
Glucuronidation	4	14	94	8.6	10	12
Glycine conjugation	2	1	10	25	26	28
Renal excretion	7	33	656	2.8	3.0	3.4

[1] Adapted from (Dorne et al., 2005). Nc = number of compounds; Ns = number of studies; N = number of subjects; LN = pathway related uncertainty factors for upper percentiles of the lognormal distributions. These potential uncertainty factors would be equated with the UF_{H-k} described in the main document. In this case the pharmacokinetic component of the interindividual variability is presented as upper percentiles of lognormal distributions of fitted data by metabolic pathway. It illustrates that a given percentile may not give an adequate level of protection depending upon the pathway critical to the toxic effect.

The studies summarized above in addition to those discussed in the text of the main document indicate that the uncertainty sub-factor to account for toxicokinetic variability in the human population is not sufficient to protect neonates and possibly infants and children. For example, in Table E2.8 above Dorne *et al.* (2005) analyze data on kinetic variability in neonates and healthy adults for five metabolic pathways (CYP1A2, CYP3A4, glucuronidation, glycine conjugation, and renal excretion). In all cases except renal excretion, uncertainty factors derived to cover 95 percent of the population, based on lognormal distributions of the study data, exceeded the default value of 3.16. The 95% values ranged from 2.8 to 25. If a more health protective criterion of 99% coverage is adopted, the range of factors would be 3.4 to 28. Even older children showed a significant lack of coverage at the 95% level with the CYP2C19 and CYP2D6 pathways with factors of 5.4 and 22, respectively, albeit with limited data. While not listed in Table E2.8, Dorne *et al*. (2005) note that limited data for CYP2D6 in two neonates showed internal doses 19- and 33-fold higher than in healthy adults. Taken together with the data in older children this may indicate a general greater susceptibility of infants and children to toxicants using the CYP2D6 pathway.

E.2.2 Published PBPK Models of Inter-individual Variability

The following section describes and reviews a selection of specific published models that have been used to address the sources and extent of inter-individual variability (between variously sensitive subpopulations of adults and between adults and children).

Pelekis et al. (2001) used a physiological model to derive adult and child pharmacokinetic uncertainty factors for selected volatile organic compounds (VOCs). The chemicals modeled were dichloromethane (DCM), tetrachloroethylene (PCE), toluene (TOL), m-xylene (XYL), styrene (ST), carbon tetrachloride (CATE), chloroform (CHLO), and trichloroethylene (TCE). Adult models of low (50 kg) and high (90 kg) body weight were compared with a 10 kg-based child model. Fat contents varied from 51 percent for the 90 kg adult model to 17 percent for the 10 kg child. Ventilation:perfusion ratios varied from 0.76 (50 kg) to 1.38 (10 kg). Fractional liver flows (of cardiac output) ranged from 0.11 (50 kg) to 0.34 (90 kg). All PBPK models were flow-limited with exposure by inhalation, arterial circulation to Fat, Slowly Perfused, Rapidly Perfused and Liver model compartments, metabolism in the Liver, and combination of compartment outputs in venous blood. The arterial and venous bloods were not explicitly modeled. Also no VOC metabolites were specifically modeled. A range of physiological parameters (blood:air and tissue:blood) were used for each body model and the eight VOC chemicals based on literature values.

Simulations involved exposure to one ppm VOC and estimation of arterial and venous blood concentrations (CA, CV), and tissue concentrations (Ci) after 30 days continuous exposure. A comparison of the two adult models (Adult high body weight and fat content versus Adult low body weight and fat content) shows relatively few significant departures from unity for the dose metrics estimated. CATE ratios ranged from 2.85 (C rapidly perfused) to 1.71 (C_{liver}). DCM ranged from 0.29 (C_{liver}) to 1.04 ($C_{arterial\ blood}$). Comparisons of the Adult high/Child average from the PBPK model show some larger differences. For the C_{liver} dose metric the PBPK models predicted the following Adult/Child values: ST (0.033), XYL (0.037), TCE (0.061), DCM (0.092), CHLO (0.11). These model predictions would indicate up to a 30-fold higher concentration of the VOC chemicals in child liver than in adult liver via the inhalation route.

This is a useful approach, involving important environmental toxicants and a relevant exposure route. However, it is limited since the models and dose metrics employed address only the parent compounds. Relevant toxic effects may in fact be more closely related to the tissue dosimetry of metabolites, which were not specifically modeled. In addition, the use of a single child body weight is probably insufficient to assess the full range of physiological variability throughout development, particularly in the neonatal period. It is worth noting, however, that the higher concentrations of the VOCs in a child's liver might be expected to result in higher peak concentrations of metabolites of those compounds in the liver, and possibly also in other tissues.

Jonsson and Johanson (2001) used a PBPK model of DCM to study the influence of metabolic polymorphism on cancer risk estimates. A flow-limited PBPK model was comprised of lung, perirenal fat, subcutaneous fat, working muscle, resting muscle, rapidly perfused tissue, and liver. Exposure was by inhalation; metabolism by glutathione *S*- transferase T1 (GSTT1) and mixed function oxidases (MFO) occurred in lung and liver. The model was fitted to published toxicokinetic data on 27 male volunteers exposed to 250-1000 ppm DCM. Excess cancer risk resulting from lifelong exposures to 1-1000 ppm DCM was estimated using Bayesian and Monte Carlo methods. The relevant dose metric used was DNA-protein cross-links (DPX) in liver, which was derived from the amount of DCM metabolized via the GSTT1 pathway. Data on the frequencies of the three GSTT1 genotypes (0/0, +/0, +/+) in the Swedish population were used in the analysis. The results indicated large inter-individual variability in estimated risk, even within the two metabolizing groups (+/0, +/+). The mean risk in +/+ individuals was 50 –71 percent higher than for the general population. The results also indicate that the 3.16 factor for PK human variability may not be adequately protective for noncancer endpoints. The authors estimated that five percent of the individuals in the Swedish population would not be covered by a factor of 2.7-3.3 away from the mean (calculated from the 95 percent upper confidence limit in Table 7 of Jonsson and Johanson. One percent of individuals would not be covered by a 4.2-7.1 factor (from 99 percent upper confidence interval (UCL) in Table 7 of the published paper) and 0.1 percent by a 7.3-14.5 factor (99.9 percent UCL in Table 7 of the published paper).

These investigators noted that:

> "These results support the cautionary point of Renwick and Lazarus (1998) that an intraspecies uncertainty factor higher than 3.16 should be considered for substances that, like DCM, have pronounced bioactivation polymorphism and therefore a flatter distribution than expected from unimodal log-normal distribution."

They also note that the most sensitive individuals possess a combination of high GSTT1 activity and low metabolic capacity for the competing MFO pathway, which is likely mediated by CYP2E1. CYP2E1 is highly inducible, a factor that would contribute to inter-individual variability. While this paper addresses risk of DCM exposures in adults, the conclusions may apply even more strongly to infants and young children where inhalation may result in greater exposures per unit body weight and metabolic systems, particularly the MFO enzymes, are still under varying stages of development.

Ginsberg et al. (2004b) used PBPK modeling to evaluate the difference between neonates and adults in the pharmacokinetic handling of theophylline and caffeine. Both chemicals are largely metabolized by CYP1A2: caffeine to theophylline, theobromine, and paraxanthine; and

theophylline to 3-methylxanthine, 1-methyluric acid, and 1,3-dimethyluric acid. In neonates theophylline is also "back" methylated to caffeine. Caffeine is cleared much more slowly in neonates than in adults (0.15 vs. 1.57 mL/kg-min, respectively); theophylline is also cleared somewhat more slowly in neonates (0.35 vs. 0.86 mL/kg-min, respectively). The PBPK models, which used biochemical parameters scaled up from *in vitro* data, were able to simulate the large differences in half-life and clearance rates between adults and neonates for these chemicals. This included the faster clearance of theophylline versus caffeine in neonates. It was concluded that the extra "back" methylation path in neonates, while relatively small in percentage terms (i.e., percent of theophylline metabolite excreted in urine), could largely account for the differences seen between adults and neonates. The results emphasize the importance of different metabolic pathways operating in neonates and infants during development.

Price et al. (2003) used age-specific regressions for physiological parameters in a PBPK model for inhaled furan. The model contained compartments for brain, slowly perfused tissues, fat, liver, and the remainder of the body. The ages modeled were six, ten, 14 years and adult. It was assumed that furan was a rapidly metabolized VOC in all age-specific models in that the rate of metabolism was limited by blood flow to the liver. In 36-hour simulations involving a 30-hour exposure to 1 μg/L furan, the authors observed up to 50% higher concentrations of furan in the blood and of furan metabolites in the liver of children compared with adults. These are relatively small differences. Younger ages, which show larger differences in metabolic enzyme profiles and other kinetic factors, were not modeled. It is also questionable whether or not metabolism is truly flow-limited at the younger ages.

Gentry et al. (2003) evaluated the impact of pharmacokinetic differences on tissue dosimetry during pregnancy and lactation with a PBPK modeling approach. Six chemicals representing a variety of physiochemical properties were selected for study: isopropanol, vinyl chloride, methylene chloride, tetrachloroethylene, nicotine and TCDD. These chemicals not only provided differences in volatility, lipophilicity, and water solubility, but also different pharmacokinetic features including metabolic production of stable or reactive metabolites in the liver and competing pathways of metabolism. Model predicted changes in dosimetry during pregnancy were largely the result of the development of metabolic pathways in the fetus or changes in the tissue composition in the mother and fetus. For example, the fetal activity of alcohol dehydrogenase (ADH) was undetectable prior to three months gestation but rose to 0.23 of the adult value at birth. Generally, predicted blood concentrations were lower in the neonate during lactation than in the fetus during gestation. This decrease was relatively slight for TCDD but four orders of magnitude for vinyl chloride. Predicted fetal/neonatal exposures versus maternal exposures ranged from two fold greater (TCDD) to several orders of magnitude lower (isopropanol). The results of this study are in general agreement with reports on pharmaceuticals indicating that the greatest child/adult pharmacokinetic differences are seen in the perinatal period (Renwick et al*.,* 2000; Ginsberg et al*.,* 2002).

Pelekis et al. (2003) estimated intraspecies adult and child pharmacokinetic uncertainty factors using a probabilistic framework applied to a PBPK model of dichloromethane. A number of variates were included as distributions in the analysis including: age, body weight, inhalation rate, activity level, liver weight, fat weight, blood volume and blood flow to the liver and biochemical parameters. The authors found that the tissue dose ratios ($UF_{H\text{-}TK}$, the ratio of the 95th percentile to the 50th percentile) varied only between 1.88 and 1.98 within the population

depending on age and tissue. Many of the assumptions employed in this study are open to question, particularly the assumption that both Phase I and Phase II metabolic elimination paths are ten times greater in adults than in infants on a body weight basis. First order elimination by Phase II metabolism usually scales to the –0.3 power of body weight, which gives an adult: infant difference closer to two-fold than ten-fold on a body weight basis. Without specific data on metabolic elimination of DCM in infants and children a health protective assumption should be used.

Sarangapani et al. (2003) used a PBPK model to evaluate the impact of age- and gender-specific lung morphology and ventilation rate on the inhalation dosimetry of model toxicants. The toxicants were selected to represent category one (irreversibly reactive; ozone), category two (nonreactive water soluble; isopropanol) and category three (nonreactive water insoluble; styrene, vinyl chloride, perchloroethylene) gases. Ten PBPK models were run for males and females from 1 month of age to 75 years. Model structure was similar to Sarangapani et al. (2002) but simplified to three main respiratory tract compartments of extra thoracic (ET), tracheobronchial (TB), and pulmonary (PU) with the ET and TB each divided into three subcompartments from airway lumen to circulating blood. In addition to different anatomical and physiological values for the age and gender models, biochemical parameters were also varied with age (e.g., relative activity of CYP2E1 26.1% at 1 month to 90% at 15 yr; and alcohol dehydrogenase (ADH) 24.9% at 1 month to 83.6% at 25 yr). Dose metrics evaluated included parent and metabolite concentrations in blood, liver and lung. According to the author's analysis, only two chemicals showed higher dose metrics in children than in adults (25 yr model). For the isopropanol model with CYP2E1 and ADH metabolism, the blood concentration of the metabolite acetone was 8-fold higher in 1 month male and 11-fold higher in 1 month female than in respective 25 yr models. Ozone PU extraction per unit surface area was 8.6- to 12.5-fold higher in 1 month male and female models than in respective 25 yr models. The results of this study are in general agreement with other PBPK studies of children. "The age of greatest concern is clearly the perinatal period. The most important factor appears to be the potential for decreased clearance of toxic chemicals in the perinatal period due to immature metabolic enzyme systems, although this same factor can also reduce risk from the reactive metabolites during the same period." Although this model is simpler in structure than the Sarangapani et al. (2002), it is less well described and it has been difficult to verify the predictions for styrene, isopropanol and ozone. In our hands the ozone model gave the closest agreement of child/adult values of 13.1 and 19.4 for PU Cmax in one month/25 yr males and females, respectively.

Clewell et al. (2004) evaluated age- and gender-specific differences in tissue dosimetry with a predictive PBPK life-stage model. The model was implemented for six environmental chemicals with various physicochemical and biochemical properties and modes of toxic action. Isopropanol was studied by oral, dermal and inhalation routes of exposure with blood concentrations of parent and acetone metabolite as dose metrics of interest. The other chemicals studied were vinyl chloride, dichloromethane, tetrachloroethylene, TCDD, and nicotine. Each of these was evaluated by the oral route with dose metrics of blood concentrations of parent and either concentration of metabolite in blood or rate of parent metabolism/kg of liver volume. The dose metrics at external exposure levels of 1 ppb (inhalation) and/or 1 μg/kg-d were estimated continuously, as well as at specific ages of 1, 3, and 6 months, and 1, 5, 10, 15, 25, 50, and 75 years. The results were summarized in age-group ranges of birth to 6 months, 6 months to 5

years, 5 to 25 years, and 25 to 75 years. In general, predictions of average pharmacokinetic dose metrics for a chemical across the life stages were within two-fold, although larger transient variations were predicted, especially during the neonatal period. For the sole chemical investigated by the inhalation route, isopropanol, the highest dose ratio relative to 25 year old was 2.0 for the parent and 3.9 for the metabolite, both in the birth to 6 months of age grouping. The respective ratios for oral (drinking water) and dermal isopropanol exposures were equal or lower than those for the inhalation route for all groups up to 25 years of age. The authors concluded that the most important age-dependent pharmacokinetic factor was the potential for decreased clearance of a toxic chemical in the perinatal period due to the immaturity of xenobiotic metabolism. They note that this same factor may also reduce the production of reactive metabolites. A limitation of this study is that only one compound was evaluated by inhalation. Vinyl chloride, dichloromethane, and tetrachloroethylene could also have been evaluated by the inhalation route.

A preliminary conclusion based on this limited modeling was that a PK UF of 10 would account for inter-individual differences including infants and children for this set of compounds. This is larger than the standard assumption that an uncertainty factor of √10 is sufficient to account for inter-individual differences in human pharmacokinetics.

E.3 OEHHA Studies using PBPK Modeling to Assess Interindividual and Interspecies Differences:

Pilot study of ethylbenzene, vinyl chloride, toluene, styrene/styrene oxide, naphthalene/naphthalene oxides and ten aliphatic aldehydes.

As noted previously, OEHHA has an interest in applying PBPK modeling, when data permit, to replace the pharmacokinetic portion of the intraspecies safety factor. The approach used in applying PBPK modeling to assessing children's environmental health risks has been similar to that of Pelekis et al. (2001) noted above. We have used a case study approach using published PBPK models of selected environmental toxicants, adjusted anatomical and physiological parameters to simulate infant and child ages from newborn to 18 years, and compared these with adult models. In these models we have scaled metabolic parameters as a function of body weight. In addition to modeling age-related differences in human pharmacokinetics, the models were run with age-appropriate parameter values for rats in order to explore interspecies comparisons and, specifically, the extent to which age-related differences in the rat resemble those anticipated in humans. A low and high concentration was modeled for each chemical, and tissue doses were compared between rodent and human models for several of the chemicals.

Where possible we have focused on dose metrics involving toxicologically relevant metabolites. The chemicals selected for this pilot study were: ethylbenzene, vinyl chloride, toluene, styrene/styrene oxide, naphthalene/naphthalene oxides, and formaldehyde. There are PBPK models available for these chemicals for both the rat and human. Several aliphatic aldehydes have been measured in ambient air monitoring studies (Uebori and Imamura, 2004). We modeled the straight chain aliphatic aldehydes from acetaldehyde to decanal (R_nCHO, n = 1-9). The model output in these investigations is the animal to human ratios for blood concentrations. PBPK estimates are bound to be highly chemical dependent and strongly influenced by the metric chosen, blood/air and fat/blood partition coefficients, fractional tissue flows, metabolic parameters, and other factors.

Initial findings by this approach were given at the Children's Environmental Health Symposium (Brown, 2001). Of the seven chemicals studied with oral and inhalation exposures (vinyl chloride, DCM, TCE, chloroform, arsenic, butadiene, and naphthalene) three chemicals showed greater internal doses in children compared to adults: DCM, TCE, and butadiene, all via the inhalation route. A preliminary conclusion based on this limited modeling was that a $UF_{H\text{-}k}$ of 10 would account for inter-individual differences including infants and children for this set of compounds.

In follow up work we have attempted to standardize the modeling approach for different chemicals as much as possible and focus on inhalation exposures only. For example, we have employed several of the age specific regressions for model parameters suggested by Price et al. (2003). Also in a few cases we have used more elaborate lung modeling, for example as proposed by Sarangapani et al. (2002) for styrene and styrene oxide, as opposed to the simpler lung modeling of Evelo et al. (1993) for butadiene. Two or three similar child models were used with differing fractional tissue flows more heavily weighted towards rapidly perfused tissues than in adults. A summary of the results obtained using this modified approach is given in Table Table E.3.13. Child/adult values around two are due solely to scaling and indicate little difference. In Table E.3.13 chloroform and furan exhibited little difference under the modeling conditions employed. The other chemicals showed child/adult differences for various metrics ranging from about three to 120. They appeared to be in increasing order as follows: naphthalene/naphthalene oxide; PCE; styrene/styrene oxide; vinyl chloride; MTBE; TCE; BaP; DCM; and butadiene.

It should be emphasized that this analysis focuses on those metrics that show increases in child/adult values and the highest of these across the age-specific models simulated, since we are trying to test whether the traditional UF_H is adequate across all chemicals. In a few cases, metrics showed lower values in children than in adults, i.e. child/adult values < 1. These metrics have not been included in the tables below.

E.3.1 Materials and Methods

Prior to our simulation study, we evaluated the purpose, structure, mathematical representation, parameter estimation (calibration), computer implementation and predictive validity of PBPK models to be used in health risk assessment.

E.3.1.1 Mathematical representation

Model structures were chosen to represent the category of gas (1, 2 or 3) traditionally used in dosimetric adjustments across species. The type of PBPK model used by OEHHA is dependent on the physicochemical characteristics and toxicokinetic properties of the agent in question. Broadly speaking, gaseous agents fall into one of three categories, based on solubility or reactivity with tissues, which affects how deep into the respiratory tract (RT) the chemicals penetrate, and where toxicity occurs (local or systemic).

- Category 1 gases interact mainly at the site of contact: either the nasal or respiratory tracts (RT) as portals of entry.

- Category 2 gases have effects both locally, on the RT, and systemically.
- Category 3 gases mainly have remote systemic effects.

E.3.1.2 Parameter estimation (calibration)

Initial comparisons were limited to rat/human data and in the absence of parameter values, scaled for adults and immature animals/children. Immature rats and human children were modeled following the recommendations of Clewell et al. (2004) and Price et al. (2003), respectively. Metabolic parameters (Vmaxs) were scaled to the ¾ power of body weight. Note that known differences in cytochrome P450 and Phase II enzymes (beyond those described by body weight scaling), which are broadest when comparing the neonate with an adult, are not included in this modeling (see discussion above of Sarangapani et al. 2003 where metabolic differences during development are incorporated into PBPK modeling for CYP2E1 and ADH mediated chemicals). All simulations were for resting animals with alveolar ventilation equaling cardiac output.

E.3.1.3 Computer implementation

Each model was constructed from published code or equations and transcribed into Berkeley Madonna code and model performance was tested for accuracy. Model simulations were conducted using Berkeley Madonna software (www.berkeleymadonna.com, version 8.0.1).

E.3.1.4 Predictive validity

For agents in Category 1, OEHHA has examined a 4-compartment RT model of the type described by Sarangapani et al. (2004) that is similar to a 3-compartment default model of the RT recommended by Hanna et al. (2001), with uptake defined by regional mass transfer coefficients. Depending on the agent being studied, for some Category 1 gases, OEHHA explored nasal models as described by Frederick et al. (1998) and Georgieva et al. (2003).

E.3.1.4.1 Category 1: nasal model for formaldehyde

- A version of a published rat nasal model for formaldehyde was adjusted to accommodate human conditions (Georgieva et al., 2003). This is a nose only model with no body. The nasal region is divided into two parts, essentially anterior and posterior, and each compartment consists of about 25 layers from air to bone. This is a diffusion-limited model using average flux values determined by computational fluid dynamics (CFD) methods (Georgieva et al., 2003). The endpoint is DPX (DNA-protein cross-links pmol/mg DNA), but HCHO tissue concentrations (pM) and DPX-AUC (pmol min/mg DNA) are also available. Diffusivity parameters are for the hydrated form of formaldehyde, methylene glycol. DPX values with this whole nose model for the rat are about one-fourth those which focus on flux hot spots within the nasal region.

In order to extend the adult model to immature rats and children we assumed:

(1) that the mucosal nasal surface was directly proportional to body weight;

(2) that saturable metabolism Vmax scaled with the ¾ power of body weight;

(3) that the first order rates of binding, loss, and DPX loss scaled with the –0.25 power of body weight; and

(4) that the average flux vs. air flow rate could be interpolated from the tables and figures in Kimbell et al. (2001b). The following relations were used to determine the formaldehyde average flux in units of pmol/mm^2/hr/ppm HCOH (y in the equations below):

Human: $y = 5.0 \times IF^{1.7281}$, where IF = inspiratory flow rate in L/min;
Rat: $y = 0.7 \times IF^{1.05}$, where IF is in mL/min

IF is 2 x minute volume, and hence a function of body weight (BW).

MODEL STRUCTURE: Georgieva et al. (2003) (rat model)

- Rat and human data sets/parameter values (Georgieva et al, 2003) were obtained by interpolation of data for average flux versus air flow rate (Kimbell et al., 2001a; 2001b).for neonatal and immature rats and human children, scaled with $BW^{0.75}$. First order rates were scaled with $BW^{0.25}$ (Clewell et al., 2003a).

E.3.1.4.2 Models for Category 2 gases

For Category 2 gases, OEHHA has examined RT-PBPK models of the type described by Sarangapani et al., (2004). These models include both RT compartments and body compartments for remote distribution and metabolism as recommended by Hanna (2001). These are complex hybrid diffusion-limited, flow-limited, "Respiratory Tract" models consisting of a 16 compartment lung (upper RT, conducting airways, terminal bronchioles, and alveoli; each times lumen, mucus, epithelial cell, and blood exchange sub-compartments) and a five compartment body (liver, fat, muscle, vessel rich group, and blood). The models predict the concentrations of both the parent and a metabolite (usually an oxide).

The model structure (Sarangapani et al., 2004) was used with rat and human data sets/parameter values for styrene and styrene oxide obtained from Sarangapani et al. (2002) and Csanady et al. (2003). Human and rat parameters for naphthalene and naphthalene oxides were obtained from Sarangapani et al. (2002) and Willems et al. (2001)

E.3.1.4.3 Models for Category 3 gases

For Category 3 gases, with mainly remote effects, OEHHA has explored either a one-compartment or, alternatively, a two-compartment lung model as described by Evelo et al. (1993), consisting of a high-perfusion alveolar exchange compartment and a low-perfusion bronchial compartment. During our exploratory analysis, we discovered that in some instances flow-limited model components may be augmented or replaced with diffusion-limited components based on physicochemical/kinetic properties and improved model performance (e.g., dioxin).

A simple flow-limited model was used, with compartments for liver, fat, muscle, and lung where the lung is divided into bronchiolar and alveolar sub-compartments (Evelo et al., 1993). Model

parameters were derived from quantitative structure parameter relations (QSPR) or published models/data. Rat body weight was 0.25 kg, and human 70 kg. While metabolic parameters were available for the aliphatic series of aldehydes in both humans and rats, chemical parameters were not available and had to be estimated.

Model predictions are based on chemical property estimation methods for partition coefficients (Lyman, 1982; Paterson and Mackay, 1989; Haddad et al., 2000). The metabolic parameters of the straight chain aliphatic aldehydes (Vmax, Km) were from Mitchell and Petersen (1989) for rats and Kelson et al. (1997) for humans.

For ethylbenzene, the model structure (Evelo et al., 1993) was used with rat flow parameters from Tardif et al. (1997), and with human parameters scaled from rat according to $BW^{0.75}$ (Haddad et al., 2001). Metabolic parameters were scaled from adult rat and human (Sams et al., 2004); rat metabolic parameters were scaled with $BW^{0.75}$ (Clewell et al., 2003a)

For vinyl chloride the same model was used with human and rat metabolic parameters scaled to $BW^{0.75}$ (Chen and Blancato, 1989) and with rat parameters from Clewell et al. (2003a). For toluene, human and rat parameters were obtained from Tardif et al. (1995), with other rat parameters from Chen and Blancato (1989)

The model (Evelo et al., 1993) was applied to the aliphatic aldehyde group (Ethanal – Decanal) using human and rat parameters from Haddad et al. (2001), Paterson and Mackay (1989), Mitchell and Petersen (1989), and Kelson et al. (1997).

Values of chronic and acute reference exposure levels for the six test chemicals ranged between four and five orders of magnitude (3.0 $\mu g/m^3$ for formaldehyde to 1.8 x 10^{+5} $\mu g/m^3$ for vinyl chloride). The chemicals were simulated at 8-hour exposures ranging from 1 $\mu g/m^3$ to 10 mg/m^3. Within this range, the models exhibited linearity of response. For the remainder of the study, we simulated low-level exposures of 1 $\mu g/m^3$ for 8 hours within a 24-hour observation period. The internal dose metrics we examined were Cmax (parent and metabolite peak concentration in the blood), AUC (parent and metabolite concentration in blood at the end of the exposure period), and AMET (amount of parent compound metabolized/kg body weight /day in tissue). For ethylbenzene, vinyl chloride, toluene, styrene, naphthalene and formaldehyde, we examined the ratio of human to rat chemical concentration or amount of metabolite among adults. We also calculated a dosimetric adjustment factor (DAF), which is simply the reciprocal of the human/rat ratios, tabulated below, which can be used to derive a human equivalent concentration (HEC), i.e., animal exposure concentration (mg/m^3) x DAF = HEC. We also compared young humans and animals for simulations for the same set of chemicals. Since the human ages and rat body weights do not correspond exactly in terms of developmental stage, chemical concentrations and metabolite amounts are compared for the youngest and averaged over all. The average human to rat values for the two human parameter sets were then averaged as well.

E.3.2 Results

E.3.2.1 Ethylbenzene, Vinyl Chloride, Toluene, Styrene, Naphthalene, Formaldehyde

E.3.2.1.1 Interspecies comparisons for adults

The dose predictions for Cmax, AUC and AMET resulting from an exposure to 1 μg/m^3 and 10 mg/m^3 for 8 h during a 24-hour exposure time, are shown in Table E.3.1 and Table E.3.2, respectively. For the most part, the model predictions are quite linear in this exposure range. Models with differing sets of metabolic parameters for a particular chemical predict different amounts of the chemical metabolite in tissue compartments, e.g., styrene oxide. For example, the model for styrene and styrene oxide (SO) shows much larger values for SO concentration metrics with the metabolic parameter set from Csanady et al. (2003) than with the parameter set of Sarangapani et al. (2002). With the exception of toluene (about four-fold) the human/animal maximum values were less than two-fold for the dose metrics examined for low and high exposure levels.

TABLE E.3.1. PBPK MODEL PREDICTIONS FOR SELECTED CHEMICALS: LOW END OF RANGE (1 μg/m³ x 8 hr/d, 24 hr SIMULATIONS)

Chemical Species	Cmax blood p*M*	AUC blood p*M*hr/d	Amount metabolized[2] pmol/kg-d	Model basis and source of metabolic parameters
Ethylbenzene[1] Human	55.9	560	870	Scaled from rat (Haddad et al., 2001)
Ethylbenzene Rat	38.2	290	900	Tardiff et al. (1997)
Ethylbenzene **Human/rat**	1.46	1.93	0.97	
Vinyl Chloride Human	15.4	126.3	106.45	Chen & Blancato (1989)
Vinyl Chloride Rat	21.9	172.4	519.36	Chen & Blancato (1989)
Vinyl Chloride **Human/Rat**	0.70	0.73	0.20	
Toluene Human	32.5	274.2	365.7	Tardif et al. (1995)
Toluene Rat	7.3	62.0	736.0	Tardif et al. (1995); Chen & Blancato (1989)
Toluene **Human/Rat**	4.45	4.42	0.50	
Styrene(ST)/Styrene Oxide (SO) Human	ST = 0.15 SO = 5.1	ST = 72.2 SO = 2.4	STp450 = 1.9 SOeh = 1.75 SOgst = 0.053	Sarangapani et al. (2002)
Styrene/SO Rat	ST = 0.38 SO = 0.065	ST = 181.2 SO = 0.031	STp450 = 22.6 SOeh = 9.32 SOgst = 9.24	Sarangapani et al. (2002)
Styrene/SO Human	ST = 0.15 SO = 0.024	ST = 73.8 SO = 11.3	STp450 = 1.77 SOeh = 0.82 SOgst = 0.29	Metabolic parameters (Sarangapani et al., 2002; Csanady et al., 2003)
Styrene/SO Rat	ST = 0.42 SO = 0.021	ST = 200.1 SO = 10.3	STp450 = 14.6 SOeh = 10.4 SOgst = 1.36	Metabolic parameters (Sarangapani et al., 2002; Csanady et al., 2003)
Styrene/SO **Human/Rat Mean**	ST = 0.38 SO = 39.8	ST = 0.38 SO = 39.2	STp450 = 0.10	

TABLE E.3.1. PBPK MODEL PREDICTIONS FOR SELECTED CHEMICALS: LOW END OF RANGE (1 μg/m³ x 8 hr/d, 24 hr SIMULATIONS)

Chemical Species	Cmax blood p*M*	AUC blood p*M*hr/d	Amount metabolized[2] pmol/kg-d	Model basis and source of metabolic parameters
Naphthalene (NAP)/Naphthalene Oxide (NPO) Human	NAP = 0.24 NPO = 0.0026	NAP = 117.5 NO = 1.29	NAPp450 = 0.012 NPOeh = 0.12 NPOgst = 1.55	Sarangapani et al. (2002); Willems et al. (2001)
Naphthalene/NPO Rat	NAP = 0.24 NPO = 0.0085	NAP = 115.3 NPO = 4.07	NAPp450 = 0.68 NPOeh = 1.24 NPOgst = 9.86	Sarangapani et al. (2002); Willems et al. (2001)
Naphthalene/NPO **Human/Rat**	NAP = 1.0 NPO = 0.31	NAP = 1.0 NPO = 0.32	NAPp450 = 0.02	

Chemical Species	Nasal Cmax p*M*	Nasal DPXmax pmol/mg DNA (/mm² nasal surface area)	Nasal AUCDPX pmol min/mg DNA/d	Model basis and source of metabolic parameters
Formaldehyde Human surface area (SA) = 21411 mm²	2800	1.4E-3 (6.5E-8)	0.72	Georgieva et al. (2003); (Kimbell et al., 2001a) (Kimbell et al., 2001b)
Formaldehyde Rat SA = 1777 mm²	1600	2.1E-3 (1.2E-6)	1.92	Georgieva et al. (2003); Kimbell et al. (2001b); Kimbell et al. (2001a)
Formaldehyde **Human/Rat**	1.75	0.67	0.38	

[1] Ethylbenzene simulations were 48 hr.
[2] p450 = cytochrome p450 epoxidation reaction, eh = epoxide hydrolase, gst = glutathione *S*-transferase.

TABLE E.3.2. PBPK MODEL PREDICTIONS FOR SELECTED CHEMICALS: HIGHEND OF RANGE (10 mg/m^3 x 8 hr/d, 24 hr SIMULATIONS)

Chemical Species	**Cmax blood n*M***	**AUC blood n*M*hr/d**	**Amount metabolized [1] nmol/kg-d**	**Model basis**
Ethylbenzene Human	290	2690	4690	Scaled from rat (Haddad et al., 2001)
Ethylbenzene, Rat	430	3240	9480	Tardif et al. (1997)
Ethylbenzene **Human/Rat**	0.67	0.83	0.49	
Vinyl Chloride Human	0.15	1260	1060	Chen & Blancato (1989)
Vinyl Chloride, Rat	0.10	812	4874	Chen & Blancato (1989)
Vinyl Chloride **Human/Rat**	1.5	1.6	0.22	
Toluene, Human	0.31	2570	3640	Tardif et al. (1995)
Toluene, Rat	0.073	620	7360	Tardif et al. (1995); (Chen and Blancato, 1989)
Toluene, **Human/Rat**	4.24	4.14	0.36	
Styrene/SO, Human	ST = 1.49 SO = 0.050	ST = 12.0 SO = 0.41	STp450 = 18.6 SOeh = 17.1 SOgst = 0.53	Sarangapani et al. (2002)
Styrene/SO, Rat	ST = 3.8 SO = 0.64	ST = 30.0 SO = 5.2	STp450 = 227 SOeh = 93.4 SOgst = 92.4	Sarangapani et al. (2002)
Styrene/SO, Human	ST = 1.53 SO =0.24	ST = 12.3 SO = 1.88	STp450 = 17.7 SOeh = 8.1 SOgst = 2.9	Metabolic parameters (Sarangapani et al., 2002; Csanady et al., 2003)
Styrene/SO, Rat	ST = 4.2 SO = 0.22	ST = 33.3 SO = 1.67	STp450 = 144 SOeh = 104 SOgst = 13.6	Metabolic Parameters (Sarangapani et al. 2002; Csanady et al., 2003)
ST/SO **Human/Rat, Mean**	ST = 0.38 SO = 0.35	ST = 0.39 SO = 0.33		

TABLE E.3.2. PBPK MODEL PREDICTIONS FOR SELECTED CHEMICALS: HIGHEND OF RANGE (10 mg/m^3 x 8 hr/d, 24 hr SIMULATIONS)

Chemical Species	Cmax blood n*M*	AUC blood n*M*hr/d	Amount metabolized [1] nmol/kg-d	Model basis
Naphthalene/NPO, Human	NAP = 2.41 NPO = 0.026	NAP = 19.7 NPO = 0.22	NAPp450 = 1.18 NPOeh = 1.21 NPOgst =15.4	Sarangapani et al. (2002); Willems et al. (2001)
Naphthalene/NPO, Rat	NAP = 2.36 NPO = 0.085	NAP = 19.2 NO = 0.68	NAPp450 = 6.92 NPOeh = 12.5 NPOgst = 98.6	Sarangapani et al. (2002); Willems et al. (2001)
Naphthalene/NPO, **Human/Rat**	NAP = 1.0 NPO = 0.3	NAP = 1.0 NPO = 0.3		

Chemical Species	Nasal Cmax μ*M*	Nasal DPXmax pmol/mg DNA	Nasal AUC DPX nmol min/mg DNA/d	Model basis and source of metabolic parameters
Formaldehyde Human SA = 21411 mm^2	29	6.66	7.65	Georgieva et al. (2003); Kimbell et al. (2001a) Kimbell et al. (2001b)
Formaldehyde Rat SA = 1777 mm^2	16	9.67	19.24	Georgieva et al. (2003); Kimbell et al. (2001a) Kimbell et al. (2001b)
Formaldehyde **Human/Rat**	1.8	0.7	0.4	

[1] p450 = cytochrome p450 epoxidation reaction, eh = epoxide hydrolase, gst = glutathione *S*-transferase; DPX = DNA-protein cross-links.

E.3.2.1.2 Intraspecies comparisons for young humans and animals

In Table E.3.3, the results of PBPK model predictions of low-level exposure to ethylbenzene for human children with two sets of metabolic parameters are presented. Sams et al. (2004) investigated the enzyme kinetics of the initial hydroxylation of ethylbenzene to form 1-phenylethanol. Human liver microsomes were obtained from TCS Cellworks. The production of 1-phenylphenol with the human microsomes exhibited biphasic kinetics with a high affinity, low Km, component (mean Km = 8 μM; Vmax = 689 pmol/min/mg protein; n = 6 livers) and a low affinity, high Km, component (Km = 391 μM; Vmax = 3039 pmol/min/mg protein; n = 6). Experiments with inhibitors and recombinant CYP isoforms indicated that CYP2E1 was the major form of the high affinity component and that CYP1A2 was very likely involved in the low affinity component. Haddad et al. (2001) investigated PBPK modeling of chemical mixtures including ethylbenzene. The biochemical parameters were based on studies in rats: VmaxC = 6.39 mg/hr/kg bw; Km = 1.04 mg/L. For human PBPK models the Vmax was scaled, i.e., Vmax = VmaxC x BW^0.75 = mg/hr.

With the parameters from Sams et al. (2004) the concentration metrics are higher and the metabolism (AMET) is lower than with the values from Haddad et al. (2001). While the differences appear large it should be appreciated that the Sams values are based on analysis of isolated microsomes in vitro. Extrapolating these values to a whole body PBPK model probably involves greater uncertainty than extrapolating from rat to human. Table E.3.4 gives the corresponding values for the immature rat. Also presented in this table are the human/rat ratios for children and adults. Since the human ages and rat body weights do not correspond exactly in terms of developmental stage, they are compared for the youngest and averaged over all. If the average immature values for human/rat for the two parameter sets are used with the blood Cmax metric, the corresponding dosimetric adjustment factor (DAF) for ethylbenzene would be 0.21. If only the neonate values are used, the DAF would be 0.22.

TABLE E.3.3. PBPK MODEL PREDICTIONS FOR ETHYLBENZENE WITH HUMAN AGE-SPECIFIC REGRESSIONS AND ALTERNATIVE METABOLIC PARAMETERS (1 μg/m^3 x 8 hr/d, 24-48 hr SIMULATIONS)

Age Group	Cmax blood p*M*	AUC blood p*M*hr/d	Amount Metabolized pmol/kg-d	Model basis
Ethyl Benzene, Human Age 1 yr	100	1300	13	Metabolic parameters scaled from adult (Sams et al., 2004)
Age 3 yr	110	1450	11	
Age 5 yr	120	1620	10	
Age 10 yr	120	1580	8.2	
Age 14 yr	120	1420	6.3	
Age 18 yr	110	1510	5.9	
Adult	110	1750	7.2	
Ethyl Benzene, Human Age 1 yr	55.9	570	370	Parameters scaled to $BW^{0.75}$(Haddad et al., 2001)
Age 3 yr	58.6	570	370	
Age 5 yr	62.2	660	475	
Age 10 yr	53.9	550	500	
Age 14 yr	48.6	470	390	
Age 18 yr	35.0	330	380	
Adult	55.9	560	870	
Rat Mature	38.2	290	900	

TABLE E.3.4. PBPK MODEL PREDICTIONS FOR ETHYLBENZENE WITH AGE-SPECIFIC PARAMETERS FROM CLEWELL ET AL**. 2003 MODELING OF NEONATAL RAT (1 μg/m^3 x 8 hr/d, 24-48 hr SIMULATIONS)**

Age Group	Cmax blood p*M*	AUC blood p*M*hr/d	Amount metabolized pmol/kg-d	Model basis
Ethylbenzene, Rat Neonate BW = 0.0075 kg	17.0	130	450	Scaled BW$^{0.75}$ (Haddad et al., 2001: Clewell et al., 2003a)
BW = 0.015 kg	17.0	135	450	
BW = 0.03 kg	17.0	138	440	
BW = 0.06 kg	17.2	140	430	
BW = 0.12 kg	17.1	140	420	
BW = 0.20 kg	17.4	145	420	
Human neonate/Rat neonate	5.88	10.0	0.029	Parameters (Sams et al., 2004)
Human neonate/Rat neonate	3.29	4.38	0.82	Parameters (Haddad et al., 2001)
Human/Rat Immature Mean	6.61	9.19	0.018	Parameters (Sams et al., 2004)
Human/Rat Immature Mean	3.06	3.61	0.97	Parameters (Haddad et al., 2001)
Mean DAF Immature	0.21	0.16	6.79 (G_{mean})	

Note: Human neonate/Rat neonate = 100pM/17.0pM = 5.88 (Sams Cmax); Human/Rat Immature Mean = (5.88+6.47+7.06+6.98+7.01+6.32)/6 = 6.61 (Sams Cmax); Gmean = geometric mean; DAF = dosimetric adjustment factor; human/rat values in this table were calculated using human values from Table E3.3. Mean DAF based on immature values i.e. 1/((6.61 + 3.06)/2).

Table E.3.5 gives PBPK simulation values for toluene for both immature rats and human children. As above, the individual human/rat ratios are given for neonates and the mean is based on all immature ages (i.e., all except adult) simulated. The mean DAFs are given at the bottom of the table. In this case the DAFs are close to unity for both concentration based metrics. Similarly Table E.3.6 gives the corresponding values for vinyl chloride. In this case the mean DAF based on blood concentration (Cmax) and average immature values was 1.19. The human/rat ratios for the three chemicals with similar model structures (Table E.3.5 to Table E.3.8) are quite similar with blood Cmax and AUC based DAFs averaging 1.62, 0.96, and 1.17, respectively for children. For adults the concentration-based ratios were very similar, averaging 1.12 for ethylbenzene and 1.47 for vinyl chloride. For toluene, the adult ratios differed substantially: 3.1 for Cmax and 0.31 for AUC.

TABLE E.3.5. PBPK MODEL PREDICTIONS FOR TOLUENE WITH AGE-SPECIFIC REGRESSIONS (1 μg/m^3 X 8 hr/d, 24 hr SIMULATIONS)

Age Group	Cmax blood p*M*	AUC blood p*M*hr/d	Amount metabolized pmol/kg-d	Model basis
Toluene, Human:				
Age 1 yr	83.2	771	551	Metabolic parameters scaled to BW$^{0.75}$ (Haddad et al., 2001)
Age 3 yr	85.6	825	637	
Age 5 yr	90.0	899	754	
Age 10 yr	61.3	580	684	
Age 15 yr	52.9	472	486	
Age 18 yr	51.7	483	440	
Adult	30.0	255	365	
Toluene, Rat				
Neonate, 0.0075 kg	108.7	873	33201	Parameters scaled to BW$^{0.75}$ (Haddad et al., 2001)
BW = 0.015 kg	86.1	688	16409	
BW = 0.03 kg	72.6	579	8149	
BW = 0.06 kg	65.0	516	4058	
BW = 0.12 kg	58.7	478	2024	
BW = 0.20 kg	52.8	457	1206	
BW = 0.25 Adult	92.4	80.2	375	
HumanNeonate/RatNeonate	0.76	0.88	0.016	
Human/RatImmatureMean	0.97	1.13	0.15	
Mean DAF	1.03	0.88	6.7	

Note: Human neonate/Rat neonate = 83.2 pM/108.7 pM = 0.76 (Cmax); Human/Rat Immature Mean = (0.76+0.99+1.24+0.94+0.90+0.98)/6 = 0.97 (Cmax); DAF = dosimetric adjustment factor. Mean DAF = 1/0.97 = 1.03 (Cmax).

TABLE E.3.6. PBPK MODEL PREDICTIONS FOR VINYL CHLORIDE WITH AGE-SPECIFIC REGRESSIONS (1 μg/m^3 x 8 hr/d, 24 hr SIMULATIONS)

Age Group	Cmax blood p*M*	AUC blood p*M*hr/d	Amount Metabolized pmol/kg-d	Model basis
Vinyl Chloride, Human, Age 1 yr	16.5	137.2	101.3	Metabolic parameters scaled as BW$^{0.75}$(Chen & Blancato 1989)
Age 3 yr	17.0	138.7	108.2	
Age 5 yr	17.4	140.0	116.6	
Age 10 yr	16.3	132.3	137.2	
Age 15 yr	16.0	131.9	102.5	
Age 18 yr	16.5	133.9	87.7	
Adult	14.4	117.6	101.0	
Vinyl Chloride, Rat Neonate, 0.0075 kg	18.9	149.6	424.4	Parameters scaled to BW$^{0.75}$ (Clewell et al., 2003a; Chen & Blancato 1989)
BW = 0.015 kg	19.0	150.3	421.3	
BW = 0.03 kg	19.2	151.9	414.7	
BW = 0.06 kg	19.7	155.5	397.8	
BW = 0.12 kg	20.7	162.9	363.8	
BW = 0.20 kg	21.7	172.2	321.5	
BW = 0.25 adult	21.6	169.4	511.4	
Human/Rat Neonate	0.89	0.92	0.24	
Human/Rat Immature Mean	0.84	0.87	0.28	
Mean DAF	1.19	1.15	3.6	

Note: Human neonate/Rat neonate = 16.5 pM/18.9 pM = 0.87 (Cmax); Human/Rat Immature Mean = (0.87+0.89+0.91+0.83+0.77+0.76)/6 = 0.84 (Cmax); DAF = dosimetric adjustment factor. Mean DAF = 1/0.84 = 1.19 (Cmax).

In Table E.3.7 are summarized the results obtained with the respiratory tract (RT) model with naphthalene. This model predicts concentrations of both parent (NP) and oxidative metabolite naphthalene oxide (NPO). The predicted values for the latter are shown in parentheses. Also included is an average lung concentration of the naphthalene oxides. In this model the isomeric naphthalene oxides are grouped together for simplicity. For the usual concentration metrics of Cmax and AUC in the blood the DAFs range from 8 to 14 for parent and oxide metabolite in the child and 8 to 6, respectively in the adult. For the predicted lung oxide concentration the DAF is 0.17 for the child and 0.07 for the adult.

TABLE E.3.7. PBPK MODEL PREDICTIONS FOR NAPHTHALENE/NAPHTHALENE OXIDES (NPO) WITH AGE-SPECIFIC REGRESSIONS (NAPHTHALENE 1 μg/m^3 x 8 hr/d, 24 hr SIMULATIONS)

Age Group	Cmax blood p*M* NP (NPO)	AUC blood p*M*hr/d NP (NPO)	Amount Naphthalene Metabolized pmol/kg-d	Avg. NPO Conc. in Lung p*M**
Human, Age 1 yr	0.22 (0.0032)	1.83 (0.027)	1.5	0.057
Age 3 yr	0.22 (0.003)	1.83 (0.025)	1.6	0.062
Age 5 yr	0.22 (0.0033)	1.83 (0.026)	1.8	0.064
Age 10 yr	0.19 (0.0031)	1.5 (0.025)	5.2	0.065
Age 15 yr	0.18 (0.0026)	1.48 (0.022)	3.8	0.07
Age 18 yr	0.18 (0.0026)	1.49 (0.021)	3.3	0.07
Adult	0.18 (0.0019)	1.49 (0.016)	4.6	0.073
Rat Neonate, 0.0075 kg	1.7 (0.3)	13.8 (2.3)	1.97	0.07
BW = 0.015 kg	1.7 (0.16)	13.7 (1.3)	2.26	0.037
BW = 0.03 kg	1.7 (0.08)	13.5 (0.65)	2.7	0.020
BW = 0.06 kg	1.68 (0.04)	13.2 (0.33)	3.17	0.011
BW = 0.12 kg	1.7 (0.023)	13.3 (0.18)	3.75	0.0072
BW = 0.20 kg	1.67 (0.016)	13.3 (0.12)	4.3	0.0050
BW = 0.25 kg (adult)	1.5 (0.012)	12.2 (0.095)	4.56	0.0048
Human/Rat Neonate	0.13 (0.011)	0.13 (0.012)	0.76	0.81
Human/Rat Immature Mean	0.10 (0.07)	0.12 (0.072)	0.92	5.88
Mean DAF Immature	10 (14.3)	8.3 (13.9)	1.1	0.17
Human/Rat Adult	0.12 (0.16)	0.12 (0.17)	1.01	15.2
DAF Adult	8.3 (6.2)	8.3 (5.9)	0.99	0.066

Note: (*)Average of upper respiratory tract and terminal bronchiole model compartments Cmax for naphthalene oxides; NP = naphthalene; NPO = oxidative metabolite; models based on Sarangapani et al. (2002); Willems et al. (2001); and Clewell et al. (2003a). Human neonate/Rat neonate = 0.22pM/1.7pM = 0.13 (NP Cmax); Human/Rat Immature Mean = (0.13+0.13+0.13+0.11+0.11+0.11)/6 = 0.103 (NP Cmax); DAF = dosimetric adjustment factor. Mean DAF = 1/0.10 = 10 (NP Cmax). HEC = DAF x Animal Exposure Concentration

The predicted values obtained with styrene exposure in a similar RT model are shown in Table E.3.8. For children, the average DAF (based on the immature values, i.e. all values except adult) for the concentration-based metrics was 0.42 ((0.41 + 0.42) /2) for the parent compound (ST) and 0.18 ((0.17 + 0.20)/2) for the oxide metabolite (SO). For the adult these values were 1.07 and 0.18, respectively. To recap if we were to calculate the human equivalent concentration (HEC) based on these values we might consider multiplying an immature rat exposure concentration by 0.42 or an adult rat value by 1.07 if the toxic effect were due to the parent compound (i.e., HEC = DAF*Animal Exposure Concentration).

TABLE E.3.8. PBPK MODEL PREDICTIONS FOR STYRENE/ STYRENE OXIDE WITH AGE-SPECIFIC REGRESSIONS (1 μg/m^3 X 8 hr/d, 24 hr SIMULATIONS)

Age group	Cmax blood p*M* ST (SO)	AUC blood p*M*hr/d ST (SO)	Amount of Styrene Metabolized pmol/kg-d	Average SO Conc. in Lung p*M**
Human				
Age 1 yr	0.27 (0.0027)	2.23 (0.022)	1.34	1E-5
Age 3 yr	0.28 (0.0032)	2.25 (0.026)	1.34	1E-5
Age 5 yr	0.28 (0.0037)	2.30 (0.030)	1.34	8E-6
Age 10 yr	0.27 (0.012)	2.22 (0.094)	1.94	9E-6
Age 15 yr	0.27 (0.012)	2.18 (0.095)	1.53	8E-6
Age 18 yr	0.27 (0.026)	2.20 (0.095)	1.39	8E-6
Adult	0.15 (0.024)	1.23 (0.18)	1.77	2.4E-5
Rat				
Neonate, 0.0075 kg	0.09 (3.7E-4)	0.73 (0.003)	6.5	8.7E-3
BW = 0.015 kg	0.097 (5.4E-4)	0.76 (0.004)	8.1	7.5E-3
BW = 0.03 kg	0.10 (0.0084)	0.83 (0.0067)	10.0	7.0E-3
BW = 0.06 kg	0.12 (0.0014)	0.93 (0.011)	13.8	6.5E-3
BW = 0.12 kg	0.14 (0.0024)	1.08 (0.018)	19.0	7.0E-3
BW = 0.20 kg	0.16 (0.0036)	1.26 (0.029)	25.0	7.5E-3
BW = 0.25 kg (adult)	0.16 (0.0041)	1.32 (0.033)	28.0	7.5E-3
Human/Rat Neonate	3.0 (7.3)	3.05 (7.3)	0.21	0.0011
Human/Rat Immature Mean	2.42 (5.74)	2.40 (5.0)	0.11	0.0012
Child Mean DAF	0.41 (0.17)	0.42 (0.2)	9.1	833
Adult DAF	1.07 (0.17)	1.07 (0.18)	15.8	3.12

*Average styrene oxide concentration of upper respiratory tract and terminal bronchiole model compartments; Cmax = maximum blood concentration for styrene (ST) and styrene oxide (SO); AUC = blood concentration x time for styrene and styrene oxide; models based on Sarangapani et al. (2002); and Clewell et al. (2003a). Human neonate/Rat neonate = 0.27 pM/0.09 pM = 3.00 (ST Cmax); Human/Rat Immature Mean = (3.00+2.87+2.80+2.25+1.93+1.69)/6 = 2.42 (ST Cmax); DAF = dosimetric adjustment factor. Mean DAF = 1/2.42 = 0.41 (ST Cmax). Human Equivalent Concentration (HEC) = DAF x Animal Concentration.

TABLE E.3.9. PBPK MODEL PREDICTIONS FOR FORMALDEHYDE WITH AGE-SPECIFIC PARAMETERS FROM CLEWELL *et al.*, 2003a: MODELING OF NEONATAL AND IMMATURE RAT (1 μg/m^3 x 8 hr/d, 24 hr SIMULATIONS)

Age Group	Nasal Cmax p*M*	Nasal DPXmax pmol/mg DNA	Nasal AUCDPX pmol min/mg DNA-d	Model basis
Rat				Scaled BW0.75 and first order rates BW-0.25 Georgieva et al. (2003); Clewell et al. (2003a)
Neonate, BW = 0.0075 kg	53	3.2 x 10-5	0.033	
BW = 0.015 kg	110	7.8 x 10^{-5}	0.080	
BW = 0.03 kg	220	1.8 x 10^{-4}	0.184	
BW = 0.06 kg	430	4.1 x 10^{-4}	0.406	
BW = 0.12 kg	820	9.4 x 10^{-4}	0.872	
BW = 0.20 kg	1320	1.8 x 10^{-3}	1.57	
Adult: BW = 0.25 kg	1600	2.1 x 10^{-3}	1.92	

Note: Cmax = maximum concentration; DPXmax = maximum DNA-protein crosslinks concentration; AUCDPX = the area under the DPX x time curve per day.

TABLE E.3.10. PBPK MODEL PREDICTIONS FOR FORMALDEHYDE WITH AGE-SPECIFIC PARAMETERS: MODELING OF HUMAN CHILDREN (1 μg/m3 x 8 hr/d, 24 hr SIMULATIONS).

Age Group	Nasal Cmax p*M*	Nasal DPXmax pmol/mg DNA	Nasal AUCDPX pmol min/mg DNA-d	Model basis
Human 3 month Neonate, BW = 5.7 kg	150	6.2×10^{-5}	0.035	Scaled $BW^{0.75}$ and first order rates $BW^{-0.25}$ (Georgieva et al., 2003; Clewell *et al*. 2003a)
1 yr, BW = 10.1 kg	390	1.7×10^{-4}	0.094	
3 yr, BW = 14.6 kg	860	3.9×10^{-4}	0.215	
5 yr, BW = 19.4 kg	1400	6.5×10^{-4}	0.348	
10 yr, BW = 32.6 kg	1700	8.4×10^{-4}	0.437	
15 yr, BW = 54.5 kg	2360	1.2×10^{-3}	0.603	
18 yr, BW = 63.1 kg	2700	1.4×10^{-3}	0.682	
Human/Rat Neonate	2.83	1.94	1.10	
DAF Neonate	0.35	0.52	0.91	
Human/Rat Immature Mean	2.90	1.47	0.80	
DAF Immature Mean	0.34	0.68	1.25	
Adult, BW = 70 kg	2700	1.4×10^{-3}	0.684	
Human/Rat Adult	1.69	0.67	0.36	
DAF Adult	0.59	1.49	2.78	

Note: Cmax = maximum concentration; DPXmax = maximum DNA-protein crosslinks concentration; AUCDPX = the area under the DPX x time curve per day. Human neonate/Rat neonate = 150 pM/53 pM = 2.83 (Cmax); Human/Rat Immature Mean = (2.83+3.54+3.91+3.26+2.07+1.79)/6 = 2.90 (Cmax); DAF = dosimetric adjustment factor. Mean DAF = 1/2.78 = 0.36 (Cmax). Human Equivalent Concentration (HEC) = DAF x Animal Concentration.

E.3.2.1.3 Summary of HEC factors for Adults and Children/pups

TABLE E.3.11. DAFs SUMMARY BASED ON PBPK MODELING OF INTERNAL DOSIMETRY

Chemical Species	Cmax blood (range)	AUC blood (range)	Amount Metabolized /kg-d	Other
Ethyl Benzene Child Average	0.21	0.16	6.79	
Ethyl Benzene Adult	0.52	0.34	11.37	
Naphthalene/NPO Child Average.	(8-14)	(8-14)	1.1	0.17 Cmax NPO lung
Naphthalene/NPO Adult	(6-8)	(6-8)	0.99	0.065 Cmax NPO lung
Toluene Child Average.	1.03	0.88	6.7	
Toluene Adult	3.1	0.31	2.0	
Vinyl Chloride (VCl) Child Average.	1.19	1.15	3.6	
VCl Adult	1.50	1.44	5.1	
Styrene Child Average	0.41	0.42	9.1	833 (child/rat pup)
SO Child Average	0.17	0.2		
Styrene Adult Average	1.07	1.07	15.8	3.12 (human/rat)
SO Adult Average	0.17	0.18		
Child Gmean	1.94	1.63	6.1	
Adult Gmean	1.85	1.30	3.9	
	Nasal Cmax	**Nasal DPXmax**	**Nasal AUCDPX**	
Formaldehyde Child Mean	0.34	0.68	1.25	
Formaldehyde Adult	0.59	1.49	2.78	

Note: Note: Cmax = maximum concentration; DPXmax = maximum DNA-protein crosslinks concentration; AUCDPX = the area under the DPX x time curve per day. Human Equivalent Concentration (HEC) = DAF x Animal Exposure Concentration.

Table E.3.11 provides a summary of Table E.3.3 - Table E.3.10. For the five test compounds that provide blood concentration metrics (Cmax, AUC), the child DAFs have geometric means of 1.94 and 1.63, respectively. Adult values were only slightly lower at 1.85 and 1.30, respectively. The results of the formaldehyde nasal model, which differs significantly in

structure from the previous five chemicals, are presented in Table E.3.9 and Table E.3.10. For the child the DAFs for nasal tissue Cmax and DPXmax were 0.34 and 0.68. The value for the AUC DPX was 1.25. For the adult these DAFs were higher at 0.59, 1.49, and 2.78, respectively. The predicted formaldehyde DAFs are also given at the bottom of Table E.3.11 with separate column headings.

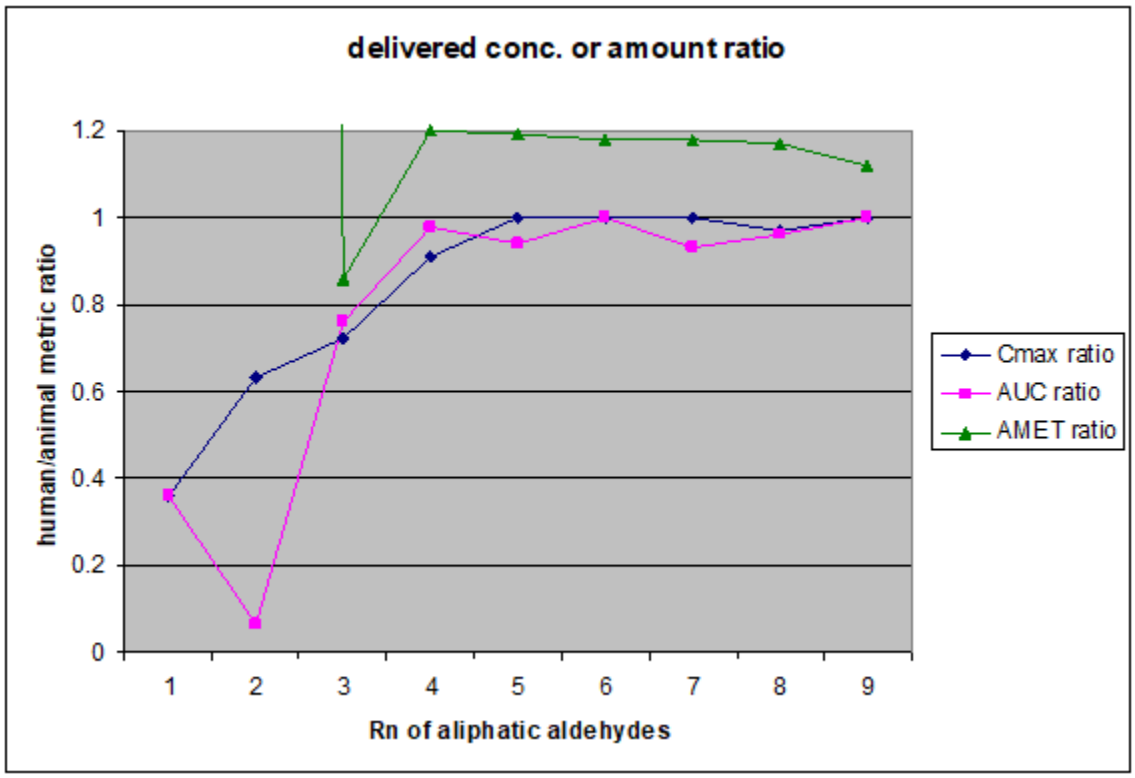
E.3.2.2 Aliphatic Aldehydes

The body of Table E.3.12 gives the ratio of Human/Rat metric values (unitless). The reciprocals of the mean (bottom) represent a factor (i.e., the DAF) by which to multiply the respective animal toxicity criteria in order to calculate the HEC. The models were formulated for adults only. There appears to be a clear difference between the shorter chain length, water-soluble aldehydes and the longer chain length, fat-soluble aldehydes. This difference is reflected in the metabolic parameters where both acetaldehyde and propionaldehyde have two saturable metabolic paths: a high-capacity, low-affinity and a low-capacity, high-affinity, as opposed to the single saturable path for the fatty aldehydes. Overall the HEC factors for the aliphatic aldehydes appear similar to the other compounds studied in adults with blood concentration ratios for each metric averaging 1.3 vs. 1.3 to 1.85 for the geometric means of the models for the five test compounds which give similar metrics. If the values for acetaldehyde and propionaldehyde are removed from the mean, the Cmax HEC factor is reduced to 1.06. This PBPK series approach may also be applicable to the straight chain aliphatic hydrocarbons and acids.

TABLE E.3.12. HUMAN/RAT PBPK MODEL PREDICTIONS FOR ALIPHATIC ALDEHYDES: (1 μg/m^3 x 8 hr/d, 24 hr SIMULATIONS)

Chemical Species	Cmax blood	AUC blood	Amount Metabolized	Model Basis
Acetaldehyde	0.36	0.36	11.4	Haddad et al. (2000); Paterson & MacKay (1989); Mitchell & Petersen (1989); Kelson et al. (1997)
Propionaldehyde	0.63	0.065	24.1	
Butyraldehyde	0.72	0.76	0.86	
Pentanal	0.91	0.98	1.20	
Hexanal	1.0	0.94	1.19	
Heptanal	1.0	1.0	1.18	
Octanal	1.0	0.93	1.18	
Nonanal	0.97	0.96	1.17	
Decanal	1.0	1.0	1.12	
Mean	0.84	0.78	4.82	
DAF	1.18	1.28	0.21	

FIGURE E.3-1 HUMAN/ANIMAL METRIC RATIOS FOR ALIPHATIC ALDEHYDES.



E.3.3 Discussion

The rat neonatal PBPK values in Tables E.3.4 to E.3.8 and Table E.3.10 are derived from the Clewell et al. (2003a) paper on neonatal perchlorate dosimetry. The values range from body weights of 0.0075 kg to 0.1985 kg. Except for fat and slowly perfused compartments, which vary inversely with each other and body weight, the tissues are a fixed percentage of body weight. Blood flows are also a fixed percentage of cardiac output, which itself is a fixed percent of body weight (14 L/hr/kg). This scheme differs from that of Price et al. (2003) and their age-specific regressions for human neonates and children. In the latter paper fractional blood flows, specifically those for liver, vary by much more than do tissue volumes. The rat values may vary more with respect to developmental age than indicated by Clewell et al. (2003a). These physiological differences may have influenced the results in Table E.3.5 and the human/rat comparisons.

In general the DAFs based on PBPK model-predicted blood concentration for adults seem lower and those for children seem higher than those produced by the current HEC methodology, which is not chemical specific but based on ventilation rates and lung surface area. Thus if we credit the chemical specific PBPK approach, the current methodology may underestimate the HEC for children and overestimate it for adults. However, these interim conclusions are based on a very limited number of chemicals and on many assumptions. HECs based on internal dosimetry PBPK estimates are bound to be highly chemical dependent and strongly influenced by the dose

metric chosen, blood/air and fat/blood partition coefficients, fractional tissue flows, metabolic parameters, and other factors.

This report also estimated values for immature rats where the examples are given in the tables, as well as for adult rat and human child, to assist in derivation of a DAF. It is anticipated that future laboratory studies will more often involve immature animals to assess accurately the toxicity of environmental agents throughout the postnatal development period.

TABLE E.3.13. SUMMARY OF INFANTS' AND CHILDREN'S PBPK MODELING BY OEHHA WITH SELECTED ENVIRONMENTAL TOXICANTS BY INHALATION

Chemical and Exposure	Tissue and Dose Metric	Age at Maximum Child/Adult	Child/Adult Maximum	Basis for the Model
Chloroform 1 ppm x 24 hr	Liver AMET	Newborn	2.3	Corley et al. (1990); Price et al. (2003)
	Kidney AMET	Newborn	2.3	
TCE 1 ppm x 24 hr	Lung $Cmax_{CH}$	Newborn	9.6	Abbas & Fisher (1997); Fisher et al. (1998); Price et al. (2003)
	Venous blood AUC_{TCE}	3 yr	10.6	
	AUC_{CH}	Newborn	12.5	
	Lung AUC_{CH}	1.5 mo	12.9	
	Liver AUC_{TCA}	3 yr	10.3	
	Liver AMET	Newborn	15.7	
Vinyl chloride 1 ppm x 24 hr	Liver Risk M	Newborn	10.2	Clewell et al. (1995); Price et al. (2003)
	Liver Risk G	Newborn	11.0	
Dichloromethane 1 ppm x 24 hr	Liver MFO AMET	Newborn	2.1	OSHA (1997); Price et al. (2003)
	Lung MFO AMET	Newborn	2.1	
	Liver GST AMET	Newborn	43.3	
	Lung GST AMET	Newborn	11.6	
DCM 1 ppm x 24 hr respiratory tract model	Liver MFO AMET	Newborn	3.0	OSHA (1997); Sarangapani et al., (2002); Price et al, (2003)
	Lung MFO AMET	Newborn	60.7	
	MFO AMET total	Newborn	3.0	
	Liver GST AMET	Newborn	42.7	
	Lung GST AMET	Newborn	65.9	
	GST AMET total	Newborn	56.6	
Styrene/styrene (ST/SO) oxide 1 ppm x 24 hr	Lung MFOAMET/L tissue-d	Newborn	9.3	Sarangapani et al., (2002; Price et al., (2003)
	Lung EH AMET/Ltissue-d	Newborn	9.2	
	Lung GST AMET/Ltissue –d	Newborn	4.7	
ST/SO 1 ppm x 24 hr respiratory tract model	Lung MFOAMET/L tissue-d	0.5 mo	2.7	Sarangapani et al. (2002); Price et al. (2003)
	Lung EH AMET/Ltissue-d	0.5 mo	2.6	
	Lung GST AMET/Ltissue–d	0.5 mo	2.7	
ST/SO 50 ppm x 2 hr respiratory tract model, Csanady et al. biochemical parameters	Lung MFO AMET/Ltissue-d	0.5 mo	2.7	Sarangapani et al. (2002); Csanady et al. (2003); Price et al. (2003)
	Lung EH AMET/Ltissue-d	0.5 mo	2.8	
	Lung GST AMET/Ltissue–d	0.5 mo	2.9	
	Liver + Lung AMET/Ltissue-d	Newborn	3.5	
ST/SO 50 ppm x 2 hr respiratory tract model, Sarangapani et al. biochemical parameters	Lung MFOAMET/L tissue-d	0.5 mo	2.5	Sarangapani et al. (2002); Price et al. (2003)
	Lung EH AMET/Ltissue-d	0.5 mo	3.0	
	Lung GST AMET/Ltissue–d	Newborn	6.0	
	Liver + Lung AMET/Ltissue-d	Newborn	6.5	

TABLE E.3.13. SUMMARY OF INFANTS' AND CHILDREN'S PBPK MODELING BY OEHHA WITH SELECTED ENVIRONMENTAL TOXICANTS BY INHALATION

Chemical and Exposure	Tissue and Dose Metric	Age at Maximum Child/Adult	Child/Adult Maximum	Basis for the Model
ST/SO 1 ppm x 24 hr respiratory tract model of Csanady et al.	Lung MFOAMET/Ltissue-d	0.5 mo	7.3	Csanady et al. (2003); Price et al. (2003)
	Venous Blood SO Cmax	3.5 mo to 1 yr	5.1	
	Lung alveoli SO Cmax	3.5 mo	4.3	
	Lung alveoli AUC_{SO}	Newborn to 5 yr	4.2	
ET/EO 1 ppm x 24 hr PBPK model of Csanady et al.	Clearance of ET and EO by liver, Venous blood Cmax, AUC EO in liver, blood, Hb and DNA adducts	Newborn (AMET EO µmol/kg-d)	32.1	Csanady et al. (2000); Price et al. (2003)
Butadiene (BD) 1 ppm x 24 hr BD/BMO/DEB model	Liver + Lung DEB AMET µmol/kg-d	Newborn	7.1	Kohn & Melnick (1993); Johanson & Filser (1993); Price et al. (2003)
	Venous blood AUC_{BMO} µM hr	Newborn	71	
	Venous blood AUC_{DEB} µM hr	Newborn	16.2	
	Liver AUC_{DEB} µM hr	Newborn	20.7	
	Lung AUC_{BMO} µM hr	Newborn	32.8	
	Lung AUC_{DEB} µM hr	Newborn	17.2	
BD/BMO 1 ppm x 24 hr respiratory tract model	Lung BMO→DEB AMET µmol/Llung-d	Newborn	33.8	Sarangapani et al. 2002; Kohn & Melnick (1993); Price et al. (2003)
	Liver BMO→DEB AMET µmol/Lliver-d	Newborn	19.2	
BD/BMO 1 ppm x 24 hr respiratory tract model	Lung alveoli BMO→DEB AMET µmol/Lalveoli-d	Newborn	120	Sarangapani et al. (2002); Kohn & Melnick (1993); Price et al. (2003)
	Lung bronchi BMO→DEB AMET µmol/Lbronchi-d	Newborn	33.8	
MTBE 1 ppm x 24 hr; 10 ppm x 8 hr VPs 0.8, 1.25	Blood, brain Cmaxs µM, AUCs µM hr, AMET µmol/kg-d	3-8 yr	1.2 to 12.4 highly dependent on VP	(Licata et al., 2001); Price et al. 2003; Evelo et al. (1993)
PCE 1ppm x 24 hr; 10 ppm x 8 hr VP = 1	AUC^{PCE} blood, liver, brain, AMET, AUC^{TCA}, TCAurine/kg-d	Newborn	1.1 to 4.6	Gearhart et al. (1993); Loizou (2001); Price et al. (2003)
Furan 1 ppm x 24 hr 0-13yr + adult Flow-limited liver metabolism	Liver AMET µmol/kg-d Brain AUC µMhr	13 yr	2.2	Price et al. (2003)
Carbon tetrachloride 1 ppm x 24 hr, 10 ppm x 8 hr	Liver AMET µmol/kg-d, Blood or liver AUC µMhr, blood or liver Cmax	Newborn	1.6	Thrall et al. (2000); Price et al. (2003)

TABLE E.3.13. SUMMARY OF INFANTS' AND CHILDREN'S PBPK MODELING BY OEHHA WITH SELECTED ENVIRONMENTAL TOXICANTS BY INHALATION

Chemical and Exposure	Tissue and Dose Metric	Age at Maximum Child/Adult	Child/Adult Maximum	Basis for the Model
Toluene 1 ppm x 24 hr	LiverAMET μmol/kg-d, Blood or liver AUC μMhr, blood or liver Cmax	5 yr	3.6	Tardiff et al. (1995); Price et al. (2003)
Xylene 1 ppm x 24 hr	LiverAMET μmol/kg-d, Blood or liver AUC μMhr, blood or liver Cmax	5 yr	4.5	Tardif et al. (1995); Price et al. (2003)
Toluene/Xylene mixed model with competitive inhibition, 10/10, 1/10, 10/1 ppm x 8 hr	Liver AMET μmol/kg-d, Blood or liver AUC μMhr, blood or liver Cmax	5 yr	5.2	Tardif et al. (1995); Price et al. (2003)
Benzo[a]pyrene vapor 10 ppb x 24 hr; Hybrid diffusion-limited-lung flow-limited-body model	Lung alveoli, bronchi. Liver AMET μmol/kg-d. AUC^{BaP} μM min; V_{max}s scaled from uninduced and 3-MC induced rats	Newborn	4.3 to 31.9 uninduced 3.7 to 26.1 induced	Wiersma and Roth (1983); Gerde et al. (1991); Moir et al. (1998); Price et al. (2003); and others
Benzo[a]pyrene particle 1 μg/m3 x 24 hr; hybrid model as above	Lung alveoli, bronchi. Liver AMET μmol/kg-d. AUC^{BaP} μM min; V_{max}s scaled from uninduced and 3-MC induced rats	Newborn to 1 yr	9.7 to 18.6 uninduced 10.8 to 22.0 induced	As above and Sun et al. (1982): Sun et al. (1984): ICRP (1994); Gerde et al. (2001); Ramiesh et al. (2001)
NAP/NO 1 ppm x 24 hr respiratory tract model	Lung AMET μmol/$L_{alveoli}$-d	Newborn	2.4	Sweeney et al. (1996); Willems et al. (2001); Price et al. (2003)
	$AMET^{NO}$ GST μmol/kg-d	Newborn	3.1	

Notes: AMET = amount metabolized; Cmax = maximum concentration in blood or tissue; CH = chloral hydrate; TCA = trichloroacetic acid; AUC = area under the concentration x time curve; Risk M = μmol metabolites DNA bound/L liver/d; Risk G = μmol metabolites conjugated with glutathione/L liver/d; MFO = mixed function oxidase (P450) pathway; EH = epoxide hydrolase pathway; GST = glutathione sulfotransferase pathway; BMO = butadiene monoxide; DEB = diepoxybutane; AMET DEB amount of BMO oxidized to DEB. Model based on [Kohn & Melnick (1993)], Evelo et al.. (1993), Sarangapani et al. (2002), Jonsson, (2001). Exposure for 24 hr, simulations 48 hr. respiratory tract model = model with diffusion limited lung (upper airways, conducting airways, transitional bronchioles, and alveoli) and flow limited body (fat muscle, vessel rich group and liver) based on Sarangapani et al.. (2002) with BD/BMO parameters from [Kohn and Melnick (1993)]. VP = ventilation:perfusion ratio (alveolar ventilation/cardiac output). MTBE = methyl *tert*-butyl ether; PCE = tetrachloroethylene; TCA = trichloroacetic acid.

E.3.4 Uncertainty Factor for Variability within the Human Population

- Traditional application and previously published analyses.

A 10-fold uncertainty factor (UF_H) has traditionally been used by risk assessors to account for variability within the human population. As understanding of the sources of interindividual variability has evolved, this uncertainty factor has been regarded as consisting of two components, both with a value of $\sqrt{10}$, attributed to differences in toxicokinetics and toxicodynamics, respectively. The overall uncertainty factor is intended to account for the greater susceptibility to chemical toxicity of various sensitive subpopulations, including infants and children. Intraspecies variability in toxicokinetics can be better quantified now because of better data and advances in modeling techniques.

A high degree of inter-individual variability (2-to-30-fold) in response to chemical exposure has been reported (Weil, 1972; Krasovskii, 1976). Hattis has shown that human variability in response to some medications may range over more than 3 orders of magnitude (>1,000-fold) (Hattis, 1996a; 1996b). Similar inter-individual variability has been shown in airway responsiveness and lung volume among normal and asthmatic subjects (O'Connor et al*.,* 1987; Bylin et al*.,* 1995). In a study of asthmatic subjects, Horstman (1986) found that there was a 7-fold distribution in the range of sulfur dioxide concentrations required to produce bronchoconstriction. Thus, it is reasonable to conclude that asthmatics may be at least seven times as sensitive to the effects of sulfur dioxide as normal individuals. The inter-individual variability has been recently modeled, indicating a distribution that ranges from 1 to >20 with a value of 10 for the 85th percentile (Gillis et al*.,* 1997). Thus, based on this analysis, the use of a 10-fold uncertainty factor might not be protective of approximately 15% of the population. Further research into the considerations, circumstances, subpopulations, and endpoints of greater susceptibility is needed.

OEHHA has, like U.S.EPA (1994a), generally applied a 10-fold uncertainty factor to address the greater susceptibility of sensitive individuals. In accordance with U.S.EPA guidelines, when an exposure level is estimated from a study that includes the assessment of a sensitive human sub-population, an intraspecies factor of 1 is used (U.S.EPA, 1994a). Since the true degree of variability of response in the human population is unknown, the effectiveness of this method in providing protection to nearly all individuals is uncertain.

As noted by Dourson and Stara (1983), the steepness of the dose-response relationship affects the adequacy of the uncertainty factor for sensitive individuals. They summarized the range of dose response slopes reported by Weil (1972), indicating that, based on studies of acute lethality, a 10-fold factor was health-protective in most cases (Weil, 1972). However, in our experience, dose response curves for acute lethality exposures are generally steeper than those for non-lethal acute or chronic exposures (Table E.14).

TABLE E.3.14. COMPARISON OF SLOPES OF MILD AND LETHAL EFFECTS[A].

Chemical	Mild Effects[b]	Lethality[c]
Acrolein (irritation)	3.3	14.4
Ammonia (irritation)	6.9	14.3
Vinyl chloride (CNS effects)	7.5	31.9

[a] Log-normal dose-response slope values are the mean of up to 5 studies.
[b] Human data for mild effects include: (Hine et al., 1961; Lester et al., 1963; MacEwen et al., 1970; Verberk, 1977).
[c] Animal LC_{50} studies include: (Silver and McGrath, 1948; Champeix and Catilina, 1967; Philippin et al., 1970; Prodan et al., 1975; Appelman et al., 1982; Kapeghian et al., 1982; U.S.EPA, 1992a; 1992b)

Because the true variability is unknown, there may be a portion of the population for whom the chronic RELs will not be protective. It is OEHHA's intent that the levels will protect the general population including those in the high end of susceptibility. As information defining susceptible individuals becomes available, it is our intent to adjust the methodology as necessary to protect such individuals.

E.3.5 Adequacy of the $UF_{H\text{-}k}$ for younger ages – newer analyses.

Dorne et al. (2001) evaluated the validity of the $10^{0.5}$ (3.16) human toxicokinetic subfactor in relation to CYP1A2 metabolism using published data on clearance (CL), AUC and peak plasma concentrations (Cmax) for caffeine, theophylline, theobromine, paraxanthine, and R-warfarin in human volunteers. After oral dosing, the variation (coefficient of variation, CV) in metabolic clearance in healthy adults of the first four compounds ranged from 25 to 63 percent (mean = 42 percent) in nine studies of 70 subjects. For i.v. dosing the variability of theophylline and R-warfarin ranged from 31 to 59 percent (mean = 43 percent) in four studies of 34 subjects. The authors concluded that in the case of kinetics of compounds metabolized by CYP1A2 "essentially the whole of the healthy adult population would be covered by the 3.16 kinetic default for both steady state (CL and AUC) and acute exposures (Cmax) assuming a normal distribution, while between <0.01 to 1.8% would be outside the default factor of 3.16 assuming a log-normal distribution". The authors identified population subgroups for which the default UF of 3.16 would be less protective. These included about one-half of pregnant women at term (based on caffeine at 38 weeks gestation), neonates (99-100 percent not covered), 13 percent of infants, but only 0.1 percent of children, who would have internal doses falling outside the default. It should be noted that these conclusions are based on a relatively few drugs administered orally or parenterally.

Ginsberg et al. (2002) also evaluated child/adult pharmacokinetic differences by analyzing the therapeutic drug literature. The authors identified about 100 chemicals with some pharmacokinetic (PK) data in children and a subset of 45 of these was selected for further study. Of the 45 chemicals, eight were excreted unchanged in urine, 18 had some form of CYP metabolism, six were unclassified, six were subject to glucuronidation, two to alcohol dehydrogenase, two to sulfation and one to glutathione conjugation. The subjects were classified as premature neonates (≤ 1 week, 7 chemicals), full-term neonates (≤ 1 week, 19 chemicals),

newborns (1 week-2 months, 14 chemicals), early infants (2-6 months, 7 chemicals), toddlers (6 mo-2 yr, 14 chemicals), preadolescents (2-12 yr, 26 chemicals), adolescents (12-18 yr, 7 chemicals) and adults (42 chemicals). The kinetic parameters evaluated (number of chemicals) were AUC (9), clearance (27), Cmax (5), half-life ($t_{1/2}$, 41), and volume of distribution (Vd, 25).

Multiple regression analysis was used to evaluate relationships between age groups and the log mean PK parameter value across chemicals. In general, for many chemicals, early life stages (premature and full-term neonates, newborns 1 week to 2 months) appeared to be different from adults in terms of clearance, $t_{1/2}$, and Vd. For 40 chemicals with half-life data, the analysis showed that half-lives in premature neonates were about four-fold longer than in adults ($P < 0.001$) and about two-fold longer in full term neonates to two months of age ($P < 0.001$). For 27 chemicals with clearance data, premature to two months of age infants showed significantly lower clearance ($P<0.01$) and six months to 12-year-old children significantly higher clearance ($P<0.0001$) than adults. For the CYP1A2 substrates caffeine and theophylline, neonates to infants two months of age showed about four to nine-fold longer half-lives than adults while older age groups six months-12 years had significantly shorter half-lives than adults. A similar pattern was observed with the CYP3A substrates (e.g., alfentanil, carbamazepine, fentanyl, lignocaine).

The overall study results indicate that premature and full-term neonates tend to have three to nine times longer half-lives than adults for the drugs studied. Like the previous work of Renwick et al. (2000) and Dorne et al. (2001) noted above, the drugs studied were administered orally or parenterally and not via inhalation. While some of the same metabolic pathways are no doubt involved, it is difficult to make direct extrapolations from drugs to environmental toxicants. The authors note that three of the included chemicals, chloral hydrate, dichloroacetic acid and trichloroacetic acid, are major metabolites of trichloroethylene (TCE) and tetrachloroethylene (PCE), both important environmental contaminants.

Dorne et al. (2005a) estimated intraspecies pharmacokinetic uncertainty factors based on analysis of a database on human variability in phase I metabolism (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, hydrolysis, alcohol dehydrogenase (ADH)), phase II metabolism (N-acetyltransferases (NAT), glucuronidation, glycine conjugation, sulfation) and renal excretion. The authors derived pathway-specific $UF_{H\text{-}k}$s covering 95%, 97.5%, and 99% of the population of healthy adults, and other subgroups. For healthy adults exposed to toxicants metabolized by monomorphic pathways (CYP1A2, CYP2A6, CYP2E1, CYP3A4, ADH, hydrolysis, glucuronidation, sulfation, glycine conjugation) the $UF_{H\text{-}k}$ of 3.16 was adequate to cover more than 99% of the population. However, for toxicants subject to polymorphic pathways, particularly CYP2C19 (99% - UF of 52) and CYP2D6 (99% - UF of 26) poor metabolizers and NAT slow acetylators (99% - UF of 5.2), these subpopulations were not adequately covered by a 3.16 $UF_{H\text{-}k}$. Children and neonates were among the subgroups analyzed. Children exposed to toxicants metabolized by CYP2C19 (99% - UF of 9.0) and CYP2D6 (99% - UF of 45) were not adequately protected by a UF of 3.16. Neonates were not adequately protected by the CYP1A2 (99% - UF of 14), CYP3A4 (99% - UF of 12), glucuronidation (99% - UF of 12), and glycine conjugation (99% - UF of 28) pathways and only marginally by the renal excretion path (99% - UF of 3.4). All of the compounds in the database evaluated were administered by the oral or intravenous routes. In addition, the UFs are estimated from internal dose metrics (AUCs or Cmaxs) for the parent compounds assuming that it is the toxicant of

concern. This may not be the case with many environmental toxicants of concern. The authors argue for the use of pathway-specific UFs in risk assessment instead of defaults. This may be feasible in some instances where metabolism, modes of action, and potential polymorphisms are well understood. However, there will still be a need for adequately protective defaults for sensitive subgroups when this is not the case. In view of the results of the authors' analysis it is apparent the UF_{H-k} of 3.16 is not adequately protective for infants and many children.

PBPK models can give useful predictions of how the body handles a particular chemical and its metabolites. The models address issues of internal body or tissue dosimetry, route to route extrapolation, and, in some cases, interspecies extrapolation. To date relatively few published models for various environmental pollutants address infant and child exposure in a systematic fashion. This is parallel to the bulk of toxicity testing in animals which is usually initiated in young adult animals.

Pelekis et al. (2001) used a physiological model to derive adult and child pharmacokinetic UFs for selected volatile organic compounds (VOCs). The chemicals modeled were dichloromethane (DCM), tetrachloroethylene (PCE), toluene (TOL), m-xylene (XYL), styrene (ST), carbon tetrachloride (CATE), chloroform (CHLO), and trichloroethylene (TCE). Adult models of low (50 kg) and high (90 kg) body weight were compared with a 10 kg-based child model. Fat contents varied from 51 percent for the 90 kg adult model to 17 percent for the 10 kg child. Ventilation:perfusion ratios varied from 0.76 (50 kg) to 1.38 (10 kg). Fractional liver flows (of cardiac output) ranged from 0.11 (50 kg) to 0.34 (90 kg). All PBPK models were flow-limited with exposure by inhalation, arterial circulation to Fat, Slowly Perfused, Rapidly Perfused and Liver model compartments, metabolism in the Liver, and combination of compartment outputs in venous blood. The arterial and venous bloods were not explicitly modeled, nor were VOC metabolites specifically modeled. A range of physiological parameters (blood:air and tissue:blood) was used for each body model and the eight VOC chemicals based on literature values.

Simulations involved exposure to one ppm VOC and estimation of arterial and venous blood concentrations (CA, CV), and tissue concentrations (Ci) after 30 days continuous exposure. A comparison of the two adult models (Adult high/Adult low) shows relatively few significant departures from unity for the dose metrics estimated. CATE ratios ranged from 2.85 ($C_{\text{rapidly perfused}}$) to 1.71 ($C_{\text{liver}}$). DCM ranged from 0.29 (C_{liver}) to 1.04 (C_{arterial} blood). Comparisons of the Adult high/Child average from the PBPK model show some larger differences. For the C_{liver} dose metric the PBPK models predicted the following Adult/Child values: ST (0.033), XYL (0.037), TCE (0.061), DCM (0.092), CHLO (0.11). These model predictions would indicate up to a 30-fold higher concentration of the VOC chemicals in child liver than in adult liver via the inhalation route.

While this is a useful approach involving important environmental toxicants and a relevant exposure route, the models and dose metrics employed address only the parent compounds where relevant toxic effects may be more closely related to the tissue dosimetry of metabolites, which were not specifically modeled. The use of a single child body weight is insufficient to assess the full range of physiological variability throughout development, particularly in the neonatal period. It is worth noting, however, that the higher concentrations of the VOCs in a child's liver

might be expected to result in higher peak concentrations of metabolites of those compounds in the liver.

E.3.6 Adequacy of the UF_{H-k} for Younger Ages – Indications from PBPK Modeling

The results of limited PBPK modeling with age-specific parameters and a range of about 20 chemicals are summarized in Table E3.13. For a variety of dose metrics for parent chemicals and metabolites it appears that a UF_{H-k} of $\sqrt{10}$ may be inadequate for one or more of the age-group models evaluated. Most frequently the newborn models showed the greatest child/adult ratios. It is important to note that the large majority of the studies and PBPK modeling exercises described above involve relatively short-term exposures that represent environmental, occupational, or therapeutic scenarios. Extreme situations of short-term high exposures or very long-term low level exposures were not simulated. Also considerable variation in child breathing rates was not modeled in a systematic fashion. Despite these limitations the results are considered indicative of the types of exposures of greatest concern with respect to infants and children.

E.4 Toxicokinetic Model Parameters for Individual Chemicals

This section provides a sampling of the parameters used in the PBPK modeling (Table E.3.13). Not all the chemical or all the age-specific parameters are given but the early age groups (ages 0-6 yr) have been emphasized.

TABLE E.4.1. PBPK MODEL PARAMETERS FOR FURAN: 0-6 YEARS OF AGE

Tissue/Compartment	Volume, Vi L	Flow, Qi, L/hr	Partition, Pi tissue/blood	Metabolism
0-6 yr Model				
Fat, f	(1)	0.053*Qtot	33.39	
Liver l	(2)	0.0795*Qtot	4.69	Cart*Ql
Muscle, m	(3)	0.03*Qtot	3.24	
Brain, brain	(4)	(8)	8.82	
Lung, Vlu	(5)	Qtot	4.69	
Lung Alveoli, Valv	0.9*Vlu	0.93*Qtot	4.69	
Lung bronchi,Vbr	0.1*Vlu	0.07*Qtot	4.69	
Other body	BW-(Vf + Vl + Vlu + Vbrain + Vm)	Qtot – (Qf + Ql + Qm + Qbrain)	4.69	
Alveolar ventilation, Qalv		0.8*Qtot		
Cardiac Output, Qtot		(6)		
Blood:Air, Pb			2.47	
Body weight, BW	(7)			

Age (yr)-specific regressions : (1) Vf = (0.0162*Age^5 – 1.9784*Age^4 + 51.963*Age^3 – 459.38*Age^2 +1566.8*Age + 1004.2)/1000; (2)Vl = (0.0072*Age^5 – 0.3975*Age^4 + 7.9052*Age^3 – 65.624*Age^2 + 262.02*Age + 157.52)/1000; (3) Vm = (-0.0623*Age^5 + 2.3433*Age^4 – 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2)/1000; (4) Vbrain = (1E4*((Age + 0.213)/(6.030 + 6.895*Age)))/1000; (5) Vlu = (-0.0346*Age^4 + 1.5069*Age^3 – 20.31*Age^2 + 123.99*Age + 59.213)/1000; (6) Qtot = 0.012*Age^3 – 1.2144*Age^2 + 40.324*Age + 44.414; (7) BW = (-1.9*Age^4 + 72.8*Age^3 – 813.1*Age^2 + 5535.6*Age + 4453.7)/1000; (8) Qbrain = -0.0024*Age^4 + 0.1305*Age^3 – 2.4822*Age^2 + 18.025*Age + 15.197. For 7-10 yr model Qf = 0.05*Qtot; Ql = 0.118*Qtot; Qm = 0.045*Qtot; Qbrain = 0.159*Qtot; For 11-18yr model Qf = 0.044*Qtot; Ql = 0.136*Qtot; Qm = 0.068*Qtot; Qbrain = 0.116*Qtot. For adult Qf = 0.052*Qtot; Ql = 0.26*Qtot; Qm = 0.1648Qtot; Qbrain = 0.1148Qtot. (Price, 2003)

TABLE E.4.2. PBPK MODEL PARAMETERS FOR MTBE: 0-6 YEARS OF AGE

Tissue/Compartment	Volume, Vi L	Flow, Qi, L/hr	Partition, Pi tissue/blood	Metabolism
0-6 yr Model				
Fat, f	(1)	0.053*Qtot	4.79	
Liver, l	(2)	0.0795*Qtot	0.723	Vmax1, Km1 Vmax2, Km2
Muscle, m	(3)	0.03*Qtot	1.181	
VRG, vrg	(4)	0.674*Qtot	0.723	
Lung, Vlu	(5)	Qtot	0.723	
Kidneys, kid		0.164*Qtot		
Lung Alveoli, Valv	0.9*Vlu	0.93*Qtot	0.723	
Lung bronchi,Vbr	0.1*Vlu	0.07*Qtot	0.723	
Alveolar ventilation, Qalv		0.8*Qtot		
Cardiac Output, Qtot		(6)		
Blood:Air, Pb			17.7	
Body weight, BW	(7)			

Age (yr)-specific regressions : (1) Vf = (0.0162*Age^5 – 1.9784*Age^4 + 51.963*Age^3 – 459.38*Age^2 +1566.8*Age + 1004.2)/1000; (2)Vl = (0.0072*Age^5 – 0.3975*Age^4 + 7.9052*Age^3 – 65.624*Age^2 + 262.02*Age + 157.52)/1000; (3) Vm = (-0.0623*Age^5 + 2.3433*Age^4 – 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2)/1000; (4) Vkid = (9.373E-4*Age^5 – 0.0569*Age^4 + 1.1729*Age^3 – 10.34*Age^2 + 44.604*Age + 28.291)/1000; (5) Vlu = (-0.0346*Age^4 + 1.5069*Age^3 – 20.31*Age^2 + 123.99*Age + 59.213)/1000; (6) Qtot = 0.012*Age^3 – 1.2144*Age^2 + 40.324*Age + 44.414; (7) BW = (-1.9*Age^4 + 72.8*Age^3 – 813.1*Age^2 + 5535.6*Age + 4453.7)/1000; For 7-10 yr model Qf = 0.05*Qtot; Ql = 0.118*Qtot; Qm = 0.045*Qtot; Qkid = 0.12*Qtot; For 11-18yr model Qf = 0.044*Qtot; Ql = 0.136*Qtot; Qm = 0.068*Qtot; Qkid = 0.136*Qtot. For adult Qf = 0.052*Qtot; Ql = 0.26*Qtot; Qm = 0.1648Qtot; Qkid = 0.26Qtot. Vmax1 = $3.38E\text{-}5*BW^{0.75}$; Vmax2 = $6.2E\text{-}6*BW^{0.75}$ mol/hr; Km1 = 6.17E-5M; Km2 = 3.8E-6M.

TABLE E.4.3. PBPK MODEL PARAMETERS FOR PCE: 0-6 YEARS OF AGE

Tissue/Compartment	Volume, Vi L	Flow, Qi, L/hr	Partition, Pi tissue/blood	Metabolism
Fat 1, f1	(1) 0.8*Vf	0.615*0.053*Qtot	125.2	
Fat 2, f2	(1) 0.2*Vf	0.385*0.053*Qtot	125.2	
Liver l	(2)	0.0795*Qtot	5.28	Vmax1, Km1,K2
Muscle, m	(3)	0.03*Qtot	6.11	
VRG, vrg	BW – (Vf+Vl+Vm+Vlu)	0.674*Qtot	5.06	
Lung, Vlu	(4)	Qtot	5.06	
Lung Alveoli, Valv	0.9*Vlu	0.93*Qtot	5.06	
Lung bronchi,Vbr	0.1*Vlu	0.07*Qtot	5.06	
Alveolar ventilation, Qalv		Qtot		
Cardiac Output, Qtot		(5)		
Blood:Air, Pb			11.58	
Body weight, BW	(6)			

Age (yr)-specific regressions : (1) Vf = (0.0162*Age^5 – 1.9784*Age^4 + 51.963*Age^3 – 459.38*Age^2 +1566.8*Age + 1004.2)/1000; (2)Vl = (0.0072*Age^5 – 0.3975*Age^4 + 7.9052*Age^3 – 65.624*Age^2 + 262.02*Age + 157.52)/1000; (3) Vm = (-0.0623*Age^5 + 2.3433*Age^4 – 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2)/1000; (4) Vlu = (-0.0346*Age^4 + 1.5069*Age^3 – 20.31*Age^2 + 123.99*Age + 59.213)/1000; (5) Qtot = 0.012*Age^3 – 1.2144*Age^2 + 40.324*Age + 44.414; (6) BW = (-1.9*Age^4 + 72.8*Age^3 – 813.1*Age^2 + 5535.6*Age + 4453.7)/1000; For 7-10 yr model Qf = 0.05*Qtot; Ql = 0.118*Qtot; Qm = 0.045*Qtot; Qkid = 0.12*Qtot; For 11-18yr model Qf = 0.044*Qtot; Ql = 0.136*Qtot; Qm = 0.068*Qtot; Qkid = 0.136*Qtot. For adult Qf = 0.052*Qtot; Ql = 0.26*Qtot; Qm = 0.1648Qtot; Qkid = 0.26Qtot. Vmax1 = 1.69E-6*$BW^{0.75}$mol/hr; Km1 = 4.6E-5M; K2 = 2.0*$BW^{-0.25}$.

TABLE E.4.4. PBPK MODEL PARAMETERS FOR BAP: 0-6 YEARS OF AGE

Tissue/Compartment	Volume, Vi L	Flow, Qi, L/hr	Partition, Pi tissue/blood	Metabolism
Fat , f	(1)	0.053*Qtot	294.7	
Liver, l	(2)	0.0795*Qtot	7.0	Vmax1, Km1, Vmaxlu Kmlu
Muscle, m	(3)	0.03*Qtot	4.0	
KVRG, kvrg	BW – (Vf+Vl+Vm+Vlu)	Qtot – (Qf + Ql + Qm)	4.0	
Lung, Vlu	(4)	Qtot		
Lung Alveoli, Valv	0.9*Vlu	0.93*Qtot	1.3	
Lung bronchi,Vbr	0.1*Vlu	0.07*Qtot	2.3	
Alveolar ventilation, Qalv		Qtot		
Cardiac Output, Qtot		(5)		
Blood:Air, Pb			10	
Body weight, BW	(6)			

Age (yr)-specific regressions : (1) Vf = (0.0162*Age^5 – 1.9784*Age^4 + 51.963*Age^3 – 459.38*Age^2 +1566.8*Age + 1004.2)/1000; (2)Vl = (0.0072*Age^5 – 0.3975*Age^4 + 7.9052*Age^3 – 65.624*Age^2 + 262.02*Age + 157.52)/1000; (3) Vm = (-0.0623*Age^5 + 2.3433*Age^4 – 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2)/1000; (4) Vlu = (-0.0346*Age^4 + 1.5069*Age^3 – 20.31*Age^2 + 123.99*Age + 59.213)/1000; (5) Qtot = 0.012*Age^3 – 1.2144*Age^2 + 40.324*Age + 44.414; (6) BW = (-1.9*Age^4 + 72.8*Age^3 – 813.1*Age^2 + 5535.6*Age + 4453.7)/1000; For 7-10 yr model Qf = 0.05*Qtot; Ql = 0.118*Qtot; Qm = 0.045*Qtot; Qkid = 0.12*Qtot; For 11-18yr model Qf = 0.044*Qtot; Ql = 0.136*Qtot; Qm = 0.068*Qtot; Qkid = 0.136*Qtot. For adult Qf = 0.052*Qtot; Ql = 0.26*Qtot; Qm = 0.1648Qtot; Qkid = 0.26Qtot. Vmax1 = 1.7E-9*$(BW/0.25)^{0.75}$mol/hr; Km1 = 5.5E-6M; Vmaxlu = 1.2E-11*$(BW/0.25)^{0.75}$ mol/hr, Kmlu = 2.2E-7M .

TABLE E.4.5. PBPK-RT MODEL PARAMETERS FOR NAP/NO: 0-5 YEARS OF AGE

Tissue/Compartment	Volume, Vi L	Flow, Qi, L/hr	Partition, Pi tissue/blood NAP/NO	Metabolism
Fat , f	(1)	0.053*Qtot	160/22.9	
Liver, l	(2)	0.0795*Qtot	7.0/7.0	Vmax1, Km1, Vmax2, Km2, Km2ih,Vmax3, Km3GSH, Km3NO
Muscle, m	(3)	0.03*Qtot	4.0/4.0	
VRG, vrg	BW – (Vf+Vl+Vm +Vlu+Vblood)	Qtot – (Qf + Ql + Qm)	4.0/4.0	
Vblood, blood	0.075*BW			
Lung, Vlu	(4)	Qtot		Vmaxlu, Kmlu, Vmax2lu, Km2, Km2ih, Vmax3, Km3GSH, Km3NO
Lung URT, Vua	0.0026*Vlu	0.0025*Qtot		
Lung CA,Vca	0.018*Vlu	0.0075*Qtot		
Lung TB,Vtb	0.043*Vlu	0.0067*Qtot		
Lung PU, Vpu	0.9378Vlu	0.983*Qtot		
Alveolar ventilation, Qalv		0.82*Qtot		
Cardiac Output, Qtot		(5)		
Blood:Air, Pb			571/571	
Body weight, BW	(6)			

Age (yr)-specific regressions : (1) Vf = 0.0162*Age^5 – 1.9784*Age^4 + 51.963*Age^3 – 459.38*Age^2 +1566.8*Age + 1004.2; (2)Vl = 0.0072*Age^5 – 0.3975*Age^4 + 7.9052*Age^3 – 65.624*Age^2 + 262.02*Age + 157.52; (3) Vm = -0.0623*Age^5 + 2.3433*Age^4 – 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2; (4) Vlu = -0.0346*Age^4 + 1.5069*Age^3 – 20.31*Age^2 + 123.99*Age + 59.213; (5) Qtot = (0.012*Age^3 – 1.2144*Age^2 + 40.324*Age + 44.414)*(1000/60); (6) BW = -1.9*Age^4 + 72.8*Age^3 – 813.1*Age^2 + 5535.6*Age + 4453.7; For 7-10 yr model Qf = 0.05*Qtot; Ql = 0.118*Qtot; Qm = 0.045*Qtot; Qkid = 0.12*Qtot; For 11-18yr model Qf = 0.044*Qtot; Ql = 0.136*Qtot; Qm = 0.068*Qtot; Qkid = 0.136*Qtot. For adult Qf = 0.052*Qtot; Ql = 0.26*Qtot; Qm = 0.1648Qtot; Qkid = 0.26Qtot. Vmax1 (P450) = 2.46E-2*MPl*Vl/(BW/250)$^{0.25}$µmol/min; Km1 = 0.003mM; Vmaxlu (P450) = 2.45E-3*MPlu*Vlu/(BW/250)$^{0.25}$ µmol/min, Kmlu = 0.006mM . Vmax2l (Epoxide Hydrolase) = 4.0E-3*MPl*Vl/(BW/250)$^{0.25}$ µmol/min, Km2 = 0.001 mM, Km2ih = 2.0E-4 mM, Vmax2lu = 9.0E-3*MPlu*Vlu/(BW/250)$^{0.25}$ µmol/min, Km2lu = 0.001 mM, Km2luih = 2E-4 mM. Vmax3 (GST) = 0.5*CPl*Vl/(BW/250)$^{0.25}$ µmol/min, Km3(GSH) = 3.3 mM, Km3(NO) = 0.05 mM, Vmax3lu = 0.4*CPlu*Vlu/(BW/250)$^{0.25}$ µmol/min. MPl = 14.5 mg/mL, MPlu = 3.0 mg/mL, CPl = 58 mg/mL, CPlu = 54 mg/mL tissue.

TABLE E.4.6. PBPK-RT MODEL PARAMETERS FOR BD/BMO: 0-5 YEARS OF AGE

Tissue/Compartment	Volume, Vi L	Flow, Qi, L/hr	Partition, Pi tissue/blood BD/BMO	Metabolism
Fat , f	(1)	0.053*Qtot	118.2/1.808	
Liver, l	(2)	0.0795*Qtot	5.49/0.654	Vmax1, Km1, Vmax2, Km2, Km2ih,VmaxG, KmG_{GSH}, KmG_{BMO} Vmax3, Km3
Muscle, m	(3)	0.03*Qtot	5.26/0.653	
VRG, vrg	BW – (Vf+Vl+Vm +Vlu+Vblood)	Qtot – (Qf + Ql + Qm)	5.34/0.635	
Vblood, blood	0.075*BW			
Lung, Vlu	(4)	Qtot		Vmaxlu, Kmlu, K1, K2, Vmax3lu
Lung URT, Vua	0.0026*Vlu	0.0025*Qtot		
Lung CA,Vca	0.018*Vlu	0.0075*Qtot		
Lung TB,Vtb	0.043*Vlu	0.0067*Qtot		
Lung PU, Vpu	0.9378Vlu	0.983*Qtot		
Alveolar ventilation, Qalv		0.82*Qtot		
Cardiac Output, Qtot		(5)		
Blood:Air, Pb			1.5/60	
Body weight, BW	(6)			

Age (yr)-specific regressions : (1) Vf = 0.0162*Age^5 – 1.9784*Age^4 + 51.963*Age^3 – 459.38*Age^2 +1566.8*Age + 1004.2; (2)Vl = 0.0072*Age^5 – 0.3975*Age^4 + 7.9052*Age^3 – 65.624*Age^2 + 262.02*Age + 157.52; (3) Vm = -0.0623*Age^5 + 2.3433*Age^4 – 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2; (4) Vlu = -0.0346*Age^4 + 1.5069*Age^3 – 20.31*Age^2 + 123.99*Age + 59.213; (5) Qtot = (0.012*Age^3 – 1.2144*Age^2 + 40.324*Age + 44.414)8(1000/60); (6) BW = -1.9*Age^4 + 72.8*Age^3 – 813.1*Age^2 + 5535.6*Age + 4453.7; For 7-10 yr model Qf = 0.05*Qtot; Ql = 0.118*Qtot; Qm = 0.045*Qtot; Qkid = 0.12*Qtot; For 11-18yr model Qf = 0.044*Qtot; Ql = 0.136*Qtot; Qm = 0.068*Qtot; Qkid = 0.136*Qtot. For adult Qf = 0.052*Qtot; Ql = 0.26*Qtot; Qm = 0.1648Qtot; Qkid = 0.26Qtot. Vmax1 (P450) = 7.08E-2*MPl*Vl*$(7E4/BW)^{0.25}$ /60 µmol/min; Km1 = 0.00514mM; Vmaxlu (P450) = 9.09E-3*MPlu*Vlu*$(7E4/BW)^{0.25}$ /60 µmol/min, Kmlu = 0.002mM. Vmax2 (Epoxide Hydrolase) = 1.1*MPl*Vl*$(7E4/BW)^{0.25}$/60 µmol/min, Km2 = 0.58 mM, Km2ih = 0.116 mM, K1 = 0.1914*Vlu*Mplu*$(7E4/BW)^{-0.25}$/60 µmol/min. VmaxGl (GST) = 2.71*CPl*Vl*$(7E4/BW)^{0.25}$/60 µmol/min, Km3G(GSH) = 0.1 mM, KmG(BMO) = 10.4 mM, K2 (GST) =0.1536*Vlu*Cplu*$(7E4/BW)^{-0.25}$/60 µmol/min. Vmax3(P450) = 14.8*Vl*MPl*$(7E4/BW)^{0.25}$/60 µmol/min , Vmax3lu = 1.7*Vlu*Cplu*$(7E4/BW)^{0.25}$/60 µmol/min. MPl = 14.5 mg/mL, MPlu = 3.0 mg/mL, CPl = 58 mg/mL, CPlu = 54 mg/mL tissue.

TABLE E.4.7. PBPK MODEL PARAMETERS FOR BD/BMO/DEB: 0-5 YEARS OF AGE

Tissue/ Compartment	Volume, Vi L	Flow, Qi, L/hr	Partition, Pi tissue/blood BD/BMO/DEB	Metabolism
Fat , f	(1)	0.053*Qtot	118.2/1.808/0.715	
Liver, l	(2)	0.0795*Qtot	5.49/0.6545/0.7	Vmaxl, Km,Vmaxl1 Km1, Km1ih, Vmaxl2, $Km2_{GSH}$, $Km2_{BMO}$ Vmaxl3, Km3, Km3ih, Ke
Muscle, m	(3)	0.03*Qtot	5.26/0.6533/0.697	
VRG, kvrg	BW – (Vf+Vl+Vm+Vlu)	Qtot – (Qf + Ql + Qm)	5.34/0.6348/0.6	
Lung, Vlu	(4)	Qtot	4.02/0.4725/0.6	Vmaxlu, Kmlu, K1, K2,Ke
Lung Alveoli, Valv	0.9*Vlu	0.93*Qtot		Vmax3pu
Lung bronchi,Vbr	0.1*Vlu	0.07*Qtot		Vmax3br
Alveolar ventilation, Qalv		0.82*Qtot		
Cardiac Output, Qtot		(5)		
Blood:Air, Pb			1.5/60/300	
Body weight, BW	(6)			

Age (yr)-specific regressions : (1) Vf = (0.0162*Age^5 – 1.9784*Age^4 + 51.963*Age^3 – 459.38*Age^2 +1566.8*Age + 1004.2)/1000; (2)Vl = (0.0072*Age^5 – 0.3975*Age^4 + 7.9052*Age^3 – 65.624*Age^2 + 262.02*Age + 157.52)/1000; (3) Vm = (-0.0623*Age^5 + 2.3433*Age^4 – 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2)/1000; (4) Vlu = (-0.0346*Age^4 + 1.5069*Age^3 – 20.31*Age^2 + 123.99*Age + 59.213)/1000; (5) Qtot = 0.012*Age^3 – 1.2144*Age^2 + 40.324*Age + 44.414; (6) BW = (-1.9*Age^4 + 72.8*Age^3 – 813.1*Age^2 + 5535.6*Age + 4453.7)/1000; For 7-10 yr model Qf = 0.05*Qtot; Ql = 0.118*Qtot; Qm = 0.045*Qtot; Qkid = 0.12*Qtot; For 11-18yr model Qf = 0.044*Qtot; Ql = 0.136*Qtot; Qm = 0.068*Qtot; Qkid = 0.136*Qtot. For adult Qf = 0.052*Qtot; Ql = 0.26*Qtot; Qm = 0.1648Qtot; Qkid = 0.26Qtot. Vmax1 (P450) = $7.08E\text{-}8*(70/BW)^{0.25}$mol/hr/mg MPl/Ltissue; Km1 = 5.14E-6M; Vmaxlu = $9.0E\text{-}9*(70/BW)^{0.25}$ mol/hr/mg MPlu/Ltissue, Kmlu = 2.0E-6M . Vmaxl1(EH) = $1.1E\text{-}6*(70/BW)^{0.25}$ mol/hr/mg MPl/Ltissue, Km1 = 5.8E-4 M, Km1ih = 1.16E-4 M, K1 = $0.1914*(70/BW)^{-0.25}$ mol/hr/mg MPlu/Ltissue. Vmaxl2 = $2.71E\text{-}6*(70/BW)^{0.25}$ mol/hr/mg CPl/Ltissue, $Km2_{GST}$ = 1.04E-2M. $Km2_{BMO}$ = 1.0E-4M, K2 = $0.1536*(70/BW)^{-0.25}$ mol/hr/mg CPlu/Ltissue. Vmaxl3 (P450) = $1.48E\text{-}5*(70/BW)^{0.25}$ mol/hr, Km3 = 1.56E-5M, Km3ih = 3.12E-6M, Vmax3pu = $1.7E\text{-}6*(70/BW)^{0.25}$ mol/hr, Vmax3br = $2.0E\text{-}7*(70/BW)^{0.25}$ mol/hr. Ke(DEB elimination) = $0.6*(70/BW)^{-0.25}$ /hr

TABLE E.4.8. PBPK-RT MODEL PARAMETERS FOR STYRENE/SO: 0-5 YEARS OF AGE

Tissue/ Compartment	Volume, Vi L	Flow, Qi, L/hr	Partition, Pi tissue/blood ST/SO	Metabolism
Fat , f	(1)	0.053*Qtot	93.8/6.1	
Liver, l	(2)	0.0795*Qtot	2.71/2.6	Vmax1, Km, Vmax2, Km2,VmaxG, KmG_{GSH}, KmG_{SO}
Muscle, m	(3)	0.0304*Qtot	1.96/1.5	
VRG, vrg	BW – (Vf+Vl+Vm+ Vlu+Vblood)	Qtot – (Qf + Ql + Qm)	2.60/0.6	
Vblood, blood	0.075*BW			
Lung, Vlu	(4)	Qtot		
Lung URT, Vua	0.0026*Vlu	0.0025*Qtot		Vmaxua, Kmlu, Vmaxua2, Kmlu2, VmaxGua, KmG_{GSH}, Km_{GSO}
Lung CA,Vca	0.018*Vlu	0.0075*Qtot		
Lung TB,Vtb	0.043*Vlu	0.0067*Qtot		Vmaxtb, Kmlu, Vmaxtb2, Kmlu2, VmaxGtb, KmG_{GSH}, Km_{GSO}
Lung PU, Vpu	0.9378Vlu	0.983*Qtot		
Alveolar ventilation, Qalv		0.82*Qtot		
Cardiac Output, Qtot		(5)		
Blood:Air, Pb			48/2000	
Body weight, BW	(6)			

Age (yr)-specific regressions : (1) Vf = 0.0162*Age^5 – 1.9784*Age^4 + 51.963*Age^3 – 459.38*Age^2 +1566.8*Age + 1004.2; (2)Vl = 0.0072*Age^5 – 0.3975*Age^4 + 7.9052*Age^3 – 65.624*Age^2 + 262.02*Age + 157.52; (3) Vm = -0.0623*Age^5 + 2.3433*Age^4 – 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2; (4) Vlu = -0.0346*Age^4 + 1.5069*Age^3 – 20.31*Age^2 + 123.99*Age + 59.213; (5) Qtot = (0.012*Age^3 – 1.2144*Age^2 + 40.324*Age + 44.414)8(1000/60); (6) BW = -1.9*Age^4 + 72.8*Age^3 – 813.1*Age^2 + 5535.6*Age + 4453.7; For 7-10 yr model Qf = 0.05*Qtot; Ql = 0.118*Qtot; Qm = 0.045*Qtot; Qkid = 0.12*Qtot; For 11-18yr model Qf = 0.044*Qtot; Ql = 0.136*Qtot; Qm = 0.068*Qtot; Qkid = 0.136*Qtot. For adult Qf = 0.052*Qtot; Ql = 0.26*Qtot; Qm = 0.1648Qtot; Qkid = 0.26Qtot. Vmax1 (P450) = $0.033*(7E4/BW)^{0.25}$ µmol/min/mLtissue; Kmlu = 0.01mM; Vmaxua = Vmaxtb (P450) = $4.17E\text{-}5*(7E4/BW)^{0.25}$ µmol/min/mLtissue, Kmlu = 0.0175mM. Vmax2 (Epoxide Hydrolase) = $0.075*(7E4/BW)^{0.25}$ µmol/min/mLtissue, Km2 = 0.01 mM. Vmaxua2 = Vmaxtb2 = $0.0112*(7E4/BW)^{0.25}$ µmol/min/mLtissue, Kmlu2 = 0.0156 mM. VmaxGl (GST) = $0.467*(7E4/BW)^{0.25}$ µmol/min/mLtissue, KmG_{GSH} = 0.1 mM, KmG_{SO} = 2.5 mM, VmaxGua = VmaxGtb = $1.36*(7E4/BW)^{0.25}$ µmol/min/mLtissue.

TABLE E.4.9. PBPK MODEL PARAMETERS FOR VINYL CHLORIDE: 0-5 YEARS OF AGE

Tissue/Compartment	Volume, Vi L	Flow, Qi, L/hr	Partition, Pi tissue/blood	Metabolism
Fat , f	(1)	0.053*Qtot	20.7	
Liver, l	(2)	0.0795*Qtot	1.45	Vmax1, Km1, Vmax2 Km2
Muscle, m	(3)	0.03*Qtot	0.83	
VRG, kvrg	BW – (Vf+Vl+Vm +Vlu)	Qtot – (Qf + Ql + Qm)	1.45	
Lung, Vlu	(4)	Qtot		
Lung alveoli, Valv	0.9*Vlu	0.93*Qtot	1.45	
Lung bronchi,Vbr	0.1*Vlu	0.07*Qtot	1.45	
Alveolar ventilation, Qalv		0.82*Qtot		
Cardiac Output, Qtot		(5)		
Blood:Air, Pb			1.16	
Body weight, BW	(6)			

Age (yr)-specific regressions : (1) Vf = (0.0162*Age^5 – 1.9784*Age^4 + 51.963*Age^3 – 459.38*Age^2 +1566.8*Age + 1004.2)/1000; (2)Vl = (0.0072*Age^5 – 0.3975*Age^4 + 7.9052*Age^3 – 65.624*Age^2 + 262.02*Age + 157.52)/1000; (3) Vm = (-0.0623*Age^5 + 2.3433*Age^4 – 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2)/1000; (4) Vlu = (-0.0346*Age^4 + 1.5069*Age^3 – 20.31*Age^2 + 123.99*Age + 59.213)/1000; (5) Qtot = 0.012*Age^3 – 1.2144*Age^2 + 40.324*Age + 44.414; (6) BW = (-1.9*Age^4 + 72.8*Age^3 – 813.1*Age^2 + 5535.6*Age + 4453.7)/1000; For 7-10 yr model Qf = 0.05*Qtot; Ql = 0.118*Qtot; Qm = 0.045*Qtot; Qkid = 0.12*Qtot; For 11-18yr model Qf = 0.044*Qtot; Ql = 0.136*Qtot; Qm = 0.068*Qtot; Qkid = 0.136*Qtot. For adult Qf = 0.052*Qtot; Ql = 0.26*Qtot; Qm = 0.1648Qtot; Qkid = 0.26Qtot. Vmax1 = $4.0*BW^{0.75}$mg/hr; Km1 = 1.0 mg/L; Vmax2 = $0.1*BW^{0.75}$ mg/hr, Km2 = 10 mg/L .

TABLE E.4.10. PBPK MODEL PARAMETERS FOR TCE AND METABOLITES: 0-5 YEARS OF AGE

Tissue/Compartment	Volume, Vi L	Flow, Qi, L/hr	Partition, Pi tissue/blood TCE/CH/TCA/ TCOH/TCOG	Metabolism
Fat, f	(1)	0.053*Qtot	36.38/	
Liver, l	(2)	0.0795*Qtot	1.73/1.42/1.18/ 1.30/0.56	Vmax1, Km1 PTCA, PTCOH, KTCA, Vmax2,Km2
Muscle, m	(3)	0.03*Qtot	2.36/	
VRG, vrg	(4)	0.674*Qtot	1.73/	
Lung, Vlu	(5)	Qtot	2.61/1.65/0.54/ 0.78/1.06	
Kidneys, kid	(6)	0.164*Qtot	2.07/0.98/0.74/ 1.02/1.44	
Lung Alveoli, Valv	0.9*Vlu	0.93*Qtot	2.61/1.65/0.54/ 0.78/1.06	
Lung bronchi,Vbr	0.1*Vlu	0.07*Qtot	2.61/1.65/0.54/ 0.78/1.06	
Body (metabolite submodels)			/1.35/0.88/1.11/ 1.11	
Alveolar ventilation, Qalv		0.8*Qtot		
Cardiac Output, Qtot		(7)		
Blood:Air, Pb			15.91/	
Body weight, BW	(8)			

Age (yr)-specific regressions : (1) Vf = (0.0162*Age^5 – 1.9784*Age^4 + 51.963*Age^3 – 459.38*Age^2 +1566.8*Age + 1004.2)/1000; (2)Vl = (0.0072*Age^5 – 0.3975*Age^4 + 7.9052*Age^3 – 65.624*Age^2 + 262.02*Age + 157.52)/1000; (3) Vm = (-0.0623*Age^5 + 2.3433*Age^4 – 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2)/1000; (4) Vkid = (9.373E-4*Age^5 – 0.0569*Age^4 + 1.1729*Age^3 – 10.34*Age^2 + 44.604*Age + 28.291)/1000; (5) Vlu = (-0.0346*Age^4 + 1.5069*Age^3 – 20.31*Age^2 + 123.99*Age + 59.213)/1000; (6)Vkid = (9.373E-4*Age^5 – 0.0569*Age^4 + 1.1729*Age^3 – 10.34*Age^2 + 44.604*Age + 28.291)/1000 (7) Qtot = 0.012*Age^3 – 1.2144*Age^2 + 40.324*Age + 44.414; (8) BW = (-1.9*Age^4 + 72.8*Age^3 – 813.1*Age^2 + 5535.6*Age + 4453.7)/1000; For 7-10 yr model Qf = 0.05*Qtot; Ql = 0.118*Qtot; Qm = 0.045*Qtot; Qkid = 0.12*Qtot; For 11-18yr model Qf = 0.044*Qtot; Ql = 0.136*Qtot; Qm = 0.068*Qtot; Qkid = 0.136*Qtot. For adult Qf = 0.052*Qtot; Ql = 0.26*Qtot; Qm = 0.1648Qtot; Qkid = 0.26Qtot. Vmax1 (TCE→CH) = 2.49E-4*$BW^{0.75}$ mol/hr, Km1 = 3.51E-5M; Vmax2 (TCOH→TCOG) = 1.11E-4*$BW^{0.75}$ mol/hr, Km2 = 1.06E-4M. PTCA(CH→TCA) = 115*BW /hr; PTCOH (CH→TCOH) = 309*BW /hr; KTCA (TCOH→TCA) = 10 /hr. Urinary excretion rates /hr: KU_{TCA} = 1.55*BW; KU_{TCOH} = 1.14*BW; KU_{TCOG} = 32.8*BW. CH = chloral hydrate; TCA = trichloroacetic acid; TCOH = trichloroethanol; TCOG = trichloroethanol glucuronide.

TABLE E.4.11. PBPK MODEL PARAMETERS FOR DCM: 0-5 YEARS OF AGE

Tissue/Compartment	Volume, Vi L	Flow, Qi, L/hr	Partition, Pi tissue/blood	Metabolism
Fat, f	(1)	0.053*Qtot	7.239	
Liver, l	(2)	0.0795*Qtot	0.824	Vmax1, Km, Kfl
Muscle, m	(3)	0.03*Qtot	1.09	
VRG, vrg	(4)	0.674*Qtot	0.788	
Lung, Vlu	(5)	Qtot	0.552	
Lung Alveoli, Valv	0.9*Vlu	0.93*Qtot	0.552	Vmaxpu, Km, Kfpu
Lung bronchi,Vbr	0.1*Vlu	0.07*Qtot	0.552	Vmaxbr, Km, Kfbr
Alveolar ventilation, Qalv		0.8*Qtot		
Cardiac Output, Qtot		(6)		
Blood:Air, Pb			9.09	
Body weight, BW	(7)			

Age (yr)-specific regressions : (1) Vf = (0.0162*Age^5 – 1.9784*Age^4 + 51.963*Age^3 – 459.38*Age^2 +1566.8*Age + 1004.2)/1000; (2)Vl = (0.0072*Age^5 – 0.3975*Age^4 + 7.9052*Age^3 – 65.624*Age^2 + 262.02*Age + 157.52)/1000; (3) Vm = (-0.0623*Age^5 + 2.3433*Age^4 – 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2)/1000; (4) Vkid = (9.373E-4*Age^5 – 0.0569*Age^4 + 1.1729*Age^3 – 10.34*Age^2 + 44.604*Age + 28.291)/1000; (5) Vlu = (-0.0346*Age^4 + 1.5069*Age^3 – 20.31*Age^2 + 123.99*Age + 59.213)/1000; (6) Qtot = 0.012*Age^3 – 1.2144*Age^2 + 40.324*Age + 44.414; (7) BW = (-1.9*Age^4 + 72.8*Age^3 – 813.1*Age^2 + 5535.6*Age + 4453.7)/1000; For 7-10 yr model Qf = 0.05*Qtot; Ql = 0.118*Qtot; Qm = 0.045*Qtot; Qkid = 0.12*Qtot; For 11-18yr model Qf = 0.044*Qtot; Ql = 0.136*Qtot; Qm = 0.068*Qtot. For adult Qf = 0.052*Qtot; Ql = 0.26*Qtot; Qm = 0.1648Qtot; Qkid = 0.26Qtot. Vmaxl (P450) = 8.58E-5*$BW^{0.7}$ mol/hr; Vmaxpu = 0.9*1.46E-3*Vmaxl; Vmaxbr = 0.1*1.46E-3*Vmaxl, Km = 8.7E-6M; Kfl (GST) = 1.26*$BW^{-0.3}$, Kfpu = 0.9*0.242*Kfl, Kfbr = 0.1*0.242*Kfl

TABLE E.4.12. PBPK MODEL PARAMETERS FOR ETHYLENE/EO: 0-6 YEARS OF AGE

Tissue/Compartment	Volume, Vi L	Flow, Qi, L/hr	Partition, Pi tissue/blood ET/EO	Metabolism
Fat , f	(1)	0.053*Qtot	8.73/0.70	
Liver, l	(2)	0.0795*Qtot	2.05/0.89	ClrET ClrEO L/hr
Muscle, m	(3)	0.0304*Qtot	2.95/1.08	
VRG, vrg	BW – (Vf+Vl+Vm +Vlu+Vblood)	Qtot – (Qf + Ql + Qm)	2.18/1.03	
Vlubld, lung blood	0.0079*BW			
Vart, arterial blood	0.0178*BW			
Vven, venous blood	0.0533*BW			
Alveolar ventilation, Qalv		0.82*Qtot		
Cardiac Output, Qtot		(4)		
Blood:Air, Pb			0.22/61	
Body weight, BW	(5)			

Age (yr)-specific regressions : (1) Vf =(0.0162*Age^5 – 1.9784*Age^4 + 51.963*Age^3 – 459.38*Age^2 +1566.8*Age + 1004.2)/1000; (2)Vl = (0.0072*Age^5 – 0.3975*Age^4 + 7.9052*Age^3 – 65.624*Age^2 + 262.02*Age + 157.52)/1000; (3) Vm = (-0.0623*Age^5 + 2.3433*Age^4 – 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2)/1000; (4) Qtot = 0.012*Age^3 – 1.2144*Age^2 + 40.324*Age + 44.414; (5) BW = (-1.9*Age^4 + 72.8*Age^3 – 813.1*Age^2 + 5535.6*Age + 4453.7)/1000; For 7-10 yr model Qf = 0.05*Qtot; Ql = 0.118*Qtot; Qm = 0.045*Qtot; For 11-18yr model Qf = 0.044*Qtot; Ql = 0.136*Qtot; Qm = 0.068*Qtot; Qkid = 0.136*Qtot. For adult Qf = 0.052*Qtot; Ql = 0.26*Qtot; Qm = 0.1648Qtot; Qkid = 0.26Qtot. Metabolic clearance by liver: ClrET (P450) = $74.9*(70/BW)^{0.25}$ L/hr; ClrEO (EH+GST) = $1.53*(70/BW)^{0.25}$ L/hr. (Csanady et al., 2000; Price et al., 2003)

TABLE E.4.13. PBPK-RT MODEL PARAMETERS FOR STYRENE/SO ADULT

Tissue/Compartment	Volume, Vi L	Flow, Qi, L/hr	Partition, Pi tissue/blood ST/SO	Metabolism
Fat , f	0.19*BW	0.05*Qtot	93.8/6.1	
Liver, l	0.026*BW	0.26*Qtot	2.71/2.6	Vmaxl1, Kml1, Vmaxl2, Kml2eh, Kml2appVmaxl3, $Kml3_{GSH}$, $Kml3_{SO}$ Kdl
Muscle, m	0.541*BW	0.25*Qtot	1.96/1.5	
VRG, vrg	BW – (Vf+Vl+Vm +Vlu+Vblood)	Qtot – (Qf + Ql + Qm)	2.60/2.6	
Vlubld, lung blood	0.0079*BW			
Vart, arterial blood	0.0178*BW			
Vven, venous blood	0.0533*BW			
Lung tissue, Vlu	0.0076*BW			
Vluc, conducting zone, fs = 0.1	fs*Vlu			Vmaxlu1, Kmlu1, Vmaxlu2, Kmlu2, Vmaxlu3, $Kmlu3_{GSH}$, Kmlu3, $Kdlu_{SO}$
Vlua, alveolar zone	(1-fs)*Vlu			Vmaxlu1, Kmlu1, Vmaxlu2, Kmlu2, Vmaxlu3, $Kmlu3_{GSH}$, Kmlu3, $Kdlu_{SO}$
Alveolar ventilation, Qalv , L/hr		300		
Cardiac Output, Qtot , L/hr		372		
Blood:Air, Pb			70/2370	
Body weight, BW kg	70			

Vmaxl = 0.002 mmol/hr/mL tissue, Kml1 = 0.01 mM; Vmaxl2 = 0.0045, Kml2eh = 0.001, Kml2app = 0.01; Vmaxl3 = 0.028, Kml3G = 0.1, Kml3so = 2.5,Kdl = 0.2; Vmaxlu1 = 2.5E-6, Kmlu1 = 0.0175; Vmaxlu2 = 6.73E-4, Kmlu2 = 0.0156; Vmaxlu3 = 0.082, Kmlu3 = 0.082; Kmlu3G = 0.1, Kmlu3so = 2.5, Kdlu = 2.0. (Csanady et al., 2003)

TABLE E.4.14. PBPK MODEL PARAMETERS FOR CARBON TETRACHLORIDE: 0-6 YEARS OF AGE

Tissue/Compartment	Volume, Vi L	Flow, Qi, L/hr	Partition, Pi tissue/blood	Metabolism
Fat , f	(1)	0.053*Qtot	79.4	
Liver, l	(2)	0.0795*Qtot	3.14	Vmax1, Km
Muscle, m	(3)	0.03*Qtot	1.00	
VRG, vrg	BW – (Vf+Vl+Vm+Vlu)	Qtot – (Qf + Ql + Qm)	1.00	
Lung, Vlu	(4)	Qtot		
Lung alveoli, Valv	0.9*Vlu	0.93*Qtot	1.00	
Lung bronchi,Vbr	0.1*Vlu	0.07*Qtot	1.00	
Alveolar ventilation, Qalv		Qtot		
Cardiac Output, Qtot		(5)		
Blood:Air, Pb			4.52	
Body weight, BW	(6)			

Age (yr)-specific regressions : (1) Vf = (0.0162*Age^5 – 1.9784*Age^4 + 51.963*Age^3 – 459.38*Age^2 +1566.8*Age + 1004.2)/1000; (2)Vl = (0.0072*Age^5 – 0.3975*Age^4 + 7.9052*Age^3 – 65.624*Age^2 + 262.02*Age + 157.52)/1000; (3) Vm = (-0.0623*Age^5 + 2.3433*Age^4 – 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2)/1000; (4) Vlu = (-0.0346*Age^4 + 1.5069*Age^3 – 20.31*Age^2 + 123.99*Age + 59.213)/1000; (5) Qtot = 0.012*Age^3 – 1.2144*Age^2 + 40.324*Age + 44.414; (6) BW = (-1.9*Age^4 + 72.8*Age^3 – 813.1*Age^2 + 5535.6*Age + 4453.7)/1000; For 7-10 yr model Qf = 0.05*Qtot; Ql = 0.118*Qtot; Qm = 0.045*Qtot; Qkid = 0.12*Qtot; For 11-18yr model Qf = 0.044*Qtot; Ql = 0.136*Qtot; Qm = 0.068*Qtot; Qkid = 0.136*Qtot. For adult Qf = 0.052*Qtot; Ql = 0.26*Qtot; Qm = 0.1648Qtot; Qkid = 0.26Qtot. Vmax1 = 1.35E-7*$BW^{0.75}$mol/hr; Km = 5.68E-5 mol/L. 23.0 mg MP/mL liver tissue. (Thrall et al., 2000; Price et al., 2003)

TABLE E.4.15: PBPK MODEL PARAMETERS FOR TOLUENE 0-6 YEARS OF AGE

Tissue/Compartment	Volume, Vi L	Flow, Qi, L/hr	Partition, Pi tissue/blood	Metabolism
Fat , f	(1)	0.053*Qtot	65.8	
Liver, l	(2)	0.0795*Qtot	2.98	Vmax1, Km, Ki
Muscle, m	(3)	0.03*Qtot	1.37	
VRG, vrg	BW – (Vf+Vl+Vm+Vlu)	Qtot – (Qf + Ql + Qm)	2.66	
Lung, Vlu	(4)	Qtot		
Lung alveoli, Valv	0.9*Vlu	0.93*Qtot	2.66	
Lung bronchi,Vbr	0.1*Vlu	0.07*Qtot	2.66	
Alveolar ventilation, Qalv		Qtot		
Cardiac Output, Qtot		(5)		
Blood:Air, Pb			15.6	
Body weight, BW	(6)			

Age (yr)-specific regressions : (1) Vf = (0.0162*Age^5 – 1.9784*Age^4 + 51.963*Age^3 – 459.38*Age^2 +1566.8*Age + 1004.2)/1000; (2)Vl = (0.0072*Age^5 – 0.3975*Age^4 + 7.9052*Age^3 – 65.624*Age^2 + 262.02*Age + 157.52)/1000; (3) Vm = (-0.0623*Age^5 + 2.3433*Age^4 – 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2)/1000; (4) Vlu = (-0.0346*Age^4 + 1.5069*Age^3 – 20.31*Age^2 + 123.99*Age + 59.213)/1000; (5) Qtot = 0.012*Age^3 – 1.2144*Age^2 + 40.324*Age + 44.414; (6) BW = (-1.9*Age^4 + 72.8*Age^3 – 813.1*Age^2 + 5535.6*Age + 4453.7)/1000; For 7-10 yr model Qf = 0.05*Qtot; Ql = 0.118*Qtot; Qm = 0.045*Qtot; Qkid = 0.12*Qtot; For 11-18yr model Qf = 0.044*Qtot; Ql = 0.136*Qtot; Qm = 0.068*Qtot; Qkid = 0.136*Qtot. For adult Qf = 0.052*Qtot; Ql = 0.26*Qtot; Qm = 0.1648Qtot; Qkid = 0.26Qtot. Vmax1 = 5.2E-5*BW*(70/BW)^0.25 mol/hr; Km = 5.97E-6 M, Ki = 3.8E-6 M. (Tardif et al., 1995; Price et al., 2003)

TABLE E.4.16. PBPK MODEL PARAMETERS FOR XYLENE: 0-6 YEARS OF AGE

Tissue/Compartment	Volume, Vi L	Flow, Qi, L/hr	Partition, Pi tissue/blood	Metabolism
Fat , f	(1)	0.053*Qtot	77.8	
Liver, l	(2)	0.0795*Qtot	3.02	Vmax1, Km, Ki
Muscle, m	(3)	0.03*Qtot	3.00	
VRG, vrg	BW – (Vf+Vl+Vm+ Vlu)	Qtot – (Qf + Ql + Qm)	4.42	
Lung, Vlu	(4)	Qtot		
Lung alveoli, Valv	0.9*Vlu	0.93*Qtot	4.42	
Lung bronchi,Vbr	0.1*Vlu	0.07*Qtot	4.42	
Alveolar ventilation, Qalv		Qtot		
Cardiac Output, Qtot		(5)		
Blood:Air, Pb			26.4	
Body weight, BW	(6)			

Age (yr)-specific regressions: (1) Vf = (0.0162*Age^5 – 1.9784*Age^4 + 51.963*Age^3 – 459.38*Age^2 +1566.8*Age + 1004.2)/1000; (2)Vl = (0.0072*Age^5 – 0.3975*Age^4 + 7.9052*Age^3 – 65.624*Age^2 + 262.02*Age + 157.52)/1000; (3) Vm = (-0.0623*Age^5 + 2.3433*Age^4 – 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2)/1000; (4) Vlu = (-0.0346*Age^4 + 1.5069*Age^3 – 20.31*Age^2 + 123.99*Age + 59.213)/1000; (5) Qtot = 0.012*Age^3 – 1.2144*Age^2 + 40.324*Age + 44.414; (6) BW = (-1.9*Age^4 + 72.8*Age^3 – 813.1*Age^2 + 5535.6*Age + 4453.7)/1000; For 7-10 yr model Qf = 0.05*Qtot; Ql = 0.118*Qtot; Qm = 0.045*Qtot; Qkid = 0.12*Qtot; For 11-18yr model Qf = 0.044*Qtot; Ql = 0.136*Qtot; Qm = 0.068*Qtot; Qkid = 0.136*Qtot. For adult Qf = 0.052*Qtot; Ql = 0.26*Qtot; Qm = 0.1648Qtot; Qkid = 0.26Qtot. Vmax1 = 7.9E-5*BW*(70/BW)^0.25 mol/hr; Km = 1.88E-6 M, Ki = 5.6E-6. (Tardif et al., 1995; Price et al., 2003)

E.5 Toxicokinetics: Berkeley Madonna Model Codes

This section provides PBPK model code for a selection of the chemicals studied. The models follow a standard format although the order is not critical for Berkeley Madonna (A = mass, Q = flow rate, V = volume, P = partition coefficient, Cv = concentration leaving the tissue, f= fat, l = liver, m = muscle (vessel poor tissues), vrg = vessel rich group of tissues, lu = lung, br = bronchi, pu = alveoli, BW = body weight = volume at 1 kg/L, Amet = amount metabolized)

E.5.1 Model Code for Furan 0-5 yr child

METHOD Stiff

STARTTIME = 0
STOPTIME= 48
DT = 0.001
{furan moles}
init Af = 0
init Al = 0
init Am = 0
init Avrg = 0
init Abr = 0
init Apu = 0
init Abrain = 0
{moles furan metabolized}
init Ametl = 0
init Ametlg = 0
Init AUCbrain = 0
{tissue flows L/hr}
Qtot = 0.012*Age^3 - 1.2144*Age^2 + 40.324*Age + 44.414
Qalv = 0.8*Qtot
Qf = 0.053*Qtot
Ql = 0.0795*Qtot
Qm = 0.03*Qtot
Qvrg = Qtot - (Qf + Ql + Qm + Qbrain)
Qpu = 0.93*Qtot
Qbr = 0.07*Qtot
Qbrain = -0.0024*Age^4 + 0.1305*Age^3 - 2.4822*Age^2 + 18.025*Age + 15.197
{tissue volumes L}
Vf = (0.0162*Age^5 - 1.9784*Age^4 + 51.963*Age^3 - 459.38*Age^2 + 1566.8*Age + 1004.2)/1000
Vl = (0.0072*Age^5 - 0.3975*Age^4 + 7.9052*Age^3 - 65.624*Age^2 + 262.02*Age + 157.52)/1000
Vm = (-0.0623*Age^5 + 2.3433*Age^4 - 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2)/1000
Vvrg = BW - (Vf + Vl + Vlu + Vbrain + Vm)
Vlu = (-0.0346*Age^4 + 1.5069*Age^3 - 20.31*Age^2 + 123.99*Age + 59.213)/1000
Vpu = 0.90*Vlu
Vbr = 0.10*Vlu

Vbrain = (1E4*((Age + 0.213)/(6.030 + 6.895*Age)))/1000
BW = (-1.9*Age^4 + 72.8*Age^3 - 813.1*Age^2 + 5535.6*Age + 4453.7)/1000
Age = 3.0
{blood/air and tissue/blood partition coefficients}
Pb = 2.47
Pl = 4.69
Pf = 33.39
Pm = 3.24
Pbrain = 8.82
Pvrg = 4.69
Ppu = 4.69
Pbr = 4.69
{metabolic parameters, E }
E = 1.0
{exposure in ppm converted to moles/L}
Cair = IF TIME <= 24 THEN 1*(1E-6/25.45) ELSE 0
{calculated concentrations of furan}
Cart = (Qpu*Cvpu + Qbr*Cvbr)/Qtot
Cvf = Af/(Vf*Pf)
Cvbrain = Abrain/(Vbrain*Pbrain)
Cvl = Al/(Vl*Pl)
Cvm = Am/(Vm*Pm)
Cvvrg = Avrg/(Vvrg*Pvrg)
Cvpu = Apu/(Vpu*Ppu)
Cvbr = Abr/(Vbr*Pbr)
Cvtot = (Ql*Cvl + Qf*Cvf + Qm*Cvm + Qvrg*Cvvrg + Qbrain*Cvbrain)/Qpu
Cvipu = (Qalv*Cair + Qpu*Cvtot)/((Qalv/Pb) + Qpu)
Cexh = Cvipu/Pb
{differential equations for furan uptake and metabolism}
d/dt(Abrain) = Qbrain*(Cart - Cvbrain)
d/dt(Apu) = Qpu*(Cvipu - Cvpu)
d/dt(Abr) = Qbr*(Cart - Cvbr)
d/dt(Al) = Ql*(Cart - Cvl) - Cart*Ql*E
d/dt(Af) = Qf*(Cart - Cvf)
d/dt(Am) = Qm*(Cart - Cvm)
d/dt(Avrg) = Qvrg*(Cart - Cvvrg)
{amount of furan metabolized in the liver and AUC in brain}
d/dt(Ametl) = Cart*Ql*E
d/dt(Ametlg) = Cart*Ql*E/BW
d/dt(AUCbrain) = Cvbrain

E.5.2 Model Code for MTBE 0-6 Yr Child

METHOD Stiff

STARTTIME = 0
STOPTIME= 48
DT = 0.001
{mtbe moles}
init Af = 0
init Al = 0
init Am = 0
init Avrg = 0
init Akid = 0
init Abr = 0
init Apu = 0
{moles mtbe metabolized}
init Amet1 = 0
init Amet2 = 0
{area under the venous blood concn x time curve, mtbe}
init AUCvtot = 0
init AUCvl = 0
init AUCvpu = 0
init AUCvbr = 0
init AUCvkid = 0
init AUCvvrg = 0
{tissue flows L/hr**}**
Qtot = 0.012*Age^3 - 1.2144*Age^2 + 40.324*Age + 44.414
Qalv = 0.8*Qtot
Qf = 0.053*Qtot
Ql = 0.0795*Qtot
Qm = 0.03*Qtot
Qkid = 0.164*Qtot
Qvrg = 0.674*Qtot
Qpu = 0.93*Qtot
Qbr = 0.07*Qtot
{tissue volumes L}
BW = (-1.9*Age^4 + 72.8*Age^3 - 813.1*Age^2 + 5535.6*Age + 4453.7)/1000
Vf = (0.0162*Age^5 - 1.9784*Age^4 + 51.963*Age^3 - 459.38*Age^2 + 1566.8*Age + 1004.2)/1000
Vl = (0.0072*Age^5 - 0.3975*Age^4 + 7.9052*Age^3 - 65.624*Age^2 + 262.02*Age + 157.52)/1000
Vm = (-0.0623*Age^5 + 2.3433*Age^4 - 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2)/1000
Vvrg = BW - (Vf + Vl + Vkid + Vm + Vlu)
Vkid = (9.737E-4*Age^5 - 0.0561*Age^4 + 1.1729*Age^3 - 10.34*Age^2 + 44.604*Age + 28.291)/1000
Vlu = (-0.0346*Age^4 + 1.5069*Age^3 - 20.31*Age^2 + 123.99*Age + 59.213)/1000
Vpu = 0.9*Vlu
Vbr = 0.1*Vlu

{blood/air and tissue/blood partition coefficients, mtbe}
Pb = 17.7
Pl = 0.723
Pf = 4.79
Pm = 1.181
Pkid = 0.723
Pvrg = 0.723
Ppu = 0.723
Pbr = 0.723
{mtbe metabolic parameters, mol/hr, mol/L}
Vmax1 = 3.38E-5*BW^0.75
Vmax2 = 6.2E-6*BW^0.75
Km1 = 6.17E-5
Km2 = 3.8E-6
{exposure in ppm converted to moles}
Cair = IF TIME <= 24 THEN 1*(1E-6/24.45) ELSE 0
Age = 0.0
{calculated concentrations of mtbe}
Cart = (Qpu*Cvpu + Qbr*Cvbr)/Qtot
Cvf = Af/(Vf*Pf)
Cvl = Al/(Vl*Pl)
Cvkid = Akid/(Vkid*Pkid)
Cvm = Am/(Vm*Pm)
Cvvrg = Avrg/(Vvrg*Pvrg)
Cvpu = Apu/(Vpu*Ppu)
Cvbr = Abr/(Vbr*Pbr)
Cvtot = (Ql*Cvl + Qf*Cvf + Qm*Cvm + Qvrg*Cvvrg + Qkid*Cvkid)/Qpu
Cvipu = (Qalv*Cair + Qpu*Cvtot)/((Qalv/Pb) + Qpu)
Cexh = Cvipu/Pb
{differential equations for mtbe uptake and metabolism}
d/dt(Apu) = Qpu*(Cvipu - Cvpu)
d/dt(Abr) = Qbr*(Cart - Cvbr)
d/dt(Al) = Ql*(Cart - Cvl) - Vmax1*Cvl/(Km1 + Cvl) - Vmax2*Cvl/(Km2 + Cvl)
d/dt(Af) = Qf*(Cart - Cvf)
d/dt(Akid) = Qkid*(Cart - Cvkid)
d/dt(Am) = Qm*(Cart - Cvm)
d/dt(Avrg) = Qvrg*(Cart - Cvvrg)
{amount of mtbe metabolized in liver by high and low affinity pathways}
d/dt(Amet1) = Vmax1*(Al/Vl)/(Km1 + (Al/Vl))
d/dt(Amet2) = Vmax2*(Al/Vl)/(Km2 + (Al/Vl))
{AUCs for mtbe}
d/dt(AUCvtot) = Cvtot
d/dt(AUCvl) = Cvl
d/dt(AUCvpu) = Cvpu

d/dt(AUCvbr) = Cvbr
d/dt(AUCvkid) = Cvkid
d/dt(AUCvvrg) = Cvvrg

E.5.3 Model Code for PCE 0-6 yr Child

METHOD Stiff

STARTTIME = 0
STOPTIME= 240
DT = 0.001
{PCE moles}
init Af1 = 0
init Af2 = 0
init Al = 0
init Am = 0
init Abrain = 0
init Akid = 0
init Avrg = 0
init Abr = 0
init Apu = 0
init TCA = 0
init TCAurine = 0
{moles PCE metabolized}
init Amet1 = 0
{area under the venous blood concn x time curve, pce, TCA}
init AUCvtot = 0
init AUCvl = 0
init AUCTCA = 0
init AUCvbrain = 0
{tissue flows L/hr}
Qtot = 0.012*Age^3 - 1.2144*Age^2 + 40.324*Age + 44.414
Qalv = K*Qtot
K = 0.8
Qf1 = 0.043*Qtot
Qf2 = 0.01*Qtot
Ql = 0.0795*Qtot
Qm = 0.03*Qtot
Qkid = 0.08*Qtot
Qbrain = -0.0024*Age^4 + 0.1305*Age^3 - 2.4822*Age^2 + 18.025*Age + 15.197
Qvrg = Qtot - (Qf1 + Qf2 + Ql + Qm + Qkid + Qbrain)
Qpu = 0.93*Qtot
Qbr = 0.07*Qtot

{tissue volumes L}
BW = (-1.9*Age^4 + 72.8*Age^3 - 813.1*Age^2 + 5535.6*Age +4453.7)/1000
Vf = (0.0165*Age^5 - 1.9784*Age^4 + 51.963*Age^3 - 459.38*Age^2 + 1566.8*Age + 1004.2)/1000
Vf1 = 0.8*Vf
Vf2 = 0.2*Vf
Vl = (0.0072*Age^5 - 0.3975*Age^4 + 7.9052*Age^3 - 65.624*Age^2 + 262.02*Age + 157.52)/1000
Vm = (-0.0623*Age^5 + 2.3433*Age^4 - 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2)/1000
Vbrain = (1E4*(Age + 0.213)/(6.030 + 6.895*Age))/1000
Vkid = (9.737E-4*Age^5 - 0.0561*Age^4 + 1.1729*Age^3 - 10.34*Age^2 + 44.604*Age + 28.291)/1000
Vvrg = BW - (Vf + Vl + Vm + Vkid + Vbrain + Vlu)
Vlu = (-0.0346*Age^4 + 1.5069*Age^3 - 20.31*Age^2 + 123.99*Age + 59.213)/1000
Vpu = 0.9*Vlu
Vbr = 0.1*Vlu
{blood/air and tissue/blood partition coefficients, PCE}
Pb = 11.6
Pl = 5.27
Pf1 = 125.0
Pf2 = 125.0
Pbrain = 125.0
Pkid = 5.05
Pm = 6.1
Pvrg = 5.27
Ppu = 5.27
Pbr = 5.27
{PCE metabolic parameters, mol/hr, mol/L}
Vmax1 = 1.69E-6*BW^0.75
Km1= 4.6E-5
KeC = 0.05
Ke = KeC/BW^0.25
Ku = 0.5
{exposure in ppm converted to moles}
Cair = IF TIME <= 24 THEN 1*(1E-6/24.45) ELSE 0
Age = 0
{calculated concentrations of PCE}
Cart = (Qpu*Cvpu + Qbr*Cvbr)/Qtot
Cvf1 = Af1/(Vf1*Pf1)
Cvf2 = Af2/(Vf2*Pf2)
Cvl = Al/(Vl*Pl)
Cvbrain = Abrain/(Vbrain*Pbrain)
Cvkid = Akid/(Vkid*Pkid)
Cvm = Am/(Vm*Pm)
Cvvrg = Avrg/(Vvrg*Pvrg)
Cvpu = Apu/(Vpu*Ppu)
Cvbr = Abr/(Vbr*Pbr)

Cvtot = (Ql*Cvl + Qf1*Cvf1 + Qm*Cvm + Qvrg*Cvvrg + Qf2*Cvf2 + Qbrain*Cvbrain + Qkid*Cvkid)/Qpu
Cvipu = (Qalv*Cair + Qpu*Cvtot)/((Qalv/Pb) + Qpu)
Cexh = Cvipu/Pb
Ctca = TCA/(BW*0.1)
{differential equations for pce uptake and metabolism}
d/dt(Apu) = Qpu*(Cvipu - Cvpu)
d/dt(Abr) = Qbr*(Cart - Cvbr)
d/dt(Al) = Ql*(Cart - Cvl) - Vmax1*Cvl/(Km1 + Cvl)
d/dt(Af1) = Qf1*(Cart - Cvf1)
d/dt(Af2) = Qf2*(Cart - Cvf2)
d/dt(Akid) = Qkid*(Cart - Cvkid)
d/dt(Abrain) = Qbrain*(Cart - Cvbrain)
d/dt(Am) = Qm*(Cart - Cvm)
d/dt(Avrg) = Qvrg*(Cart - Cvvrg)
d/dt(TCA) = 0.15*Vmax1*Cvl/(Km1 + Cvl) - Ke*TCA - Ku*TCA
d/dt(TCAurine) = TCA*Ku
{amount of PCE metabolized in liver }
d/dt(Amet1) = Vmax1*(Al/Vl)/(Km1 + (Al/Vl))
init Ametg = 0
d/dt(Ametg) = Amet1/BW
{AUCs for PCE}
d/dt(AUCvtot) = Cvtot
d/dt(AUCvl) = Cvl
d/dt(AUCTCA) = Ctca
d/dt(AUCvbrain) = Cvbrain

E.5.4 Model Code for BaP vapor 0-6 yr Child

METHOD Stiff

STARTTIME = 0
STOPTIME= 2880
DT = 0.001
{Alveolar compartments, moles}
init AAP = 0
init AAVA = 0
init AAV1 = 0
limit AAV1 >= 0
init AAV2 = 0
limit AAV2 >= 0
init AAVE = 0
limit AAVE >= 0

init AAVB = 0
limit AAVE >= 0
init Ameta1 = 0
init Ameta2 = 0
init LNth = 0
init AUCCalv = 0
{Bronchiolar compartments, moles}
init ABP = 0
init ABM = 0
init ABL1 = 0
init ABL2 = 0
init ABL3 = 0
init ABBL = 0
init Ametb1 = 0
init Ametb2 = 0
init Ametb3 = 0
init AUCCbron = 0
{Venous and arterial blood, moles}
init Aven = 0
init Aart = 0
{Body compartments, input, output, moles}
init Af = 0
init Am = 0
init Akvrg = 0
init Aliv = 0
init Aurine = 0
init Aet = 0
init Ametliv = 0
init AUCCliv = 0
{Model parameters, constants}
Vf = (0.0165*Age^5 - 1.9784*Age^4 + 51.963*Age^3 - 459.38*Age^2 + 1566.8*Age + 1004.2)/1000
Vm = (-0.0623*Age^5 + 2.3433*Age^4 - 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2)/1000
Vkvrg = BW - (Vf + Vm + Vliv + Vlu + Vart + Vven)
Vliv = (0.0072*Age^5 - 0.3975*Age^4 + 7.9052*Age^3 - 65.624*Age^2 + 262.02*Age + 157.52)/1000
Vlu = (-0.0346*Age^4 + 1.5069*Age^3 - 20.31*Age^2 + 123.99*Age + 59.213)/1000
Valv = 0.9*Vlu
Vbron = 0.1*Vlu
Vart = BW*0.05/3
Vven = BW*0.05*2/3
Ka = 1.0E-3
Kb = 100
Kbln = 6.9E-6
Kaln = 6.9E-7
Kln = 1.16E-5

DL = 2.14E-11
SF = 1.04
Vmaxlu = 1.2E-11*(BW/.25)^0.75
Vmaxliv = 1.7E-9*(BW/.25)^0.75
Kmliv = 5.5E-6
Kmlu = 2.2E-7
Pf = 294.7
Pm = 4.0
Pkvrg = 4.0
Pliv = 7.0
Pb =10
Palv = 1.3
Pbron = 2.3
BW = (-1.9*Age^4 + 72.8*Age^3 - 813.1*Age^2 + 5535.6*Age + 4453.7)/1000
Qtot = (0.012*Age^3 - 1.2144*Age^2 + 40.324*Age + 44.414)/60
Qvent = ((17.874*Age) + 39.785)/60
Qalv = 0.93*Qtot
Qbron = 0.07*Qtot
Qf = 0.053*Qtot
Qm = 0.03*Qtot
Qkvrg = Qtot - (Qf + Qliv + Qm)
Qliv = 0.0795*Qtot
MPliv = 5.8E4
MPlu = 3E3
{Concentrations, mol/L, ppm}
Cairex = Exposure
Exposure = IF TIME < 1440 THEN 1E-2*(1E-6/25.45) ELSE 0 {ppm to mol/L}
Age = 0
Cair = AAVA/(0.5*Vlu)
Calv = (AAV1+AAV2+AAVE)/Valv
Cbron = (ABL1+ABL2+ABL3)/Vbron
Cart = Aart/Vart
Cven = Aven/Vven
Cliv = Aliv/Vliv
{differential equations, alveoli moles, L, min}
d/dt(AAVA) = Qvent*(AAV1/Valv) - Qvent*(AAVA/0.5) + Cairex*Qvent
d/dt(AAP) = - AAP*0.9*4.8E-4 - AAP*0.1*4.8E-4
d/dt(AAV1) = AAP*0.9*4.8E-4 - Ka*((AAV1/(Valv*0.25*0.9)) - (AAVE/(Valv*0.75))) + Qvent*(AAVA/0.5) - Qvent*(AAV1/Valv) - SF*Vmaxlu*MPlu*AAV1/(Kmlu + (AAV1/(Valv*0.9*0.25)))
d/dt(AAV2) = AAP*0.1*4.8E-4
- Ka*((AAV2/(Valv*0.25*0.1)) - (AAVE/(Valv*0.75))) - SF*Vmaxlu*MPlu*AAV2/(Kmlu + (AAV2/(Valv*0.1*0.25)))
d/dt(AAVE) = Ka*((AAV1/(Valv*0.25*0.9)) - (AAVE/(Valv*0.75))) + Ka*((AAV2/(Valv*0.25*0.1)) - (AAVE/(Valv*0.75))) - Ka*((AAVE/(Valv*0.75)) - (AAVB/(Vven*Palv))) + Kln*LNth - Kaln*AAVE

d/dt(AAVB) = Ka*((AAVE/(Valv*0.75)) - (AAVB/(Vven*Palv))) + (Aven/Vven)*Qalv - AAVB*Qalv/(Vven*Palv)

d/dt(Ameta1) = SF*Vmaxlu*MPlu*AAV1/(Kmlu + (AAV1/(Valv*0.9*0.25)))

d/dt(Ameta2) = SF*Vmaxlu*MPlu*AAV2/(Kmlu + (AAV2/(Valv*0.1*0.25)))

d/dt(LNth) = Kbln*ABL1 + Kbln*ABL2 + Kbln*ABL3 + Kaln*AAVE - Kln*LNth

d/dt(AUCCalv) = Calv

{differential equations, bronchi}

d/dt(ABP) = - ABP*4.8E-4

d/dt(ABM) = ABP*4.8E-4 - Ka*Kb*((ABM/0.06) - (ABL1/(Vbron*0.333)))

d/dt(ABL1) = Ka*Kb*((ABM/0.06) - (ABL1/(Vbron*0.333))) - Ka*(ABL1/(Vbron*0.333) - ABL2/(Vbron*0.333)) + DL*Kb*(ABL1/(Vbron*0.333) - ABL3/(Vbron*0.333)) - SF*Vmaxlu*MPlu*ABL1/(Kmlu + (ABL1/(Vbron*0.333))) - Kbln*ABL1 + Kln*LNth

d/dt(ABL2) = Ka*(ABL1/(Vbron*0.333) - ABL2/(Vbron*0.333)) + DL*Kb*(ABL1/(Vbron*0.333) - ABL3/(Vbron*0.333)) - Ka*Kb*(ABL2/(Vbron*0.333) - ABL3/(Vbron*0.333)) - SF*Vmaxlu*MPlu*ABL2/(Kmlu + (ABL2/(Vbron*0.333))) - Kbln*ABL2 + Kln*LNth

d/dt(ABL3) = Ka*Kb*(ABL2/(Vbron*0.333) - ABL3/(Vbron*0.333)) - Ka*ABL3/(Vbron*0.333) - SF*Vmaxlu*MPlu*ABL3/(Kmlu + (ABL3/(Vbron*0.333))) - Kbln*ABL3 + Kln*LNth

d/dt(ABBL) = Ka*ABL3/(Vbron*0.333) + Qbron*(Aven/Vven) - ABBL*Qbron/(Vven*Pbron)

d/dt(Ametb1) = SF*Vmaxlu*MPlu*ABL1/(Kmlu + (ABL1/(Vbron*0.333)))

d/dt(Ametb2) = SF*Vmaxlu*MPlu*ABL2/(Kmlu + (ABL2/(Vbron*0.333)))

d/dt(Ametb3) = SF*Vmaxlu*MPlu*ABL3/(Kmlu + (ABL3/(Vbron*0.333)))

d/dt(AUCCbron) = Cbron

{differential equations, body}

d/dt(Aart) = AAVB*Qalv/(Vven*Palv) + ABBL*Qbron/(Vven*Pbron) - (Aart/Vart)*(Qf + Qm + Qkvrg + Qliv)

d/dt(Aven) = Af*Qf/(Vf*Pf) + Am*Qm/(Vm*Pm) + Akvrg*Qkvrg/(Vkvrg*Pkvrg) + Aliv*Qliv/(Vliv*Pliv) - (Aven/Vven)*Qalv -(Aven/Vven)*Qbron

d/dt(Af) = Cart*Qf - Af*Qf/(Vf*Pf)

d/dt(Am) = Cart*Qm - Am*Qm/(Vm*Pm)

d/dt(Akvrg) = Cart*Qkvrg - Akvrg*Qkvrg/(Vkvrg*Pkvrg) - Akvrg*0.2

d/dt(Aliv) = Cart*Qliv - Aliv*Qliv/(Vliv*Pliv) - SF*Vmaxliv*MPliv*Aliv/(Kmliv + (Aliv/Vliv)) + Aet*0.01

d/dt(Aet) = - Aet*0.01

d/dt(Aurine) = Akvrg*0.2

d/dt(Ametliv) = SF*Vmaxliv*MPliv*Aliv/(Kmliv + (Aliv/Vliv))

d/dt(AUCCliv) = Cliv

E.5.5 Model Code for NAP/NO RT 0-6 yr Child

METHOD Stiff

STARTTIME = 0

STOPTIME= 2880

DT = 0.0001

{Naphthalene (NAP) in upper respiratory tract compartment (URT) umoles}

init ANURTa = 0
init ANURTmuc = 0
init ANURTepi = 0
Limit ANURTepi >= 0
init ANURTex = 0
Limit ANURTex >= 0
init AMETua = 0
{NAP oxide (NO) in upper respiratory compartment (URT) umoles}
init ABURTa = 0
init ABURTmuc = 0
init ABURTepi = 0
init GSHua = 1.0*VURTepi
init ABURTex = 0
Limit ABURTex >= 0
init ABMET2ua = 0
init ABMETGua = 0
{NAP in conducting airways compartment (CA), umoles}
init ANCAa = 0
init ANCAmuc = 0
init ANCAepi = 0
init ANCAex = 0
Limit ANCAex >= 0
init AMETca = 0
{NO in conducting airways compartment (CA), umoles}
init ABCAa = 0
init ABCAmuc = 0
init ABCAepi = 0
init ABCAex = 0
Limit ABCAex >= 0
init GSHca = 1.0*VCA
init ABMET2ca = 0
init ABMETGca = 0
{NAP in transitional bronchioles compartment (TB), umoles}
init ANTBa = 0
init ANTBmuc = 0
init ANTBepi = 0
init ANTBex = 0
Limit ANTBex >= 0
init AMETtb = 0
{NO in transitional bronchioles compartment (TB), umoles}
init ABTBa = 0
init ABTBmuc = 0
init ABTBepi = 0
init GSHtb = 1.0*VTBepi

init ABTBex = 0
Limit ABTBex >= 0
init ABMET2tb = 0
init ABMETGtb = 0
{NAP in pulmonary compartment (PU), umoles}
init ANPUa = 0
init ANPUmuc = 0
init ANPUepi = 0
init ANPUex = 0
Limit ANPUex >= 0
init ANex = 0
Limit ANex >= 0
init AMETpu = 0
{NO in pulmonary compartment (PU), umoles}
init ABPUa = 0
init ABPUmuc = 0
init ABPUepi = 0
init ABPUex = 0
init ABex = 0
Limit ABex >= 0
init GSHpu = 1.0*VPU
init ABMET2pu = 0
init ABMETGpu = 0
{model equations}
Q = RPM*TVOL
Cairin = exposure/(24.36*1E3)
VURTepi = SAURT*WUA
VURTmuc = SAURT*WSMua
VURTex = SAURT*WUAs
VCAmuc = SACA*WSMca
VCAepi = SACA*WCA
VCAex = SACA*WCAs
VTBmuc = SATB*WSMtb
VTBepi = SATB*WTA
VTBex = SATB*WTAs
VPUmuc = SAPU*WSMpu
VPUepi = SAPU*WPA
VPUex = SAPU*WTAs
Vlu = 59.213 + 123.99*Age - 20.31*Age^2 + 1.5069*Age^3 - 0.0346*Age^4
VURT = 0.0026*Vlu
VCA = 0.018*Vlu
VTB = 0.043*Vlu
VPU = 0.937*Vlu
{calculated concentrations of NAP umol/mL}

Curtepil = (ANURTepi/VURTepi)
Ccaepil = (ANCAepi/VCAepi)
Ctbepil = (ANTBepi/VTBepi)
Cpuepil = (ANPUepi/VPUepi)
Cvurtex = (ANURTex/(VURTex*Pvrg))
Cvcaex = (ANCAex/(VCAex*Pvrg))
Cvtbex = (ANTBex/(VTBex*Pvrg))
Cvpuex = (ANPUex/(VPUex*Pvrg))
Cvex = (ANURTex+ANCAex+ANTBex+ANPUex)/((VURTex+VCAex+VTBex+VPUex)*Pvrg)
{calculated concentrations of NO umol/mL}
CBurtepil = (ABURTepi/VURTepi)
CBcaepil = (ABCAepi/VCAepi)
CBtbepil = (ABTBepi/VTBepi)
CBpuepil = (ABPUepi/VPUepi)
CBvurtex = (ABURTex/(VURTex*PBvrg))
CBvcaex = (ABCAex/(VCAex*PBvrg))
CBvtbex = (ABTBex/(VTBex*PBvrg))
CBvpuex = (ABPUex/(VPUex*PBvrg))
CBvex = (ABURTex+ABCAex+ABTBex+ABPUex)/((VURTex+VCAex+VTBex+VPUex)*PBvrg)
{concentrations of GSH, mM}
CGSHuab = 2.5
CGSHua = GSHua/VURT
CGSHcab = 2.0
CGSHca = GSHca/VCA
CGSHtbb = 1.0
CGSHtb = GSHtb/VTB
CGSHpub = 1.0
CGSHpu = GSHpu/VPU
init inhaleddose = 0
d/dt(Inhaleddose) = Cairin*Qalv
Exposure = IF TIME <= 1440 THEN 1 ELSE 0
ExposureB = IF TIME <= 1440 THEN 0 ELSE 0
Age = 3.0
{upper respiratory tract constants}
PMA = 30 {mucus:air partition coeff}
KOURT = 198.0 {mass transfer coeffs., cm/min}
KTRURT = 1.92
KBOURT = 0.192
KOCA = 18.1
KTRCA = 1.92
KBOCA = 0.192
KOTB = 15.8
KTRTB = 1.92
KBOTB = 0.192

KOPU = 15.8
KTRPU = 1.92
KBOPU = 0.192
KMUC = 0.001 {diffusion constants, cm2/min}
KSQM = 0.0002
KG = 6.0
SAURT = VURT/WUA {surface areas, cm2}
SACA = VCA/WCA
SATB = VTB/WTA
SAPU = VPU/WPA
VURTa = 0.00035*TLC {luminal volumes, cm3}
VCAa = 0.0105*TLC
VTBa = 0.042*TLC
VPUa = 0.944*TLC
TLC = 236.5 + 282*Age - 4.775*Age^2 + 0.285*Age^3 {mL}
RPM = 53.5*(BW/1E3)^-0.26 {breaths/min}
TVOL = 35.45 + 33.56*Age - 1.47*Age^2 + 0.0793*Age^3 {tidal volume mL/breath}
{thicknesses (W) of upper airways epithelium (UA), submucosa (UAs);mucus (SM); conducting airways epi (CA), submucosa (CAs); transitional airways epi (TA), submucosa (TAs); and pulmonary airways epi (PA), cm}
WUA = 0.005
WSMua = 0.001
WSMca = 0.0005
WSMtb = 0.0002
WSMpu = 0.0001
WCA = 0.0025
WTA = 0.001
WPA = 0.0005
WUAs = 0.01
WCAs = 0.005
WTAs = 0.002
Qua = 0.0025*Qtot {blood flow to the URT region}
Qca = 0.0075*Qtot {blood flow to the CA}
Qta = 0.0067*Qtot {blood flow to the TA}
{metabolic constants umol/min, umol/mL, based on Sweeny et al. 1996, Willems et al. 2001 rat values scaled to larger BWs, 2 = EH, G = conj}
Vmaxua = 2.45E-3*3.0*VURTepi/(BW/250)^0.25
Vmaxca = 2.45E-3*3.0*VCAepi/(BW/250)^0.25
Vmaxtb = 2.45E-3*3.0*VTBepi/(BW/250)^0.25
Vmaxpu = 2.45E-3*3.0*VPUepi/(BW/250)^0.25
Vmaxl = 2.46E-2*14.5*Vl/(BW/250)^0.25
Km = 0.003 {umol/mL}
Kmlu = 0.006
Vmaxl2 = 4.0E-3*14.5*Vl/(BW/250)^0.25 {EH}
Vmax2ua = 9.0E-3*3.0*VURTepi/(BW/250)^0.25

Vmax2ca = 9.0E-3*3.0*VCAepi/(BW/250)^0.25

Vmax2tb = 9.0E-3*3.0*VTBepi/(BW/250)^0.25

Vmax2pu = 9.0E-3*3.0*VPUepi/(BW/250)^0.25

Km2lu = 0.001

Km2 = 0.001

Km2ih = 2E-4

Kec = 400

init Kgshl = 0.003*Vl {GSH /min}

d/dt(Kgshl) = (2.4E-4*((CGSHlb + 2.0)/ (CGSHl + 2.0)) - 0.005*0.003)/58

Kgshua = 0.003*VURT

Kgshca = 0.003*VCA

Kgshtb = 0.003*VTB

Kgshpu = 0.003*VPU

Kge = 2.5E-3

VmaxGl = 0.5*58*Vl/(BW/250)^0.25 {umol/min/liver, GST}

VmaxGua = 0.4*54.0*VURTepi/(BW/250)^0.25

VmaxGca = 0.4*54.0*VCAepi/(BW/250)^0.25

VmaxGtb = 0.4*54.0*VTBepi/(BW/250)^0.25

VmaxGpu = 0.4*54.0*VPUepi/(BW/250)^0.25

KmG1 = 3.3 {GSH}

KmG2 = 0.05 {NO}

MPl = 14.5 {mg microsomal protein /mL tissue}

MPlu = 3.0 {mg microsomal protein/mL tissue}

CPl = 58 {mg cytosolic protein/mL tissue}

CPlu = 54 {mg cytosolic protein/mL tissue}

KNOH = 0.25 {naphthol fomation}

{differential equations for NAP in URT compartment, URT}

d/dt(ANURTa) = Q*(Cairin - (ANURTa/VURTA)) - KOURT*SAURT*((ANURTa/VURTA)-(ANURTmuc/(PMA*VURTmuc)))

d/dt(ANURTmuc) = KOURT*SAURT*((ANURTa/VURTa) - (ANURTmuc/(PMA*VURTmuc))) - KTRURT*SAURT*((ANURTmuc/(VURTmuc*PMA)) - (ANURTepi/(VURTepi*Pvrg)))

d/dt(ANURTepi) = KTRURT*SAURT*((ANURTmuc/(VURTmuc*PMA)) - (ANURTepi/(VURTepi*Pvrg))) - KBOURT*SAURT*((ANURTepi/(VURTepi*Pvrg)) - (ANURTex/(VURTex*Pvrg))) - Vmaxua*(ANURTepi/(VURTepi*Pvrg))/(Kmlu + (ANURTepi/(VURTepi*Pvrg)))

d/dt(ANURTex) = KBOURT*SAURT*((ANURTepi/VURTepi) - (ANURTex/VURTex)) + Qua*(Cart - (ANURTex/(VURTex*Pvrg)))

d/dt(AMETua) = Vmaxua*(ANURTepi/(VURTepi*Pvrg))/(Kmlu + (ANURTepi/(VURTepi*Pvrg)))

d/dt(GSHua) = Kgshua*(CGSHuab - (GSHua/VURTepi)) - Kge*GSHua - VmaxGua*(ABURTepi/(VURTepi*PBvrg))*CGSHua/(KmG1*(ABURTepi/(VURTepi*PBvrg)) + KmG2*CGSHua + CGSHua*(ABURTepi/(VURTepi*PBvrg)))

{differential equations for NO in URT compartment, URT}

d/dt(ABURTa) = Q*(CBairin - (ABURTa/VURTa)) - KOURT*SAURT*((ABURTa/VURTa)-(ABURTmuc/(PMA*VURTmuc)))

d/dt(ABURTmuc) = KOURT*SAURT*((ABURTa/VURTa) - (ABURTmuc/(PMA*VURTmuc))) - KTRURT*SAURT*((ABURTmuc/(VURTmuc*PMA)) - (ABURTepi/(VURTepi*PBvrg)))

d/dt(ABURTepi) = KTRURT*SAURT*((ABURTmuc/(VURTmuc*PMA)) - (ABURTepi/(VURTepi*PBvrg))) - KBOURT*SAURT*((ABURTepi/(VURTepi*PBvrg)) - (ABURTex/(VURTex*PBvrg))) + Vmaxua*(ANURTepi/(VURTepi*PBvrg))/(Kmlu + (ANURTepi/(VURTepi*PBvrg))) - Vmax2ua*(ABURTepi/(VURTepi*PBvrg))/(Km2lu + (ABURTepi/VURTepi)) - VmaxGua*(ABURTepi/(VURTepi*PBvrg))*CGSHua/(KmG1*(ABURTepi/(VURTepi*PBvrg)) + KmG2*CGSHua + CGSHua*(ABURTepi/(VURTepi*PBvrg))) - KNOH*(ABURTepi/(VURTepi*PBvrg))*1E3

d/dt(ABMET2ua) = (Vmax2ua*ABURTepi/(VURTepi*PBvrg)/(Km2lu + (ABURTepi/VURTepi)))/2

d/dt(ABMETGua) = (VmaxGua*(ABURTepi/(VURTepi*PBvrg))*CGSHua/(KmG1*(ABURTepi/(VURTepi*PBvrg)) + KmG2*CGSHua + CGSHua*(ABURTepi/(VURTepi*PBvrg))))/2

d/dt(ABNOHua) = KNOH*(ABURTepi/(VURTepi*PBvrg))*1E3

init ABNOHua = 0

d/dt(ABURTex) = KBOURT*SAURT*((ABURTepi/VURTepi) - (ABURTex/(VURTex*PBvrg))) + Qua*(CBart - (ABURTex/(VURTex*PBvrg)))

{differential equations for NAP in CA compartment, CA}

d/dt(ANCAa) = Q*(Cairin - (ANCAa/VCAa)) - KOCA*SACA*((ANCAa/VCAa)-(ANCAmuc/(PMA*VCAmuc)))

d/dt(ANCAmuc) = KOCA*SACA*((ANCAa/VCAa) - (ANCAmuc/(PMA*VCAmuc))) - KTRCA*SACA*((ANCAmuc/(VCAmuc*PMA)) - (ANCAepi/(VCAepi*Pvrg)))

d/dt(ANCAepi) = KTRCA*SACA*((ANCAmuc/(VCAmuc*PMA)) - (ANCAepi/(VCAepi*Pvrg))) - KBOCA*SACA*((ANCAepi/(VCAepi*Pvrg)) - (ANCAex/(VCAex*Pvrg))) - Vmaxca*(ANCAepi/(VCAepi*Pvrg))/(Kmlu + (ANCAepi/(VCAepi*Pvrg)))

d/dt(ANCAex) = KBOCA*SACA*((ANCAepi/(VCAepi*Pvrg)) - (ANCAex/(VCAex*Pvrg))) + Qca*(Cart - (ANCAex/(VCAex*Pvrg)))

d/dt(AMETca) = Vmaxca*(ANCAepi/(VCAepi*Pvrg))/(Kmlu + (ANCAepi/(VCAepi*Pvrg)))

d/dt(GSHca) = Kgshca*(CGSHcab - (GSHca/VCAepi)) - Kge*GSHca - VmaxGca*(ABCAepi/(VCAepi*PBvrg))*CGSHca/(KmG1*(ABCAepi/(VCAepi*PBvrg)) + KmG2*CGSHca + CGSHca*(ABCAepi/(VCAepi*PBvrg)))

{differential equations for NO in CA compartment, CA}

d/dt(ABCAa) = Q*(CBairin - (ABCAa/VCAa)) - KOCA*SACA*((ABCAa/VCAa)-(ABCAmuc/(PMA*VCAmuc)))

d/dt(ABCAmuc) = KOCA*SACA*((ABCAa/VCAa) - (ABCAmuc/(PMA*VCAmuc))) - KTRCA*SACA*((ABCAmuc/(VCAmuc*PMA)) - (ABCAepi/(VCAepi*PBvrg)))

d/dt(ABCAepi) = KTRCA*SACA*((ABCAmuc/(VCAmuc*PMA)) - (ABCAepi/(VCAepi*PBvrg)))

+ Vmaxca*(ANCAepi/(VCAepi*Pvrg))/(Kmlu + (ANCAepi/(VCAepi*Pvrg))) - KBOCA*SACA*((ABCAepi/(VCAepi*PBvrg)) - (ABCAex/(VCAex*PBvrg))) - Vmax2ca*ABCAepi/(VCAepi*PBvrg)/(Km2lu + (ABCAepi/VCAepi)) - VmaxGca*(ABCAepi/(VCAepi*PBvrg))*CGSHca/(KmG1*(ABCAepi/(VCAepi*PBvrg)) + KmG2*CGSHca + CGSHca*(ABCAepi/(VCAepi*PBvrg))) - KNOH*(ABCAepi/(VCAepi*PBvrg))*1E3

d/dt(ABCAex) = KBOCA*SACA*((ABCAepi/(VCAepi*PBvrg)) - (ABCAex/(VCAex*PBvrg))) + Qca*(CBart - (ABCAex/(VCAex*PBvrg)))

d/dt(ABMET2ca) = (Vmax2ca*ABCAepi/(VCAepi*PBvrg)/(Km2lu + (ABCAepi/VCAepi)))/2

d/dt(ABMETGca) = (VmaxGca*(ABCAepi/(VCAepi*PBvrg))*CGSHca/(KmG1*(ABCAepi/(VCAepi*PBvrg)) + KmG2*CGSHca + CGSHca*(ABCAepi/(VCAepi*PBvrg))))/2

d/dt(ABNOHca) = KNOH*(ABCAepi/(VCAepi*PBvrg))*1E3

init ABNOHca = 0

{differential equations for NAP in TB compartment umoles, TB}

d/dt(ANTBa) = Q*(Cairin - (ANTBa/VTBa)) - KOTB*SATB*((ANTBa/VTBa)-(ANTBmuc/(PMA*VTBmuc)))

d/dt(ANTBmuc) = KOTB*SATB*((ANTBa/VTBa) - (ANTBmuc/(PMA*VTBmuc))) - KTRTB*SATB*((ANTBmuc/(VTBmuc*PMA)) - (ANTBmuc/(VTBmuc*PMA)))

d/dt(ANTBepi) = KTRTB*SATB*((ANTBmuc/(VTBmuc*PMA)) - (ANTBepi/(VTBepi*Pvrg))) - KBOTB*SATB*((ANTBepi/(VTBepi*Pvrg)) - (ANTBex/(VTBex*Pvrg))) - Vmaxtb*(ANTBepi/(VTBepi*Pvrg))/(Kmlu + (ANTBepi/(VTBepi*Pvrg)))

d/dt(ANTBex) = KBOTB*SATB*((ANTBepi/(VTBepi*Pvrg)) - (ANTBex/(VTBex*Pvrg))) + Qta*(Cart - (ANTBex/(VTBex*Pvrg)))

d/dt(AMETtb) = Vmaxtb*(ANTBepi/(VTBepi*Pvrg))/(Kmlu + (ANTBepi/(VTBepi*Pvrg)))

d/dt(GSHtb) = Kgshtb*(CGSHtbb - (GSHtb/VTBepi)) - Kge*GSHtb - VmaxGtb*(ABTBepi/(VTBepi*PBvrg))*CGSHtb/(KmG1*(ABTBepi/(VTBepi*PBvrg)) + KmG2*CGSHtb + CGSHtb*(ABTBepi/(VTBepi*PBvrg)))

{differential equations for NO in TB compartment umoles, TB}

d/dt(ABTBa) = Q*(CBairin - (ABTBa/VTBa)) - KOTB*SATB*((ABTBa/VTBa)-(ABTBmuc/(PMA*VTBmuc)))

d/dt(ABTBmuc) = KOTB*SATB*((ABTBa/VTBa) - (ABTBmuc/(PMA*VTBmuc))) - KTRTB*SATB*((ABTBmuc/(VTBmuc*PMA)) - (ABTBepi/(VTBepi*PBvrg)))

d/dt(ABTBepi) = KTRTB*SATB*((ABTBmuc/(VTBmuc*PMA)) - (ABTBepi/(VTBepi*PBvrg))) - KBOTB*SATB*((ABTBepi/(VTBepi*PBvrg)) - (ABTBex/(VTBex*PBvrg))) + Vmaxtb*(ANTBepi/(VTBepi*Pvrg))/(Kmlu + (ANTBepi/(VTBepi*Pvrg))) - Vmax2tb*ABTBepi/(VTBepi*PBvrg)/(Km2lu + (ABTBepi/VTBepi)) - VmaxGtb*(ABTBepi/(VTBepi*PBvrg))*CGSHtb/(KmG1*(ABTBepi/(VTBepi*PBvrg)) + KmG2*CGSHtb + CGSHtb*(ABTBepi/(VTBepi*PBvrg))) - KNOH* (ABTBepi/(VTBepi*PBvrg))*1E3

d/dt(ABMET2tb) = (Vmax2tb*(ABTBepi/(VTBepi*PBvrg))/(Km2lu + (ABTBepi/VTBepi)))/2

d/dt(ABMETGtb) = (VmaxGtb*(ABTBepi/(VTBepi*PBvrg))*CGSHtb/(KmG1*(ABTBepi/(VTBepi*PBvrg)) + KmG2*CGSHtb + CGSHtb*(ABTBepi/(VTBepi*PBvrg))))/2

d/dt(ABNOHtb) = KNOH* (ABTBepi/(VTBepi*PBvrg))*1E3

init ABNOHtb = 0

d/dt(ABTBex) = KBOTB*SATB*(ABTBepi/(VTBepi*PBvrg) - (ABTBex/(VTBex*PBvrg))) + Qta*(CBart - (ABTBex/(VTBex*PBvrg)))

{differential equations for NAP in PU compartment umoles, PU}

d/dt(ANPUa) = Q*(Cairin - (ANPUa/VPUa)) - KOPU*SAPU*((ANPUa/VPUa)-(ANPUmuc/(PMA*VPUmuc)))

d/dt(ANPUmuc) = KOPU*SAPU*((ANPUa/VPUa) - (ANPUmuc/(PMA*VPUmuc))) - KTRPU*SAPU*((ANPUmuc/VPUmuc) - (ANPUepi/(VPUepi*Pvrg)))

d/dt(ANPUepi) = KTRPU*SAPU*((ANPUmuc/(VPUmuc*PMA)) - (ANPUepi/(VPUepi*Pvrg))) - KBOPU*SAPU*((ANPUepi/(VPUepi*Pvrg)) - (ANPUex/(VPUex*Pvrg))) - Vmaxpu*(ANPUepi/(VPUepi*Pvrg))/(Kmlu + (ANPUepi/(VPUepi*Pvrg)))

d/dt(ANPUex) = KBOPU*SAPU*((ANPUepi/(VPUepi*Pvrg)) - (ANPUex/(VPUex*Pvrg))) + Qtot*(Cart - (ANPUex/(VPUex*Pvrg)))

d/dt(GSHpu) = Kgshpu*(CGSHpub - (GSHpu/VPUepi)) - Kge*GSHpu - VmaxGpu*(ABPUepi/(VPUepi*PBvrg))*CGSHpu/(KmG1*(ABPUepi/(VPUepi*PBvrg)) + KmG2*CGSHpu + CGSHpu*(ABPUepi/(VPUepi*PBvrg)))

d/dt(AMETpu) = Vmaxpu*(ANPUepi/(VPUepi*Pvrg))/(Kmlu + (ANPUepi/(VPUepi*Pvrg)))

{differential equations for NO in PU compartment umoles, PU}

d/dt(ABPUa) = Q*(Cairin - (ANPUa/VPUa)) - KOPU*SAPU*((ANPUa/VPUa)-(ANPUmuc/(PMA*VPUmuc)))

d/dt(ABPUmuc) = KOPU*SAPU*((ABPUa/VPUa) - (ABPUmuc/(PMA*VPUmuc))) - KTRPU*SAPU*((ABPUmuc/(VPUmuc*PMA)) - (ABPUepi/(VPUepi*PBvrg)))

d/dt(ABPUepi) = KTRPU*SAPU*((ABPUmuc/(VPUmuc*PMA)) - (ABPUepi/(VPUepi*PBvrg))) - KBOPU*SAPU*((ABPUepi/(VPUepi*PBvrg)) - (ABPUex/(VPUex*PBvrg))) + Vmaxpu*(ANPUepi/(VPUepi*Pvrg))/(Kmlu + (ANPUepi/(VPUepi*Pvrg))) - Vmax2pu*ABPUepi/(VPUepi*PBvrg)/(Km2lu + (ABPUepi/VPUepi)) - VmaxGpu*(ABPUepi/(VPUepi*PBvrg))*CGSHpu/(KmG1*(ABPUepi/(VPUepi*PBvrg)) + KmG2*CGSHpu + CGSHpu*(ABPUepi/(VPUepi*PBvrg))) - KNOH*(ABPUepi/(VPUepi*PBvrg))*1E3

d/dt(ABPUex) = KBOPU*SAPU*((ABPUepi/(VPUepi*PBvrg)) - (ABPUex/(VPUex*PBvrg))) + Qtot*(CBart - (ABPUex/(VPUex*PBvrg)))

d/dt(ABMET2pu) = (Vmax2pu*(ABPUepi/(VPUepi*PBvrg))/(Km2lu + (ABPUepi/VPUepi)))/2

d/dt(ABMETGpu) = (VmaxGpu*(ABPUepi/(VPUepi*PBvrg))*CGSHpu/(KmG1*(ABPUepi/(VPUepi*PBvrg)) + KmG2*CGSHpu + CGSHpu*(ABPUepi/(VPUepi*PBvrg))))/2

d/dt(ABNOHpu) = KNOH*(ABPUepi/(VPUepi*PBvrg))*1E3

init ABNOHpu = 0

{Sum of Lung NAP}

d/dt(ANex) = Qtot*((Cart-Cvurtex) + (Cart-Cvcaex) + (Cart-Cvtbex) + (Cart-Cvpuex))

{Sum of Lung NO}

d/dt(ABex) = Qtot*((CBart-CBvurtex) +(CBart-CBvcaex) + (CBart-CBvtbex) + (CBart-CBvpuex))

{NAP ex respiratory tract, umoles}

init Af = 0

init Al = 0

Limit Al >= 0

init Am = 0

Limit Am >= 0

init Avrg = 0

Limit Avrg >= 0

init Ablood = 0

init GSHl = 6.0*Vl

{NO oxide ex respiratory tract, umoles}

init ABf = 0

init ABler = 0

Limit ABler >= 0

init ABlcy = 0

Limit ABlcy >= 0

init ABm = 0

Limit ABm >= 0

init ABvrg = 0

Limit ABvrg >= 0

init ABblood = 0

{umoles NAP metabolized}

init AMETl = 0

{umoles NO ex rt metabolized EH, GST and P450 pathways}

init ABMETl2 = 0

init ABMETGl = 0

{AUCs NAP}
init AUCvtot = 0
init AUCvl = 0
{AUCs NO}
init AUCBvtot = 0
init AUCBvl = 0
{tissue flows mL/min}
Qtot = (0.012*Age^3 - 1.2144*Age^2 + 40.32*Age + 44.144)*1000/60
Qalv = 0.82*Qtot
Qf = 0.0528*Qtot
Ql = 0.0795*Qtot
Qm = 0.0304*Qtot
Qvrg = 0.837*Qtot
{tissue volumes mL}
BW = -1.9*Age^4 + 72.8*Age^3 - 813.1*Age^2 + 5535.6*Age + 4453.7
Vf = 0.0165*Age^5 - 1.9784*Age^4 + 51.963*Age^3 - 459.38*Age^2 + 1566.8*Age + 1004.2
Vl = 0.0072*Age^5 - 0.3975*Age^4 + 7.9052*Age^3 - 65.625*Age^2 + 262.02*Age + 157.2
Vm = - 0.0623*Age^5 + 2.3433*Age^4 - 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2
Vvrg = BW - (Vf + Vl + Vm + Vlu + Vblood)
Vblood = 0.075*BW
{blood/air and tissue/blood partition coefficients, NAP}
Pb = 571
Pl = 7.0
Pf = 160.0
Pm = 4.0
Pvrg = 4.0
{blood/air and tissue/blood partition coefficients, NO}
PBb = 571
PBl = 7.0
PBf = 22.9
PBm = 4.0
PBvrg = 4.0
{calculated concentrations of NAP umol/mL}
Cblood = Ablood/Vblood
Cart = Cvex
Cvf = Af/(Vf*Pf)
Cvl = Al/(Vl*Pl)
Cvm = Am/(Vm*Pm)
Cvvrg = Avrg/(Vvrg*Pvrg)
Cvtot = (Ql*Cvl + Qf*Cvf + Qm*Cvm + Qvrg*Cvvrg)/Qtot
Cairin = exposure/(24.45*1E3)
CGSHl = GSHl/Vl
CGSHlb = 6.0
{calculated concentrations of NO umol/mL}

CBblood = ABblood/Vblood
CBart = CBvex
CBvf = ABf/(Vf*PBf)
CBvler = ABler/(Vl*PBl)
CBvlcy = ABlcy/(Vl*PBl)
CBvm = ABm/(Vm*PBm)
CBvvrg = ABvrg/(Vvrg*PBvrg)
CBvtot = (Ql*CBvlcy + Qf*CBvf + Qm*CBvm + Qvrg*CBvvrg)/Qtot
CBairin = exposureB/(24.45*1E3)
{differential equations for NAP uptake and metabolism, umoles}
d/dt(Al) = Ql*(Cart - Cvl) - Vmaxl*Cvl/(Km + Cvl)
d/dt(Af) = Qf*(Cart - Cvf)
d/dt(Am) = Qm*(Cart - Cvm)
d/dt(Avrg) = Qvrg*(Cart - Cvvrg)
d/dt(Ablood) = Ql*Cvl + Qf*Cvf + Qm*Cvm + Qvrg*Cvvrg + Qtot*Cvex
{differential equations for NO uptake and metabolism, umoles}
d/dt(ABf) = Qf*(CBart - CBvf)
d/dt(ABm) = Qm*(CBart - CBvm)
d/dt(ABvrg) = Qvrg*(CBart - CBvvrg)
d/dt(ABblood) = Ql*CBvlcy + Qf*CBvf + Qm*CBvm + Qvrg*CBvvrg + Qtot*CBvex
d/dt(ABler) = Vmaxl*Cvl/(Km + Cvl) - Kec*(CBvler - CBvlcy) - Vmaxl2*CBvler/(Km2ih + CBvler)
d/dt(ABlcy) = Kec*(CBvler - CBvlcy) + Ql*(CBart - CBvlcy) - VmaxGl*CBvlcy*CGSHl/(KmG2*CBvlcy + KmG1*CGSHl + CBvlcy*CGSHl)
d/dt(GSHl) = Kgshl*(CGSHlb - (GSHl/Vl)) - Kge*GSHl - VmaxGl*CBvlcy*CGSHl/(KmG1*CBvlcy + KmG2*CGSHl + CBvlcy*CGSHl) - KNOH*CBvlcy*1E3
{amount of BD metabolized in liver to NO, umoles}
d/dt(AMETl) = Vmaxl*Cvl/(Km+ Cvl)
{amount of NO metabolized in liver and lung to diol, umoles}
d/dt(ABMETl2) = (Vmaxl2*CBvler/(Km2ih + CBvler))/2
{amount of NO metabolized in liver and lung to GSH conjugate, umoles}
d/dt(ABMETGl) = (VmaxGl*CBVlcy*CGSHl/(KmG1*CBvlcy + KmG2*CGSHl + CGSHl*CBvlcy))/2
{amount of NO rearranged to NOH, umoles}
d/dt(ABNOHl) = KNOH*CBvlcy*1E3
init ABNOHl = 0
{AUCs for NAP, umolmin/mL}
d/dt(AUCvtot) = Cvtot
d/dt(AUCvl) = Cvl
{AUCs for NO, umolmin/mL}
d/dt(AUCBvtot) = CBvtot
d/dt(AUCBvl) = CBvlcy

E.5.6 Model Code for BD/BMO RT 0-5 yr Child

METHOD Stiff

STARTTIME = 0
STOPTIME= 2880
DT = 0.0001
{Butadiene (BD) in upper respiratory tract compartment (URT) umoles}
init ANURTa = 0
init ANURTmuc = 0
init ANURTepi = 0
Limit ANURTepi >= 0
init ANURTex = 0
init AMETua = 0
{Butadienemonoxide (BMO) in upper respiratory compartment (URT) umoles}
init ABURTa = 0
init ABURTmuc = 0
init ABURTepi = 0
init GSHua = 1.0*VURTepi
init ABURTex = 0
init ABMET2ua = 0
init ABMETGua = 0
init ABMET3ua = 0
Limit ABMET3ua >= 0
{BD in conducting airways compartment (CA), umoles}
init ANCAa = 0
init ANCAmuc = 0
init ANCAepi = 0
init ANCAex = 0
init AMETca = 0
{BMO in conducting airways compartment (CA), umoles}
init ABCAa = 0
init ABCAmuc = 0
init ABCAepi = 0
init ABCAex = 0
init GSHca = 1.0*VCA
init ABMET2ca = 0
init ABMETGca = 0
init ABMET3ca = 0
{BD in transitional bronchioles compartment (TB), umoles}
init ANTBa = 0
init ANTBmuc = 0
init ANTBepi = 0
init ANTBex = 0

init AMETtb = 0
{BMO in transitional bronchioles compartment (TB), umoles}
init ABTBa = 0
init ABTBmuc = 0
init ABTBepi = 0
init GSHtb = 1.0*VTBepi
init ABTBex = 0
init ABMET2tb = 0
init ABMETGtb = 0
init ABMET3tb = 0
{BD in pulmonary compartment (PU), umoles}
init ANPUa = 0
init ANPUmuc = 0
init ANPUepi = 0
init ANPUex = 0
init ANex = 0
init AMETpu = 0
{BMO in pulmonary compartment (PU), umoles}
init ABPUa = 0
init ABPUmuc = 0
init ABPUepi = 0
init ABPUex = 0
init ABex = 0
init GSHpu = 1.0*VPU
init ABMET2pu = 0
init ABMETGpu = 0
init ABMET3pu = 0
{model equations}
Q = RPM*TVOL
Cairin = exposure/(24.36*1E3)
VURTepi = SAURT*WUA
VURTmuc = SAURT*WSMua
VURTex = SAURT*WUAs
VCAmuc = SACA*WSMca
VCAepi = SACA*WCA
VCAex = SACA*WCAs
VTBmuc = SATB*WSMtb
VTBepi = SATB*WTA
VTBex = SATB*WTAs
VPUmuc = SAPU*WSMpu
VPUepi = SAPU*WPA
VPUex = SAPU*WTAs
Vlu = 59.213 + 123.99*Age - 20.31*Age^2 + 1.5069*Age^3 - 0.0346*Age^4
VURT = 0.0026*Vlu

VCA = 0.018*Vlu
VTB = 0.043*Vlu
VPU = 0.937*Vlu
Curtepil = (ANURTepi/VURTepi)
Ccaepil = (ANCAepi/VCAepi)
Ctbepil = (ANTBepi/VTBepi)
Cpuepil = (ANPUepi/VPUepi)
Cvurtex = (ANURTex/(VURTex*Pvrg))
Cvcaex = (ANCAex/(VCAex*Pvrg))
Cvtbex = (ANTBex/(VTBex*Pvrg))
Cvpuex = (ANPUex/(VPUex*Pvrg))
Cvex = (ANURTex+ANCAex+ANTBex+ANPUex)/((VURTex+VCAex+VTBex+VPUex)*Pvrg)
CBurtepil = (ABURTepi/VURTepi)
CBcaepil = (ABCAepi/VCAepi)
CBtbepil = (ABTBepi/VTBepi)
CBpuepil = (ABPUepi/VPUepi)
CBvurtex = (ABURTex/(VURTex*PBvrg))
CBvcaex = (ABCAex/(VCAex*PBvrg))
CBvtbex = (ABTBex/(VTBex*PBvrg))
CBvpuex = (ABPUex/(VPUex*PBvrg))
CBvex = (ABURTex+ABCAex+ABTBex+ABPUex)/((VURTex+VCAex+VTBex+VPUex)*PBvrg)
CGSHuab = 2.5
CGSHcab = 2.0
CGSHtbb = 1.0
CGSHpub = 1.0
Exposure = IF TIME <= 1440 THEN 1 ELSE 0
ExposureB = IF TIME <= 1440 THEN 0 ELSE 0
Age = 3.0
{upper respiratory tract constants}
PMA = 30 {mucus:air partition coeff}
KOURT = 1980 {mass transfer coeffs., cm/min}
KTRURT = 19.2
KBOURT = 19.2
KOCA = 181
KTRCA = 19.2
KBOCA = 19.2
KOTB = 158
KTRTB = 19.2
KBOTB = 19.2
KOPU = 158
KTRPU = 19.2
KBOPU = 19.2
KMUC = 0.001 {diffusion constants, cm2/min}
KSQM = 0.0002

KG = 6.0
SAURT = VURT/WUA {surface areas, cm2}
SACA = VCA/WCA
SATB = VTB/WTA
SAPU = VPU/WPA
VURTa = 0.00035*TLC {luminal volumes, cm3}
VCAa = 0.0105*TLC
VTBa = 0.042*TLC
VPUa = 0.944*TLC
TLC = 236.5 + 282*Age - 4.775*Age^2 + 0.285*Age^3
RPM = 53.5*(BW/1000)^-0.26 {breaths/min}
TVOL = 35.45 + 33.56*Age - 1.47*Age^2 + 0.0793*Age^3 {tidal volume mL/breath}
{thicknesses (W) of upper airways epithelium (UA), submucosa (UAs);mucus (SM); conducting airways epi (CA), submucosa (CAs); transitional airways epi (TA), submucosa (TAs); and pulmonary airways epi (PA), cm}
WUA = 0.005
WSMua = 0.001
WSMca = 0.0005
WSMtb = 0.0002
WSMpu = 0.0001
WCA = 0.0025
WTA = 0.001
WPA = 0.0005
WUAs = 0.01
WCAs = 0.005
WTAs = 0.002
Qua = 0.0025*Qtot {blood flow to the URT region}
Qca = 0.0075*Qtot {blood flow to the CA}
Qta = 0.0067*Qtot {blood flow to the TA}
{metabolic constants umol/min, umol/mL, based on Csanady et al. 2003 scaled to smaller BWs, 1 = EH, 2 = conj, 3 = oxid}
Vmaxua = 9.09E-3*3.0*VURTepi*(7E4/BW)^0.25/60
Vmaxca = 9.09E-3*3.0*VCAepi*(7E4/BW)^0.25/60
Vmaxtb = 9.09E-3*3.0*VTBepi*(7E4/BW)^0.25/60
Vmaxpu = 9.09E-3*3.0*VPUepi*(7E4/BW)^0.25/60
Vmaxl = 7.08E-2*14.5*Vl*(7E4/BW)^0.25/60
Vmaxl2 = 1.1*14.5*Vl*(7E4/BW)^0.25/60 {EH}
K1ua = 0.1914*3.0*VURTepi*(7E4/BW)^-0.25/60
K1ca = 0.1914*3.0*VCAepi*(7E4/BW)^-0.25/60
K1tb = 0.1914*3.0*VTBepi*(7E4/BW)^-0.25/60
K1pu = 0.1914*3.0*VPUepi*(7E4/BW)^-0.25/60
Kgsh = 0.012 {GSH /min}
Kge = 0.15/60
VmaxGl = 2.71*58*Vl*(7E4/BW)^0.25/60 {umol/min/liver, GST}
K2ua = 0.1536*54*VURTepi*(7E4/BW)^-0.25/60 {umol/min/URT}

K2ca = 0.1536*54*VCAepi*(7E4/BW)^-0.25/60 {umol/min/CA}

K2tb = 0.1536*54*VTBepi*(7E4/BW)^-0.25/60 {umol/min/TB}

K2pu = 0.1536*54*VPUepi*(7E4/BW)^-0.25/60 {umol/min/PU}

MPl = 14.5 {mg microsomal protein /mL tissue}

MPlu = 3.0 {mg microsomal protein/mL tissue}

CPl = 58 {mg cytosolic protein/mL tissue}

CPlu = 54 {mg cytosolic protein/mL tissue}

Km = 0.00514 {umol/mL}

Kmlu = 0.002

Km2 = 0.58

Km2ih = 0.116

KmG1 = 0.1 {GSH}

KmG2 = 10.4 {BMO}

Kec = 400

Vmaxua3 = 0.0066*0.2/(7E4/BW)^0.25/60

Vmaxca3 = 0.1986*0.2/(7E4/BW)^0.25/60

Vmaxtb3 = 0.7947*0.2/(7E4/BW)^0.25/60

Vmaxpu3 = 1.7/(7E4/BW)^0.25/60

Vmaxl3 = 14.8/(7E4/BW)^0.25/60

Km3 = 0.0156

{differential equations for BD in URT compartment, URT}

d/dt(ANURTa) = Q*(Cairin - (ANURTa/VURTA)) - KOURT*SAURT*((ANURTa/VURTA)-(ANURTmuc/(PMA*VURTmuc)))

d/dt(ANURTmuc) = KOURT*SAURT*((ANURTa/VURTa) - (ANURTmuc/(PMA*VURTmuc))) - KTRURT*SAURT*((ANURTmuc/(VURTmuc*PMA)) - (ANURTepi/(VURTepi*Pvrg)))

d/dt(ANURTepi) = KTRURT*SAURT*((ANURTmuc/(VURTmuc*PMA)) - (ANURTepi/(VURTepi*Pvrg))) - KBOURT*SAURT*((ANURTepi/(VURTepi*Pvrg)) - (ANURTex/(VURTex*Pvrg))) - Vmaxua*(ANURTepi/(VURTepi*Pvrg))/(Kmlu + (ANURTepi/(VURTepi*Pvrg)))

d/dt(ANURTex) = KBOURT*SAURT*((ANURTepi/VURTepi) - (ANURTex/VURTex)) + Qua*(Cart - (ANURTex/(VURTex*Pvrg)))

d/dt(AMETua) = Vmaxua*(ANURTepi/(VURTepi*Pvrg))/(Kmlu + (ANURTepi/(VURTepi*Pvrg)))

d/dt(GSHua) = Kgsh*(CGSHuab - (GSHua/VURTepi)) - Kge*GSHua - K2ua*ABURTepi

{differential equations for BMO in URT compartment, URT}

d/dt(ABURTa) = Q*(CBairin - (ABURTa/VURTa)) - KOURT*SAURT*((ABURTa/VURTa)-(ABURTmuc/(PMA*VURTmuc)))

d/dt(ABURTmuc) = KOURT*SAURT*((ABURTa/VURTa) - (ABURTmuc/(PMA*VURTmuc))) - KTRURT*SAURT*((ABURTmuc/(VURTmuc*PMA)) - (ABURTepi/(VURTepi*PBvrg)))

d/dt(ABURTepi) = KTRURT*SAURT*((ABURTmuc/(VURTmuc*PMA)) - (ABURTepi/(VURTepi*PBvrg))) - KBOURT*SAURT*((ABURTepi/(VURTepi*PBvrg)) - (ABURTex/(VURTex*PBvrg))) + Vmaxua*(ANURTepi/(VURTepi*PBvrg))/(Kmlu + (ANURTepi/(VURTepi*PBvrg))) - K1ua*ANURTepi - K2ua*ANURTepi - Vmaxua3*(ABURTepi/(VURTepi*PBvrg))/(Km3 + (ABURTepi/(VURTepi*PBvrg)))

d/dt(ABMET2ua) = K1ua*ANURTepi

d/dt(ABMETGua) = K2ua*ANURTepi

d/dt(ABMET3ua) = Vmaxua3*(ABURTepi/(VURTepi*PBvrg))/(Km3 + (ABURTepi/(VURTepi*PBvrg)))

d/dt(ABURTex) = KBOURT*SAURT*((ABURTepi/VURTepi) - (ABURTex/(VURTex*PBvrg))) + Qua*(CBart - (ABURTex/(VURTex*PBvrg)))

{differential equations for BD in CA compartment, CA}

d/dt(ANCAa) = Q*(Cairin - (ANCAa/VCAa)) - KOCA*SACA*((ANCAa/VCAa)-(ANCAmuc/(PMA*VCAmuc)))

d/dt(ANCAmuc) = KOCA*SACA*((ANCAa/VCAa) - (ANCAmuc/(PMA*VCAmuc))) - KTRCA*SACA*((ANCAmuc/(VCAmuc*PMA)) - (ANCAepi/(VCAepi*Pvrg)))

d/dt(ANCAepi) = KTRCA*SACA*((ANCAmuc/(VCAmuc*PMA)) - (ANCAepi/(VCAepi*Pvrg))) - KBOCA*SACA*((ANCAepi/(VCAepi*Pvrg)) - (ANCAex/(VCAex*Pvrg))) - Vmaxca*(ANCAepi/(VCAepi*Pvrg))/(Kmlu + (ANCAepi/(VCAepi*Pvrg)))

d/dt(ANCAex) = KBOCA*SACA*((ANCAepi/(VCAepi*Pvrg)) - (ANCAex/(VCAex*Pvrg))) + Qca*(Cart - (ANCAex/(VCAex*Pvrg)))

d/dt(AMETca) = Vmaxca*(ANCAepi/(VCAepi*Pvrg))/(Kmlu + (ANCAepi/(VCAepi*Pvrg)))

d/dt(GSHca) = Kgsh*(CGSHcab - (GSHca/VCAepi)) - Kge*GSHca - K2ca*ABCAepi

{differential equations for BMO in CA compartment, CA}

d/dt(ABCAa) = Q*(CBairin - (ABCAa/VCAa)) - KOCA*SACA*((ABCAa/VCAa)-(ABCAmuc/(PMA*VCAmuc)))

d/dt(ABCAmuc) = KOCA*SACA*((ABCAa/VCAa) - (ABCAmuc/(PMA*VCAmuc))) - KTRCA*SACA*((ABCAmuc/(VCAmuc*PMA)) - (ABCAepi/(VCAepi*PBvrg)))

d/dt(ABCAepi) = KTRCA*SACA*((ABCAmuc/(VCAmuc*PMA)) - (ABCAepi/(VCAepi*PBvrg))) + Vmaxca*(ANCAepi/(VCAepi*Pvrg))/(Kmlu + (ANCAepi/(VCAepi*Pvrg))) - KBOCA*SACA*((ABCAepi/(VCAepi*PBvrg)) - (ABCAex/(VCAex*PBvrg))) - K1ca*ABCAepi - K2ca*ABCAepi - Vmaxca3*(ABCAepi/(VCAepi*PBvrg))/(Km3 + (ABCAepi/(VCAepi*PBvrg)))

d/dt(ABCAex) = KBOCA*SACA*((ABCAepi/(VCAepi*PBvrg)) - (ABCAex/(VCAex*PBvrg))) + Qca*(CBart - (ABCAex/(VCAex*PBvrg)))

d/dt(ABMET2ca) = K1ca*ABCAepi

d/dt(ABMETGca) = K2ca*ABCAepi

d/dt(ABMET3ca) = Vmaxca3*(ABCAepi/(VCAepi*PBvrg))/(Km3 + (ABCAepi/(VCAepi*PBvrg)))

{differential equations for BD in TB compartment umoles, TB}

d/dt(ANTBa) = Q*(Cairin - (ANTBa/VTBa)) - KOTB*SATB*((ANTBa/VTBa)-(ANTBmuc/(PMA*VTBmuc)))

d/dt(ANTBmuc) = KOTB*SATB*((ANTBa/VTBa) - (ANTBmuc/(PMA*VTBmuc))) - KTRTB*SATB*((ANTBmuc/(VTBmuc*PMA)) - (ANTBmuc/(VTBmuc*PMA)))

d/dt(ANTBepi) = KTRTB*SATB*((ANTBmuc/(VTBmuc*PMA)) - (ANTBepi/(VTBepi*Pvrg))) - KBOTB*SATB*((ANTBepi/(VTBepi*Pvrg)) - (ANTBex/(VTBex*Pvrg))) - Vmaxtb*(ANTBepi/(VTBepi*Pvrg))/(Kmlu + (ANTBepi/(VTBepi*Pvrg)))

d/dt(ANTBex) = KBOTB*SATB*((ANTBepi/(VTBepi*Pvrg)) - (ANTBex/(VTBex*Pvrg))) + Qta*(Cart - (ANTBex/(VTBex*Pvrg)))

d/dt(AMETtb) = Vmaxtb*(ANTBepi/(VTBepi*Pvrg))/(Kmlu + (ANTBepi/(VTBepi*Pvrg)))

d/dt(GSHtb) = Kgsh*(CGSHtbb - (GSHtb/VTBepi)) - Kge*GSHtb - K2tb*ABTBepi

{differential equations for BMO in TB compartment umoles, TB}

d/dt(ABTBa) = Q*(CBairin - (ABTBa/VTBa)) - KOTB*SATB*((ABTBa/VTBa)-(ABTBmuc/(PMA*VTBmuc)))

d/dt(ABTBmuc) = KOTB*SATB*((ABTBa/VTBa) - (ABTBmuc/(PMA*VTBmuc))) - KTRTB*SATB*((ABTBmuc/(VTBmuc*PMA)) - (ABTBepi/(VTBepi*PBvrg)))

d/dt(ABTBepi) = KTRTB*SATB*((ABTBmuc/(VTBmuc*PMA)) - (ABTBepi/(VTBepi*PBvrg))) - KBOTB*SATB*((ABTBepi/(VTBepi*PBvrg)) - (ABTBex/(VTBex*PBvrg))) + Vmaxtb*(ANTBepi/(VTBepi*Pvrg))/(Kmlu + (ANTBepi/(VTBepi*Pvrg))) - K1tb*ABTBepi - K2tb*ABTBepi - Vmaxtb3*(ANTBepi/(VTBepi*Pvrg))/(Km3 + (ANTBepi/(VTBepi*Pvrg)))

d/dt(ABMET2tb) = K1tb*ABTBepi

d/dt(ABMETGtb) = K2tb*ABTBepi

d/dt(ABMET3tb) = Vmaxtb3*(ANTBepi/(VTBepi*Pvrg))/(Km3 + (ANTBepi/(VTBepi*Pvrg)))

d/dt(ABTBex) = KBOTB*SATB*(ABTBepi/(VTBepi*PBvrg) - (ABTBex/(VTBex*PBvrg))) + Qta*(CBart - (ABTBex/(VTBex*PBvrg)))

{differential equations for BD in PU compartment umoles, PU}

d/dt(ANPUa) = Q*(Cairin - (ANPUa/VPUa)) - KOPU*SAPU*((ANPUa/VPUa)-(ANPUmuc/(PMA*VPUmuc)))

d/dt(ANPUmuc) = KOPU*SAPU*((ANPUa/VPUa) - (ANPUmuc/(PMA*VPUmuc))) - KTRPU*SAPU*((ANPUmuc/VPUmuc) - (ANPUepi/(VPUepi*Pvrg)))

d/dt(ANPUepi) = KTRPU*SAPU*((ANPUmuc/(VPUmuc*PMA)) - (ANPUepi/(VPUepi*Pvrg))) - KBOPU*SAPU*((ANPUepi/(VPUepi*Pvrg)) - (ANPUex/(VPUex*Pvrg))) - Vmaxpu*(ANPUepi/(VPUepi*Pvrg))/(Kmlu + (ANPUepi/(VPUepi*Pvrg)))

d/dt(ANPUex) = KBOPU*SAPU*((ANPUepi/(VPUepi*Pvrg)) - (ANPUex/(VPUex*Pvrg))) + Qtot*(Cart - (ANPUex/(VPUex*Pvrg)))

d/dt(GSHpu) = Kgsh*(CGSHpub - (GSHpu/VPUepi)) - Kge*GSHpu - K2pu*ABPUepi

d/dt(AMETpu) = Vmaxpu*(ANPUepi/(VPUepi*Pvrg))/(Kmlu + (ANPUepi/(VPUepi*Pvrg)))

{differential equations for BMO in PU compartment umoles, PU}

d/dt(ABPUa) = Q*(Cairin - (ANPUa/VPUa)) - KOPU*SAPU*((ANPUa/VPUa)-(ANPUmuc/(PMA*VPUmuc)))

d/dt(ABPUmuc) = KOPU*SAPU*((ABPUa/VPUa) - (ABPUmuc/(PMA*VPUmuc))) - KTRPU*SAPU*((ABPUmuc/(VPUmuc*PMA)) - (ABPUepi/(VPUepi*PBvrg)))

d/dt(ABPUepi) = KTRPU*SAPU*((ABPUmuc/(VPUmuc*PMA)) - (ABPUepi/(VPUepi*PBvrg))) - KBOPU*SAPU*((ABPUepi/(VPUepi*PBvrg)) - (ABPUex/(VPUex*PBvrg))) + Vmaxpu*(ANPUepi/(VPUepi*Pvrg))/(Kmlu + (ANPUepi/(VPUepi*Pvrg))) - K1pu*ABPUepi - K2pu*ABPUepi - Vmaxpu3*(ABPUepi/(VPUepi*Pvrg))/(Km3 + (ABPUepi/(VPUepi*Pvrg)))

d/dt(ABPUex) = KBOPU*SAPU*((ABPUepi/(VPUepi*PBvrg)) - (ABPUex/(VPUex*PBvrg))) + Qtot*(CBart - (ABPUex/(VPUex*PBvrg)))

d/dt(ABMET2pu) = K1pu*ABPUepi

d/dt(ABMETGpu) = K2pu*ABPUepi

d/dt(ABMET3pu) = Vmaxpu3*(ABPUepi/(VPUepi*Pvrg))/(Km3 + (ABPUepi/(VPUepi*Pvrg)))

{Sum of Lung BD}

d/dt(ANex) = Qtot*((Cart-Cvurtex) + (Cart-Cvcaex) + (Cart-Cvtbex) + (Cart-Cvpuex))

{Sum of Lung BMO}

d/dt(ABex) = Qtot*((CBart-CBvurtex) +(CBart-CBvcaex) + (CBart-CBvtbex) + (CBart-CBvpuex))

{BD ex respiratory tract, umoles}

init Af = 0

init Al = 0

init Am = 0

init Avrg = 0

init Ablood = 0

init GSHl = 6.0*Vl

{BMO oxide ex respiratory tract, umoles}

init ABf = 0

init ABler = 0

init ABlcy = 0

init ABm = 0

init ABvrg = 0

init ABblood = 0

{umoles BD metabolized}
init AMETl = 0
{umoles BMO ex rt metabolized EH, GST and P450 pathways}
init ABMETl2 = 0
init ABMETGl = 0
init ABMETl3 = 0
{AUCs BD}
init AUCvtot = 0
init AUCvl = 0
{AUCs BMO}
init AUCBvtot = 0
init AUCBvl = 0
{tissue flows mL/min}
Qtot = (0.012*Age^3 - 1.2144*Age^2 + 40.32*Age + 44.144)*(1000/60)
Qalv = (17.874*Age + 39.785)*(1000/60)
Qf = 0.0528*Qtot
Ql = 0.0795*Qtot
Qm = 0.0304*Qtot
Qvrg = 0.837*Qtot
{tissue volumes mL}
BW = - 1.9*Age^4 + 72.8*Age^3 - 813.1*Age^2 + 5535.6*Age + 4453.7
Vf = 0.0165*Age^5 - 1.9784*Age^4 + 51.963*Age^3 - 459.38*Age^2 + 1566.8*Age + 1004.2
Vl = 0.0072*Age^5 - 0.3975*Age^4 + 7.9052*Age^3 - 65.625*Age^2 + 262.02*Age + 157.52
Vm = -0.0623*Age^5 + 2.3433*Age^4 - 26.559*Age^3 + 144.75*Age^2 +339.84*Age + 1648.2
Vvrg = BW - (Vf + Vl + Vm + Vlu + Vblood)
Vblood = 0.075*BW
{blood/air and tissue/blood partition coefficients, BD}
Pb = 1.5
Pl = 5.49
Pf = 118.2
Pm = 5.26
Pvrg = 5.34
{blood/air and tissue/blood partition coefficients, BMO}
PBb = 60
PBl = 0.6545
PBf = 1.808
PBm = 0.6533
PBvrg = 0.6348
{calculated concentrations of BD umol/mL}
Cblood = Ablood/Vblood
Cart = Cvex
Cvf = Af/(Vf*Pf)
Cvl = Al/(Vl*Pl)
Cvm = Am/(Vm*Pm)

Cvvrg = Avrg/(Vvrg*Pvrg)
Cvtot = (Ql*Cvl + Qf*Cvf + Qm*Cvm + Qvrg*Cvvrg)/Qtot
Cairin = exposure/(24.45*1E3)
CGSHl = GSHl/Vl
CGSHlb = 6.0
{calculated concentrations of BMO umol/mL}
CBblood = ABblood/Vblood
CBart = CBvex
CBvf = ABf/(Vf*PBf)
CBvler = ABler/(Vl*PBl)
CBvlcy = ABlcy/(Vl*PBl)
CBvm = ABm/(Vm*PBm)
CBvvrg = ABvrg/(Vvrg*PBvrg)
CBvtot = (Ql*CBvlcy + Qf*CBvf + Qm*CBvm + Qvrg*CBvvrg)/Qtot
CBairin = exposureB/(24.45*1E3)
{differential equations for BD uptake and metabolism, umoles}
d/dt(Al) = Ql*(Cart - Cvl) - Vmaxl*Cvl/(Km + Cvl)
d/dt(Af) = Qf*(Cart - Cvf)
d/dt(Am) = Qm*(Cart - Cvm)
d/dt(Avrg) = Qvrg*(Cart - Cvvrg)
d/dt(Ablood) = Ql*Cvl + Qf*Cvf + Qm*Cvm + Qvrg*Cvvrg + Qtot*Cvex
{differential equations for BMO uptake and metabolism, umoles}
d/dt(ABf) = Qf*(CBart - CBvf)
d/dt(ABm) = Qm*(CBart - CBvm)
d/dt(ABvrg) = Qvrg*(CBart - CBvvrg)
d/dt(ABblood) = Ql*CBvlcy + Qf*CBvf + Qm*CBvm + Qvrg*CBvvrg + Qtot*CBvex
d/dt(ABler) = Vmaxl*Cvl/(Km + Cvl) - Kec*(CBvler - CBvlcy) - Vmaxl2*CBvler/(Km2ih + CBvler)
d/dt(ABlcy) = Kec*(CBvler - CBvlcy) + Ql*(CBart - CBvlcy) - VmaxGl*CBvlcy*CGSHl/(KmG2*CBvlcy + KmG1*CGSHl + CBvlcy*CGSHl)
d/dt(GSHl) = Kgsh*(CGSHlb - (GSHl/Vl)) - Kge*GSHl - VmaxGl*CBvlcy*CGSHl/(KmG2*CBvlcy + KmG1*CGSHl + CBvlcy*CGSHl) - Vmaxl3*CBvlcy/(Km3 + CBvlcy)
{amount of BD metabolized in liver to BMO, umoles}
d/dt(AMETl) = Vmaxl*Cvl/(Km+ Cvl)
{amount of BMO metabolized in liver and lung to diol, umoles}
d/dt(ABMETl2) = Vmaxl2*CBvler/(Km2ih + CBvler)
{amount of bmo metabolized in liver and lung to GSH conjugate, umoles}
d/dt(ABMETGl) = VmaxGl*CBVlcy*CGSHl/(KmG2*CBvlcy + KmG1*CGSHl + CGSHl*CBvlcy)
{amount of BMO oxidized to DEB, umoles}
d/dt(ABMETl3) = Vmaxl3*CBvlcy/(Km3 + CBvlcy)
{AUCs for BD, umolmin/mL}
d/dt(AUCvtot) = Cvtot
d/dt(AUCvl) = Cvl
{AUCs for BMO, umolmin/mL}
d/dt(AUCBvtot) = CBvtot
d/dt(AUCBvl) = CBvlcy

E.5.7 Model Code for BD/BMO/DEB 0-5 Yr Child

METHOD Stiff

STARTTIME = 0
STOPTIME= 48
DT = 0.001
{butadiene BD, moles}
init Af = 0
init Al = 0
init Am = 0
init Avrg = 0
init Abr = 0
init Apu = 0
{butadienemonoxide BMO, moles}
init ABf = 0
init ABler = 0
init ABlcy = 0
init ABm = 0
init ABvrg = 0
init ABbr = 0
init ABpu = 0
{diepoxybutane DEB, moles}
init ACf = 0
init ACl = 0
init ACm = 0
init ACvrg = 0
init ACbr = 0
init ACpu = 0
{moles of GSH in liver and lung}
init GSHl = 5.9E-3*Vl
GSHl0 = 5.9E-3*Vl
init GSHlu = 1.12E-3*Vlu
GSHlu0 = 1.12E-3*Vlu
Kgsh = 0.72
Kge = 0.15
CGSHl = GSHl/Vl
CGSHlu = GSHlu/Vlu
{moles butadiene metabolized}
init Ametl = 0
init Ametpu = 0
init Ametbr = 0
{moles of butadienemonoxide metabolized}
init ABmetl1 = 0
init ABmetl2 = 0

init ABmetpu1 = 0
init ABmetpu2 = 0
init ABmetbr1 = 0
init ABmetbr2 = 0
init ABmetl3 = 0
init ABmetpu3 = 0
init ABmetbr3 = 0
{area under the venous blood concn x time curve, butadiene}
init AUCvtot = 0
init AUCvl = 0
init AUCvpu = 0
init AUCvbr = 0
init AUCvlung = 0
{area under the venous blood concn x time curve, butadienemonoxide}
init AUCBvtot = 0
init AUCBvl = 0
init AUCBvpu = 0
init AUCBvbr = 0
init AUCBvlung = 0
{area under the venous blood concn x time curve, diepoxybutene}
init AUCCvtot = 0
init AUCCvl = 0
init AUCCvpu = 0
init AUCCvbr = 0
init AUCCvlung = 0
{tissue flows L/hr}
Qtot = 0.012*Age^3 - 1.2144*Age^2 + 40.32*Age + 44.144
Qalv = 17.874*Age + 39.785
Qf = 0.0528*Qtot
Ql = 0.0795*Qtot
Qm = 0.0304*Qtot
Qvrg = 0.837*Qtot
Qpu = 0.93*Qtot
Qbr = 0.07*Qtot
Age = 0.0
{tissue volumes L}
BW = (-1.9*Age^4 + 72.8*Age^3 - 813.1*Age^2 + 5535.6*Age +4453.7)/1000
Vf = (0.0165*Age^5 - 1.9784*Age^4 + 51.963*Age^3 - 459.38*Age^2 + 1566.8*Age + 1004.2)/1000
Vl = (0.0072*Age^5 - 0.3975*Age^4 + 7.9052*Age^3 - 65.625*Age^2 + 262.02*Age + 157.52)/1000
Vm = (-0.0623*Age^5 + 2.3433*Age^4 - 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2)/1000
Vvrg = BW - (Vf + Vl + Vm +Vlu)
Vlu = (-0.0346*Age^4 + 1.5069*AGe^3 - 20.31*Age^2 + 123.99*AGe + 59.213)/1000
Vpu = 0.9*Vlu
Vbr = 0.1*Vlu

{blood/air and tissue/blood partition coefficients, butadiene}
Pb = 1.5
Pl = 5.49
Pf = 118.2
Pm = 5.26
Pvrg = 5.34
Ppu = 4.02
Pbr = 4.02
{blood/air and tissue/blood partition coefficients, butadienemonoxide}
PBb = 60
PBl = 0.6545
PBf = 1.8083
PBm = 0.6533
PBvrg = 0.6348
PBpu = 0.4725
PBbr = 0.4725
{blood/air and tissue/blood partition coefficients, diepoxybutene}
PCb = 300
PCl = 0.70
PCf = 0.715
PCm = 0.697
PCvrg = 0.6
PCpu = 0.6
PCbr = 0.6
{butadiene oxidation metabolic parameters, mol/hr, mol/L}
Vmaxlu = 9.0E-9*Vlu*3E3*(70/BW)^0.25
Vmaxbr = 0.1*Vmaxlu
Vmaxpu = 0.9*Vmaxlu
Vmaxl = 7.08E-8*Vl*1.45E4*(70/BW)^0.25
Km = 5.14E-6
Kmlu = 2.0E-6
{butadienemonoxide metabolic parameters, mol/hr, mol/L, /hr; 1 = hydrolysis, 2 = conjugation, 3 = oxidation}
Vmaxl1 = 1.1E-6*Vl*1.45E4*(70/BW)^0.25
Km1 = 5.8E-4
Km1ih = 0.2*Km1
Kec = 400
Vmaxl2 = 2.71E-6*Vl*5.8E4*(70/BW)^0.25
Km2 = 1.04E-2
Km2bmo = 1E-4
k1 = 0.1914*3E3*Vlu*(70/BW)^-0.25
k2 = 0.1536*5.8E4*Vlu*(70/BW)^-0.25
Vmaxl3 = 1.48e-5*(70/BW)^0.25
Vmaxpu3 = 1.7E-6*(70/BW)^0.25

Vmaxbr3 = 2.0E-7*(70/BW)^0.25
Km3 = 1.56E-5
Km3ih = 0.2*Km3
{diepoxybutene elimination constant, /hr}
Ke = 0.6*(70/BW)-0.25
{exposure in ppm converted to moles}
Cair = IF TIME <= 24 THEN 1*(1E-6/25.45) ELSE 0
{calculated concentrations of butadiene}
Cart = (Qpu*Cvpu + Qbr*Cvbr)/Qtot
Cvf = Af/(Vf*Pf)
Cvl = Al/(Vl*Pl)
Cvm = Am/(Vm*Pm)
Cvvrg = Avrg/(Vvrg*Pvrg)
Cvpu = Apu/(Vpu*Ppu)
Cvbr = Abr/(Vbr*Pbr)
Cvtot = (Ql*Cvl + Qf*Cvf + Qm*Cvm + Qvrg*Cvvrg)/Qpu
Cvipu = (Qalv*Cair + Qpu*Cvtot)/((Qalv/Pb) + Qpu)
Cexh = Cvipu/Pb
{calculated concentrations of butadienemonoxide}
CBart = (Qpu*CBvpu + Qbr*CBvbr)/Qtot
CBvf = ABf/(Vf*PBf)
CBvler = ABler/(Vl*PBl)
CBvlcy = ABlcy/(Vl*PBl)
CBvm = ABm/(Vm*PBm)
CBvvrg = ABvrg/(Vvrg*PBvrg)
CBvpu = ABpu/(Vpu*PBpu)
CBvbr = ABbr/(Vbr*PBbr)
CBvtot = (Ql*CBvlcy + Qf*CBvf + Qm*CBvm + Qvrg*CBvvrg)/Qtot
CBair = CBvtot/PBb
CBvipu = (Qalv*CBair + Qpu*CBvtot)/((Qalv/PBb) + Qpu)
CBexh = CBvipu/PBb
{calculated concentrations of diepoxybutene}
CCart = (Qpu*CCvpu + Qbr*CCvbr)/Qtot
CCvf = ACf/(Vf*PCf)
CCvl = ACl/(Vl*PCl)
CCvm = ACm/(Vm*PCm)
CCvvrg = ACvrg/(Vvrg*PCvrg)
CCvpu = ACpu/(Vpu*PCpu)
CCvbr = ACbr/(Vbr*PCbr)
CCvtot = (Ql*CCvl +Qf*CCvf + Qm*CCvm + Qvrg*CCvvrg)/Qtot
CCair = CCvtot/PCb
CCvipu = (Qalv*CCair + Qpu*CCvtot)/((Qalv/PCb) + Qpu)
CCexh = CCvipu/PCb
{differential equations for butadiene uptake and metabolism}

d/dt(Apu) = Qpu*(Cvipu - Cvpu) - Vmaxpu*Cvpu/(Kmlu + Cvpu)

d/dt(Abr) = Qbr*(Cart - Cvbr) - Vmaxbr * Cvbr/(Kmlu + Cvbr)

d/dt(Al) = Ql*(Cart - Cvl) - Vmaxl*Cvl/(Km + Cvl)

d/dt(Af) = Qf*(Cart - Cvf)

d/dt(Am) = Qm*(Cart - Cvm)

d/dt(Avrg) = Qvrg*(Cart - Cvvrg)

{amount of butadiene metabolized in liver and lung}

d/dt(Ametl) = Vmaxl*Cvl/(Km + Cvl)

d/dt(Ametpu) = Vmaxpu*Cvpu/(Kmlu + Cvpu)

d/dt(Ametbr) = Vmaxbr*Cvbr/(Kmlu + Cvbr)

{AUCs for butadiene}

d/dt(AUCvtot) = Cvtot

d/dt(AUCvl) = Cvl

d/dt(AUCvpu) = Cvpu

d/dt(AUCvbr) = Cvbr

d/dt(AUCvlung) =Cvpu + Cvbr

{differential equations for butadienemonoxide metabolism}

d/dt(ABpu) = Qpu*(CBart - CBvpu) + Vmaxpu*Cvpu/(Kmlu + Cvpu) -k1*ABpu -k2*ABpu - Vmaxpu3*CBvpu/(Km3 + CBvpu)

d/dt(ABbr) = Qbr*(CBart - CBvbr) + Vmaxbr * Cvbr/(Kmlu + Cvbr) -k1*ABbr -k2*ABbr - Vmaxbr3*CBvbr/(Km3 + CBvbr)

d/dt(ABler) = Vmaxl*Cvl/(Km + Cvl) - Kec*(CBvler - CBvlcy) - Vmaxl1*CBvler/(Km1ih + CBvler) - Vmaxl3*CBvler/(Km3ih + CBvler)

d/dt(ABlcy) = Ql*(CBart - CBvlcy)+ Kec*(CBvler - CBvlcy) - Vmaxl2*CBvlcy*CGSHl/(Km2*CGSHl + Km2bmo*CBvlcy + CGSHl*CBvlcy)

d/dt(ABf) = Qf*(CBart - CBvf)

d/dt(ABm) = Qm*(CBart - CBvm)

d/dt(ABvrg) = Qvrg*(CBart - CBvvrg)

{AUCs for butadienemonoxide}

d/dt(AUCBvtot) = CBvtot

d/dt(AUCBvl) = CBvler + CBvlcy

d/dt(AUCBvpu) = CBvpu

d/dt(AUCBvbr) = CBvbr

d/dt(AUCBvlung) = CBvpu + CBvbr

{amounts of butadienemonoxide metabolized in liver and lung}

d/dt(ABmetl1) = Vmaxl1*CBvler/(Km1ih + CBvler)

d/dt(ABmetl2) = Vmaxl2*CBvlcy*CGSHl/(Km2*CGSHl + Km2bmo*CBvlcy + CGSHl*CBvlcy)

d/dt(ABmetpu1) = k1*ABpu

d/dt(ABmetpu2) = k2*ABpu

d/dt(ABmetbr1) = k1*ABbr

d/dt(ABmetbr2) = k2*ABbr

d/dt(ABmetl3) = Vmaxl3*CBvler/(Km3ih + CBvler)

d/dt(ABmetpu3) = Vmaxpu3*CBvpu/(Km3 + CBvpu)

d/dt(ABmetbr3) = Vmaxbr3*Cbvbr/(Km3 + CBvbr)

{differential equations for diepoxybutene}

d/dt(ACpu) = Qpu*(CCart - CCvpu) + Vmaxpu3*(ABpu/Vpu)/(Km3 + (ABpu/Vpu)) - Ke*ACpu
d/dt(ACbr) = Qbr*(CCart - CCvbr) + Vmaxbr3*(ABbr/Vbr)/(Km3 + (ABbr/Vbr)) - Ke*ACbr
d/dt(ACl) = Ql*(CCart - CCvl) + Vmaxl3*CBvler/(Km3ih + CBvler) - Ke*ACl
d/dt(ACf) = Qf*(CCart - CCvf)
d/dt(ACm) = Qm*(CCart - CCvm)
d/dt(ACvrg) = Qvrg*(CCart - CCvvrg)
{AUCs for diepoxybutene}
d/dt(AUCCvtot) = CCvtot
d/dt(AUCCvl) = CCvl
d/dt(AUCCvpu) = CCvpu
d/dt(AUCCvbr) = CCvbr
d/dt(AUCCVlung) = CCvpu + CCvbr
{differential equation for GSH}
d/dt(GSHl) = Kgsh*Vl*(GSHl0 - CGSHl) - Kge*GSHl - Vmaxl2*CBvlcy*Cgshl/(Km2*CGSHl + Km2bmo*CBvlcy + CGSHl*CBvlcy)
d/dt(GSHlu) = Kgsh*Vlu*(GSHlu0 - CGSHlu) - Kge*GSHlu

E.5.8 Model Code for Styrene/SO RT (Sarangapani et al*. 2002) 0-5 yr Child*

METHOD Stiff

STARTTIME = 0
STOPTIME= 2880
DT = 0.0001
{Styrene in upper respiratory tract compartment (URT) umoles}
init ANURTa = 0
init ANURTmuc = 0
init ANURTepi = 0
init ANURTex = 0
init AMETurt = 0
{Styrene oxide in upper respiratory compartment (URT) umoles}
init ABURTa = 0
init ABURTmuc = 0
init ABURTepi = 0
init ABURTer = 0
init ABURTcy = 0
init GSHua = 1.0*VURTepi
init ABURTex = 0
init AMET2urt = 0
init AMET3urt = 0
{Styrene in conducting airways compartment (CA), umoles}
init ANCAa = 0

init ANCAmuc = 0
init ANCAepi = 0
init ANCAex = 0
{Styrene oxide in conducting airways compartment (CA), umoles}
init ABCAa = 0
init ABCAmuc = 0
init ABCAepi = 0
init ABCAex = 0
{Styrene in terminal bronchioles compartment (TB), umoles}
init ANTBa = 0
init ANTBmuc = 0
init ANTBepi = 0
init ANTBex = 0
init AMETtb = 0
{Styrene oxide in terminal bronchioles compartment (TB), umoles}
init ABTBa = 0
init ABTBmuc = 0
init ABTBepi = 0
init ABTBer = 0
init ABTBcy = 0
init GSHtb = 1.0*VTBepi
init ABTBex = 0
init AMET2tb = 0
init AMET3tb = 0
{Styrene in pulmonary compartment (PU), umoles}
init ANPUa = 0
init ANPUmuc = 0
init ANPUepi = 0
init ANPUex = 0
init ANex = 0
{Styrene oxide in pulmonary compartment (PU), umoles}
init ABPUa = 0
init ABPUmuc = 0
init ABPUepi = 0
init ABPUex = 0
init ABex = 0
{model equations}
Q = RPM*TVOL
Cairin = exposure/(24.36*1E3)
VURTepi = SAURT*WUA
VURTmuc = SAURT*WSMua
VURTex = SAURT*WUAs
VCAmuc = SACA*WSMca
VCAepi = SACA*WCA

VCAex = SACA*WCAs
VTBmuc = SATB*WSMtb
VTBepi = SATB*WTA
VTBex = SATB*WTAs
VPUmuc = SAPU*WSMpu
VPUepi = SAPU*WPA
VPUex = SAPU*WTAs
Vlu = 59.213 + 123.99*Age - 20.31*Age^2 + 1.5069*Age^3 - 0.0346*Age^4
VURT = 0.0026*Vlu
VCA = 0.018*Vlu
VTB = 0.043*Vlu
VPU = 0.937*Vlu
Curtepil = (ANURTepi/VURTepi)
Ccaepil = (ANCAepi/VCAepi)
Ctbepil = (ANTBepi/VTBepi)
Cpuepil = (ANPUepi/VPUepi)
Cvurtex = (ANURTex/(VURTex*Pvrg))
Cvcaex = (ANCAex/(VCAex*Pvrg))
Cvtbex = (ANTBex/(VTBex*Pvrg))
Cvpuex = (ANPUex/(VPUex*Pvrg))
Cvex = (ANURTex+ANCAex+ANTBex+ANPUex)/((VURTex+VCAex+VTBex+VPUex)*Pvrg)
CBurtepil = (ABURTepi/VURTepi)
CBcaepil = (ABCAepi/VCAepi)
CBtbepil = (ABTBepi/VTBepi)
CBpuepil = (ABPUepi/VPUepi)
CBvurtex = (ABURTex/(VURTex*PBvrg))
CBvcaex = (ABCAex/(VCAex*PBvrg))
CBvtbex = (ABTBex/(VTBex*PBvrg))
CBvpuex = (ABPUex/(VPUex*PBvrg))
CBvex = (ABURTex+ABCAex+ABTBex+ABPUex)/((VURTex+VCAex+VTBex+VPUex)*PBvrg)
GSHuab = 2.5
GSHtbb = 1.0
Exposure = IF TIME <= 1440 THEN 1 ELSE 0
ExposureB = IF TIME <= 1440 THEN 0 ELSE 0
Age = 3.0
{upper respiratory tract constants}
PMA = 30 {mucus:air partition coeff}
KOURT = 1980 {mass transfer coeffs., cm/min}
KTRURT = 19.2
KBOURT = 19.2
KOCA = 181
KTRCA = 19.2
KBOCA = 19.2
KOTB = 158

KTRTB = 19.2
KBOTB = 19.2
KOPU = 158
KTRPU = 19.2
KBOPU = 19.2
KMUC = 0.001 {diffusion constants, cm2/min}
KSQM = 0.0002
KG = 6.0
SAURT = VURT/WUA {surface areas, cm2}
SACA = VCA/WCA
SATB = VTB/WTA
SAPU = VPU/WPA
VURTa = 0.00035*TLC {luminal volumes, cm3}
VCAa = 0.0105*TLC
VTBa = 0.042*TLC
VPUa = 0.944*TLC
TLC = 236*5 + 282*Age - 4.775*Age^2 + 0.285*Age^3
RPM = 53.5*(BW/1000)^-0.26 {breaths/min}
TVOL = 35.45 + 33.56*Age - 1.47*Age^2 + 0.0793*Age^3 {tidal volume mL/breath}
{thicknesses (W) of upper airways epithelium (UA), submucosa (UAs);mucus (SM); conducting airways epi (CA), submucosa (CAs); transitional airways epi (TA), submucosa (TAs); and pulmonary airways epi (PA), cm}
WUA = 0.005
WSMua = 0.001
WSMca = 0.0005
WSMtb = 0.0002
WSMpu = 0.0001
WCA = 0.0025
WTA = 0.001
WPA = 0.0005
WUAs = 0.01
WCAs = 0.005
WTAs = 0.002
Qua = 0.0025*Qtot {blood flow to the URT region}
Qca = 0.0075*Qtot {blood flow to the CA}
Qta = 0.0067*Qtot {blood flow to the TA}
{metabolic constants umol/min, umol/mL, based on Csanady et al. 2003 scaled to smaller BWs}
Vmaxua = 4.17E-5*VURTepi*(70/BW)^0.25
Vmaxtb = 4.17E-5*VTBepi*(70/BW)^0.25
Vmaxl = 0.033*Vl*(70/BW)^0.25
Vmaxl2 = 0.075*Vl*(70/BW)^0.25 {EH}
Vmaxua2 = 0.0112*VURTepi*(70/BW)^0.25
Vmaxtb2 = 0.0112*VTBepi*(70/BW)^0.25
Kgsh = 0.012 {/min}

VmaxGl = 0.467*Vl*(70/BW)^0.25 {umol/min/liver, GST}

VmaxGua = 1.36*VURTepi*(70/BW)^0.25 {umol/min/URT}

VmaxGtb = 1.36*VTBepi*(70/BW)^0.25 {umol/min/TB}

MPl = 23 {mg microsomal protein /mL tissue}

MPlu = 3.8 {mg microsomal protein/mL tissue}

CPl = 45 {mg cytosolic protein/mL tissue}

CPlu = 43 {mg cytosolic protein/mL tissue}

Km1 = 0.01 {umol/mL}

Km2 = 0.01

Kmlu1 = 0.0175

Kmlu2 = 0.0156

KmG1 = 0.1 {GST}

KmG2 = 2.5 {SO}

Kec = 400

{differential equations for ST in URT compartment, URT}

d/dt(ANURTa) = Q*(Cairin - (ANURTa/VURTA)) - KOURT*SAURT*((ANURTa/VURTA)-(ANURTmuc/(PMA*VURTmuc)))

d/dt(ANURTmuc) = KOURT*SAURT*((ANURTa/VURTa) - (ANURTmuc/(PMA*VURTmuc))) - KTRURT*SAURT*((ANURTmuc/(VURTmuc*PMA)) - (ANURTepi/(VURTepi*Pvrg)))

d/dt(ANURTepi) = KTRURT*SAURT*((ANURTmuc/(VURTmuc*PMA)) - (ANURTepi/(VURTepi*Pvrg))) - KBOURT*SAURT*((ANURTepi/(VURTepi*Pvrg)) - (ANURTex/(VURTex*Pvrg))) - Vmaxua*(ANURTepi/(VURTepi*Pvrg))/(Kmlu1 + (ANURTepi/(VURTepi*Pvrg)))

d/dt(ANURTex) = KBOURT*SAURT*((ANURTepi/VURTepi) - (ANURTex/VURTex)) + Qua*(Cart - (ANURTex/(VURTex*Pvrg)))

d/dt(AMETurt) = Vmaxua*(ANURTepi/(VURTepi*Pvrg))/(Kmlu1 + (ANURTepi/(VURTepi*Pvrg)))

d/dt(GSHua) = Kgsh*(GSHuab - (GSHua/VURTepi)) - VmaxGua*(ABURTcy/VURTepi)*(GSHua/VURTepi)/(KmG1*(ABURTcy/VURTepi) + KmG2*(GSHua/VURTepi) + (ABURTcy/VURTepi)*(GSHua/VURTepi))

{differential equations for ST oxide in URT compartment, URT}

d/dt(ABURTa) = Q*(CBairin - (ABURTa/VURTa)) - KOURT*SAURT*((ABURTa/VURTa)-(ABURTmuc/(PMA*VURTmuc)))

d/dt(ABURTmuc) = KOURT*SAURT*((ABURTa/VURTa) - (ABURTmuc/(PMA*VURTmuc))) - KTRURT*SAURT*((ABURTmuc/(VURTmuc*PMA)) - (ABURTepi/(VURTepi*PBvrg)))

d/dt(ABURTepi) = KTRURT*SAURT*((ABURTmuc/(VURTmuc*PMA)) - (ABURTepi/(VURTepi*PBvrg))) - KBOURT*SAURT*((ABURTepi/(VURTepi*PBvrg)) - (ABURTex/(VURTex*PBvrg))) + Vmaxua*(ANURTepi/(VURTepi*PBvrg))/(Kmlu1 + (ANURTepi/(VURTepi*PBvrg)))

d/dt(ABURTer) = Vmaxua*(ANURTepi/(VURTepi*Pvrg))/(Kmlu1 + (ANURTepi/(VURTepi*Pvrg))) - Kec*((ABURTer/(VURTepi*PBvrg)) - (ABURTcy/(VURTepi*PBb))) - Vmaxua2*(ABURTer/(VURTepi*PBvrg))/(Kmlu2 + (ABURTer/(VURTepi*PBvrg)))

d/dt(AMET2urt) = Vmaxua2*(ABURTer/(VURTepi*PBvrg))/(Kmlu2 + (ABURTer/(VURTepi*PBvrg)))

d/dt(ABURTcy) = Kec*((ABURTer/(VURTepi*PBvrg)) - (ABURTcy/(VURTepi*PBb))) + Qua*(CBart - ABURTcy/(VURTepi*PBvrg)) - VmaxGua*(ABURTcy/VURTepi)*(GSHua/VURTepi)/(KmG1*(ABURTcy/VURTepi) + KmG2*(ABURTcy/VURTepi) + KmG2*(GSHua/VURTepi) + (ABURTcy/VURTepi)*(GSHua/VURTepi))

d/dt(AMET3urt) = VmaxGua*(ABURTcy/VURTepi)*(GSHua/VURTepi)/(KmG1*(ABURTcy/VURTepi) + KmG2*(ABURTcy/VURTepi) + KmG2*(GSHua/VURTepi) + (ABURTcy/VURTepi)*(GSHua/VURTepi))

d/dt(ABURTex) = KBOURT*SAURT*((ABURTepi/VURTepi) - (ABURTex/(VURTex*PBvrg))) + Qua*(CBart - (ABURTex/(VURTex*PBvrg)))

{differential equations for ST in CA compartment, CA}

d/dt(ANCAa) = Q*(Cairin - (ANCAa/VCAa)) - KOCA*SACA*((ANCAa/VCAa)-(ANCAmuc/(PMA*VCAmuc)))

d/dt(ANCAmuc) = KOCA*SACA*((ANCAa/VCAa) - (ANCAmuc/(PMA*VCAmuc))) - KTRCA*SACA*((ANCAmuc/(VCAmuc*PMA)) - (ANCAepi/(VCAepi*Pvrg)))

d/dt(ANCAepi) = KTRCA*SACA*((ANCAmuc/(VCAmuc*PMA)) - (ANCAepi/(VCAepi*Pvrg))) - KBOCA*SACA*((ANCAepi/(VCAepi*Pvrg)) - (ANCAex/(VCAex*Pvrg)))

d/dt(ANCAex) = KBOCA*SACA*((ANCAepi/(VCAepi*Pvrg)) - (ANCAex/(VCAex*Pvrg))) + Qca*(Cart - (ANCAex/(VCAex*Pvrg)))

{differential equations for ST oxide in CA compartment, CA}

d/dt(ABCAa) = Q*(CBairin - (ABCAa/VCAa)) - KOCA*SACA*((ABCAa/VCAa)-(ABCAmuc/(PMA*VCAmuc)))

d/dt(ABCAmuc) = KOCA*SACA*((ABCAa/VCAa) - (ABCAmuc/(PMA*VCAmuc))) - KTRCA*SACA*((ABCAmuc/(VCAmuc*PMA)) - (ABCAepi/(VCAepi*PBvrg)))

d/dt(ABCAepi) = KTRCA*SACA*((ABCAmuc/(VCAmuc*PMA)) - (ABCAepi/(VCAepi*PBvrg))) - KBOCA*SACA*((ABCAepi/(VCAepi*PBvrg)) - (ABCAex/(VCAex*PBvrg)))

d/dt(ABCAex) = KBOCA*SACA*((ABCAepi/(VCAepi*PBvrg)) - (ABCAex/(VCAex*PBvrg))) + Qca*(CBart - (ABCAex/(VCAex*PBvrg)))

{differential equations for ST in TB compartment umoles, TB}

d/dt(ANTBa) = Q*(Cairin - (ANTBa/VTBa)) - KOTB*SATB*((ANTBa/VTBa)-(ANTBmuc/(PMA*VTBmuc)))

d/dt(ANTBmuc) = KOTB*SATB*((ANTBa/VTBa) - (ANTBmuc/(PMA*VTBmuc))) - KTRTB*SATB*((ANTBmuc/(VTBmuc*PMA)) - (ANTBmuc/(VTBmuc*PMA)))

d/dt(ANTBepi) = KTRTB*SATB*((ANTBmuc/(VTBmuc*PMA)) - (ANTBepi/(VTBepi*Pvrg))) - KBOTB*SATB*((ANTBepi/(VTBepi*Pvrg)) - (ANTBex/(VTBex*Pvrg))) - Vmaxtb*(ANTBepi/(VTBepi*Pvrg))/(Kmlu1 + (ANTBepi/(VTBepi*Pvrg)))

d/dt(ANTBex) = KBOTB*SATB*((ANTBepi/(VTBepi*Pvrg)) - (ANTBex/(VTBex*Pvrg))) + Qta*(Cart - (ANTBex/(VTBex*Pvrg)))

d/dt(AMETtb) = Vmaxtb*(ANTBepi/(VTBepi*Pvrg))/(Kmlu1 + (ANTBepi/(VTBepi*Pvrg)))

d/dt(GSHtb) = Kgsh*(GSHtbb - (GSHtb/VTBepi)) - VmaxGtb*(ABTBcy/VTBepi)*(GSHtb/VTBepi)/(KmG1*(ABTBcy/VTBepi) + KmG2*(GSHtb/VTBepi) + (ABTBcy/VTBepi)*(GSHtb/VTBepi))

{differential equations for ST oxide in TB compartment umoles, TB}

d/dt(ABTBa) = Q*(CBairin - (ABTBa/VTBa)) - KOTB*SATB*((ABTBa/VTBa)-(ABTBmuc/(PMA*VTBmuc)))

d/dt(ABTBmuc) = KOTB*SATB*((ABTBa/VTBa) - (ABTBmuc/(PMA*VTBmuc))) - KTRTB*SATB*((ABTBmuc/(VTBmuc*PMA)) - (ABTBepi/(VTBepi*PBvrg)))

d/dt(ABTBepi) = KTRTB*SATB*((ABTBmuc/(VTBmuc*PMA)) - (ABTBepi/(VTBepi*PBvrg))) - KBOTB*SATB*((ABTBepi/(VTBepi*PBvrg)) - (ABTBex/(VTBex*PBvrg))) + Vmaxtb*(ANTBepi/(VTBepi*Pvrg))/(Kmlu1 + (ANTBepi/(VTBepi*Pvrg)))

d/dt(ABTBer) = Vmaxtb*(ANTBepi/(VTBepi*Pvrg))/(Kmlu1 + (ANTBepi/(VTBepi*Pvrg))) - Kec*((ABTBer/(VTBepi*PBvrg)) - (ABTBcy/(VTBepi*PBvrg))) - Vmaxtb2*(ABTBer/(VTBepi*PBvrg))/(Kmlu2 + (ABTBer/(VTBepi*PBvrg)))

d/dt(AMET2tb) = Vmaxtb2*(ABTBer/(VTBepi*PBvrg))/(Kmlu2 + (ABTBer/(VTBepi*PBvrg)))

d/dt(ABTBcy) = Kec*((ABTBer/(VTBepi*PBvrg)) - (ABTBcy/(VTBepi*PBvrg))) + Qta*(CBart - (ABTBcy/(VTBepi*PBvrg))) - VmaxGtb*(ABTBcy/VTBepi)*(GSHtb/VTBepi)/(KmG1*(ABTBcy/VTBepi) + KmG2*(ABTBcy/VTBepi) + KmG2*(GSHtb/VTBepi) + (ABTBcy/VTBepi)*(GSHtb/VTBepi))

d/dt(AMET3tb) = VmaxGtb*(ABTBcy/VTBepi)*(GSHtb/VTBepi)/(KmG1*(ABTBcy/VTBepi) + KmG2*(ABTBcy/VTBepi) + KmG2*(GSHtb/VTBepi) + (ABTBcy/VTBepi)*(GSHtb/VTBepi))

d/dt(ABTBex) = KBOTB*SATB*((ABTBepi/(VTBepi*PBvrg)) - (ABTBex/(VTBex*PBvrg))) + Qta*(CBart - (ABTBex/(VTBex*PBvrg)))

{differential equations for ST in PU compartment umoles, PU}

d/dt(ANPUa) = Q*(Cairin - (ANPUa/VPUa)) - KOPU*SAPU*((ANPUa/VPUa)-(ANPUmuc/(PMA*VPUmuc)))

d/dt(ANPUmuc) = KOPU*SAPU*((ANPUa/VPUa) - (ANPUmuc/(PMA*VPUmuc))) - KTRPU*SAPU*((ANPUmuc/VPUmuc) - (ANPUepi/(VPUepi*Pvrg)))

d/dt(ANPUepi) = KTRPU*SAPU*((ANPUmuc/(VPUmuc*PMA)) - (ANPUepi/(VPUepi*Pvrg))) - KBOPU*SAPU*((ANPUepi/(VPUepi*Pvrg)) - (ANPUex/(VPUex*Pvrg)))

d/dt(ANPUex) = KBOPU*SAPU*((ANPUepi/(VPUepi*Pvrg)) - (ANPUex/(VPUex*Pvrg))) + Qtot*(Cart - (ANPUex/(VPUex*Pvrg)))

{differential equations for ST oxide PU compartment umoles, PU}

d/dt(ABPUa) = Q*(Cairin - (ANPUa/VPUa)) - KOPU*SAPU*((ANPUa/VPUa)-(ANPUmuc/(PMA*VPUmuc)))

d/dt(ABPUmuc) = KOPU*SAPU*((ABPUa/VPUa) - (ABPUmuc/(PMA*VPUmuc))) - KTRPU*SAPU*((ABPUmuc/(VPUmuc*PMA)) - (ABPUepi/(VPUepi*PBvrg)))

d/dt(ABPUepi) = KTRPU*SAPU*((ABPUmuc/(VPUmuc*PMA)) - (ABPUepi/(VPUepi*PBvrg))) - KBOPU*SAPU*((ABPUepi/(VPUepi*PBvrg)) - (ABPUex/(VPUex*PBvrg)))

d/dt(ABPUex) = KBOPU*SAPU*((ABPUepi/(VPUepi*PBvrg)) - (ABPUex/(VPUex*PBvrg))) + Qtot*(CBart - (ABPUex/(VPUex*PBvrg)))

{Sum of Lung Styrene}

d/dt(ANex) = Qtot*((Cart-Cvurtex) + (Cart-Cvcaex) + (Cart-Cvtbex) + (Cart-Cvpuex))

{Sum of Lung Styrene Oxide}

d/dt(ABex) = Qtot*((CBart-CBvurtex) +(CBart-CBvcaex) + (CBart-CBvtbex) + (CBart-CBvpuex))

{ST ex respiratory tract, umoles}

init Af = 0

init Al = 0

init Am = 0

init Avrg = 0

init Ablood = 0

init GSHl = 6.0*Vl

{ST oxide ex respiratory tract, umoles}

init ABf = 0

init ABl = 0

init ABler = 0

init ABlcy = 0

init ABm = 0

init ABvrg = 0

init ABblood = 0

{umoles ST metabolized}

init Ametl = 0

{umoles ST oxide ex rt metabolized by EH and GST pathways}

init ABmetl = 0

init ABmetGl = 0

{AUCs}
init AUCvtot = 0
init AUCvl = 0
{AUCs BaP oxide}
init AUCBvtot = 0
init AUCBvl = 0
{tissue flows mL/min}
Qtot = (0.012*Age^3 - 1.2144*Age^2 + 40.32*Age + 44.144)*(1000/60)
Qalv = (17.874*Age + 39.785)*(1000/60)
Qf = 0.0528*Qtot
Ql = 0.0795*Qtot
Qm = 0.0304*Qtot
Qvrg = 0.837*Qtot
{tissue volumes mL}
BW = - 1.9*Age^4 + 72.8*Age^3 - 813.1*Age^2 + 5535.6*Age + 4453.7
Vf = 0.0165*Age^5 - 1.9784*Age^4 + 51.963*Age^3 - 459.38*Age^2 + 1566.8*Age + 1004.2
Vl = 0.0072*Age^5 - 0.3975*Age^4 + 7.9052*Age^3 - 65.625*Age^2 + 262.02*Age + 157.52
Vm = -0.0623*Age^5 + 2.3433*Age^4 - 26.559*Age^3 + 144.75*Age^2 +339.84*Age + 1648.2
Vvrg = BW - (Vf + Vl + Vm + Vlu + Vblood)
Vblood = 0.075*BW
{blood/air and tissue/blood partition coefficients, ST}
Pb = 48
Pl = 2.0
Pf = 50
Pm = 1.3
Pvrg = 1.3
{blood/air and tissue/blood partition coefficients, ST oxide}
PBb = 2000
PBl = 1.0
PBf = 14.0
PBm = 0.6
PBvrg = 0.6
{calculated concentrations of ST umol/mL}
Cblood = Ablood/Vblood
Cart = Cvex
Cvf = Af/(Vf*Pf)
Cvl = Al/(Vl*Pl)
Cvm = Am/(Vm*Pm)
Cvvrg = Avrg/(Vvrg*Pvrg)
Cvtot = (Ql*Cvl + Qf*Cvf + Qm*Cvm + Qvrg*Cvvrg)/Qtot
Cairin = exposure/(24.45*1E3)
CGSHl = GSHl/Vl
GSHlb = 6.0
{calculated concentrations of ST oxide umol/mL}

CBblood = ABblood/Vblood

CBart = CBvex

CBvf = ABf/(Vf*PBf)

CBvl = ABl/(Vl*PBl)

CBler = ABler/Vl

CBlcy = ABlcy/Vl

CBvm = ABm/(Vm*PBm)

CBvvrg = ABvrg/(Vvrg*PBvrg)

CBvtot = (Ql*CBvl + Qf*CBvf + Qm*CBvm + Qvrg*CBvvrg)/Qtot

CBairin = exposureB/(24.45*1E3)

{differential equations for ST uptake and metabolism, umoles}

d/dt(Al) = Ql*(Cart - Cvl) - Vmaxl*Cvl/(Km1 + Cvl)

d/dt(Af) = Qf*(Cart - Cvf)

d/dt(Am) = Qm*(Cart - Cvm)

d/dt(Avrg) = Qvrg*(Cart - Cvvrg)

d/dt(Ablood) = Ql*Cvl + Qf*Cvf + Qm*Cvm + Qvrg*Cvvrg + Qtot*Cvex

{differential equations for ST oxide uptake and metabolism, umoles}

d/dt(ABl) = Ql*(CBart - CBvl) + Vmaxl*Cvl/(Km1 + Cvl) - Vmaxl2*CBvl/(Km2 + CBvl)

d/dt(ABf) = Qf*(CBart - CBvf)

d/dt(ABm) = Qm*(CBart - CBvm)

d/dt(ABvrg) = Qvrg*(CBart - CBvvrg)

d/dt(ABblood) = Ql*CBvl + Qf*CBvf + Qm*CBvm + Qvrg*CBvvrg + Qtot*CBvex

d/dt(ABler) = Vmaxl*Cvl/(Km1 + Cvl) - Kec*((ABler/(Vl*PBl)) - (ABlcy/(Vl*PBl))) - Vmaxl2*(ABler/(Vl*PBl))/(Km2 + (ABler/(Vl*PBl)))

d/dt(ABlcy) = Kec*((ABler/(Vl*PBl)) - (ABlcy/(Vl*PBl))) + Ql*(CBart - ABlcy/(Vl*PBl)) - (VmaxGl*(ABlcy/Vl)*(GSHl/Vl)/(KmG1*(ABlcy/Vl) + KmG2*(ABlcy/Vl) + KmG2*(GSHl/Vl) + (ABlcy/Vl)*(GSHl/Vl)))

d/dt(GSHl) = Kgsh*(GSHlb - (GSHl/Vl)) - VmaxGl*(ABlcy/Vl)*(GSHl/Vl)/(KmG1*(ABlcy/Vl) + KmG2*(GSHl/Vl) + (ABlcy/Vl)*(GSHl/Vl))

{amount of ST metabolized in liver to Styrene oxide, umoles}

d/dt(Ametl) = Vmaxl*Cvl/(Km1 + Cvl)

{amount of ST oxide metabolized in liver and lung to diol, umoles}

d/dt(ABmetl) = Vmaxl2*CBvl/(Km2 + CBvl)

{amount of ST oxide metabolized in liver and lung to GSH conjugate, umoles}

d/dt(ABmetGl) = VmaxGl*CBlcy*CGSHl/(KmG1*CBlcy + KmG2*CBlcy + KmG2*CGSHl + CGSHl*CBlcy)

{AUCs for ST, umolmin/mL}

d/dt(AUCvtot) = Cvtot

d/dt(AUCvl) = Cvl

{AUCs for ST oxide, umolmin/mL}

d/dt(AUCBvtot) = CBvtot

d/dt(AUCBvl) = CBvl

E.5.9 Model Code for Vinyl Chloride 0-5 yr Child

METHOD Stiff

STARTTIME = 0
STOPTIME = 48
DT = 0.005
{vinyl chloride moles or equivalents}
init Af = 0
init Al = 0
init Am = 0
init Avrg = 0
init Abr = 0
init Apu = 0
init Areactive = 0
init ACO2 = 0
init Aconj = 0
init ADNAad = 0
init AGl = 0
init AGSH = 0.058*Vl
init AMET = 0
init AUCrm = 0
init RISKM =0
init RISKG = 0
{tissue flows L/hr}
Qtot = 0.012*Age^3 - 1.2144*Age^2 + 40.324*Age + 44.414
Qalv = 17.875*Age + 39.785
Qf = 0.0528*Qtot
Ql = 0.0795*Qtot
Qm = 0.0304*Qtot
Qvrg = 0.837*Qtot
Qpu = 0.93*Qtot
Qbr = 0.07*Qtot
{tissue volumes L}
Vf = (0.0165*Age^5 - 1.9784*Age^4 + 51.963*Age^3 - 459.38*Age^2 + 1566.8*Age + 1004.2)/1000
Vl = (0.0072*Age^5 - 0.3975*Age^4 + 7.9052*Age^3 - 65.624*Age^2 + 262.02*Age + 157.52)/1000
Vvrg = BW - (Vf+Vl+Vm+Vlu)
Vlu = (-0.0346*Age^4 + 1.5069*Age^3 - 20.13*Age^2 + 123.99*Age + 59.213)/1000
Vm = (-0.0623*Age^5 + 2.3433*Age^4 - 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2)/1000
Vpu = 0.90*Vlu
Vbr = 0.10*Vlu
{blood/air and tissue/blood partition coefficients, vinyl chloride}
Pb = 1.16
Pl = 1.45

Pf = 20.7
Pm = 0.83
Pvrg = 1.45
Ppu = 1.45
Pbr = 1.45
{calculated concentrations of vinyl chloride}
Cart = (Qpu*Cvpu + Qbr*Cvbr)/Qtot
Cvf = Af/(Vf*Pf)
Cvl = Al/(Vl*Pl)
Cvm = Am/(Vm*Pm)
Cvvrg = Avrg/(Vvrg*Pvrg)
Cvpu = Apu/(Vpu*Ppu)
Cvbr = Abr/(Vbr*Pbr)
Cvtot = (Ql*Cvl + Qf*Cvf + Qm*Cvm + Qvrg*Cvvrg)/Qpu
Cvipu = (Qalv*Cair + Qpu*Cvtot)/((Qalv/Pb) + Qpu)
Cexh = Cvipu/Pb
{exposure in ppm converted to moles}
Cair = IF TIME <= 24 THEN 1*(1E-6/25.45) ELSE 0
{constants and conversions}
BW = (-1.9*Age^4 + 72.8*Age^3 - 813.1*Age^2 + 5535.6*Age + 4453.7)/1000
Age = 0.0
MW = 62.5
Vmax1c = 4.0
Vmax2c = 0.1
Km1 = 1.0
Km2 = 10.0
KGSMc = 0.13
KFEEc = 35.0
KCO2c = 1.6
KOC = 28.5
KBC = 0.12
KS = 2000
KA = 3.0
GSO = 0.058
H2O = 55.0
KGSM = KGSMc/BW^0.25
KFEE = KFEEc/BW^0.25
KO = KOC*BW^0.75
KB = KBC/BW^0.25
KCO2 = KCO2c/BW^0.25
Vmax1 = Vmax1c*BW^0.75
Vmax2 = Vmax2c*BW^0.75
Vmax1M = Vmax1c*(BW^0.75)/(1000*MW)
Vmax2M = Vmax2c*(BW^0.75)/(1000*MW)

KmM = Km1/(1000*MW)

Km2M = Km2/(1000*MW)

{differential equations for vinyl chloride uptake and metabolism}

d/dt(Apu) = Qpu*(Cvipu - Cvpu)

d/dt(Abr) = Qbr*(Cart - Cvbr)

d/dt(Al) = Ql*(Cart - Cvl) - Vmax1M*(Al/Vl)/(KmM + (Al/Vl)) - Vmax2M*(Al/Vl)/(Km2M + (Al/Vl)) + KA*AGI

d/dt(Areactive) = Vmax1M*(Al/Vl)/(KmM + (Al/Vl)) + Vmax2M*(Al/Vl)/(Km2M + (Al/Vl)) - KGSM*(AGSH/Vl)*(Areactive/Vl) - KFEE*(Areactive/Vl) - KCO2*(Areactive/Vl)*H2O*Vl

d/dt(AGSH) = KO*(KS +GSO)/(KS + (AGSH/Vl))

d/dt(ACO2) = KCO2*(Areactive/Vl)*H2O*Vl

d/dt(ADNAad) = KFEE*(Areactive/Vl)

d/dt(Aconj) = KGSM*(AGSH/Vl)*(Areactive/Vl)

d/dt(Af) = Qf*(Cart - Cvf)

d/dt(Am) = Qm*(Cart - Cvm)

d/dt(Avrg) = Qvrg*(Cart - Cvvrg)

d/dt(AMET) = Vmax1M*Cvl/(KmM + Cvl) + Vmax2M*Cvl/(Km2M + Cvl)

d/dt(AUCrm) = (Areactive/Vl)*TIME

d/dt(AGI) = - KA*AGI

d/dt(RISKM) = ADNAad/Vl

d/dt(RISKG) = Aconj/Vl

E.5.10 Model Code for TCE 0-5 yr child

METHOD Auto

STARTTIME = 0

STOPTIME= 120

DT = 0.001

{TCE moles}

init Af = 0

init Al = 0

init Am = 0

init Avrg = 0

init Abr = 0

init Apu = 0

init Alu = 0

init Akid = 0

init Astom = 0

init Agi = 0

init AUCvtot = 0

init Aexh = 0

{CH moles}

init ABl = 0
init ABbody = 0
init ABlu = 0
init ABkid = 0
init AUCBvtot = 0
init AUCBlu = 0
init ABurine = 0
{TCA moles}
init ACl = 0
init ACbody = 0
init AClu = 0
init ACkid = 0
init AUCCl = 0
init AUCCvtot = 0
init AUCCl = 0
init ACurine = 0
{TCOH moles}
init ADl = 0
init ADbody = 0
init ADlu = 0
init ADkid = 0
init AUCDvtot = 0
init ADurine = 0
{TCOG moles}
init AEl = 0
init AEbody = 0
init AElu = 0
init AEkid = 0
init AUCEvtot = 0
init AUCEkid = 0
init AEurine = 0
init AEfec = 0
{moles of TCE metabolized}
init Ametl1 = 0
{tissue flows L/hr}
Qtot = 0.012*Age^3 - 1.2144*Age^2 + 40.324*Age + 44.414
Qalv = 17.875*Age + 39.785
Qf = 0.0528*Qtot
Ql = 0.0795*Qtot
Qm = 0.0304*Qtot
Qvrg = 0.687*Qtot
Qpu = 0.93*Qtot
Qbr = 0.07*Qtot
Qkid = 0.15*Qtot

Qbody = 0.24*Qtot
{tissue volumes, L}
Vf = (0.0165*Age^5 - 1.9784*Age^4 + 51.963*Age^3 - 459.38*Age^2 + 1566.8*Age + 1004.2)/1000
Vl = (0.0072*Age^5 - 0.3975*Age^4 + 7.9052*Age^3 - 65.624*Age^2 + 262.02*Age + 157.52)/1000
Vm = (-0.0623*Age^5 + 2.3433*Age^4 - 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2)/1000
Vvrg = BW - (Vf + Vl + Vm + Vlu + Vkid)
Vpu = 0.9*Vlu
Vbr = 0.1*Vlu
Vlu = (-0.0346*Age^4 + 1.5069*Age^3 - 20.31*Age^2 + 123.99*Age + 59.213)/1000
Vkid = (0.000973*Age^5 - 0.0561*Age^4 + 1.1729*Age^3 - 10.34*Age^2 + 44.604*Age + 28.291)/1000
Vbody = BW
{blood/air and tissue/blood partition coefficients, TCE}
Pb = 15.91
Pl = 1.73
Pf = 36.38
Pm = 2.36
Pvrg = 1.73
Ppu = 2.61
Pbr = 2.61
Pkid = 2.07
{blood/air and tissue/blood partition coefficients, CH}
PBl = 1.42
PBlu = 1.65
PBbody = 1.35
PBkid = 0.98
{tissue/blood partition coefficients, TCA}
PCl = 1.18
PClu = 0.54
PCbody = 0.88
PCkid = 0.74
{blood/air and tissue/blood partition coefficients, TCOH}
PDl = 1.30
PDlu = 0.78
PDbody = 1.11
PDkid = 1.02
{blood/air and tissue/blood partition coefficients, TCOG}
PEl = 0.56
PElu = 1.06
PEbody = 1.11
PEkid = 1.44
{TCE oxidation metabolic parameters, mol/hr, mol/L, /hr, fraction}
Vmaxl1C = 3.04E-5
Vmaxl1 = Vmaxl1C*BW^0.75
Km1 = 1.37E-5

{CH conversion to TCA and TCOH}
PTCA = 115*BW
PTCOH = 309*BW
KUB = 0.06*BW
{TCOH conversion to TCA and TCOG}
KTCA = 10
Vmaxl2C = 1.11E-4
Vmaxl2 = Vmaxl2C*BW^0.75
Km2 = 1.06E-4
KUD = 1.14*BW
KUC = 1.55*BW
KFE = 4.61*BW
KUE = 32.8*BW
Age = 5.0
BW = (-1.9*Age^4 + 72.8*Age^3 - 813.1*Age^2 + 5535.6*Age + 4453.7)/1000
{exposure in ppm converted to moles}
Cair = IF TIME <= 24 THEN 1*(1E-6/24.45) ELSE 0.0
Cart = (Qpu*Cvpu + Qbr*Cvbr)/Qtot
Cvf = Af/(Vf*Pf)
Cvl = Al/(Vl*Pl)
Cl = Al/Vl
Cvm = Am/(Vm*Pm)
Cvvrg = Avrg/(Vvrg*Pvrg)
Cvpu = Apu/(Vpu*Ppu)
Cvbr = Abr/(Vbr*Pbr)
Cvkid = Akid/(Vkid*Pkid)
Cvtot = (Ql*Cvl + Qf*Cvf + Qm*Cvm + Qvrg*Cvvrg + Qkid*Cvkid)/Qpu
Cvipu = (Qalv*Cair + Qpu*Cvtot)/((Qalv/Pb) + Qpu)
Cexh = Cvipu/Pb
A = Sum(Alu,Al,Am,Akid,Agi,Aexh)
Mass = Sum(A,B,C,D,E)
{calculated concentrations of CH}
CBart = CBvlu
CBvl = ABl/(Vl*PBl)
CBvlu = ABlu/(Vlu*PBlu)
CBlu = ABlu/Vlu
CBvbody = ABbody/(Vbody*PBbody)
CBvkid = ABkid/(Vkid*PBkid)
CBvtot = (Ql*CBvl + Qbody*CBvbody + Qkid*CBvkid)/Qtot
B = Sum(ABlu,ABl,ABkid,ABbody,ABurine)
{calculated concentrations of TCA}
CCart = CCvlu
CCvl = ACl/(Vl*PCl)
CCl = ACl/Vl

CCvlu = AClu/(Vlu*PClu)
CCvbody = ACbody/(Vbody*PCbody)
CCvkid = ACkid/(Vkid*PCkid)
CCvtot = (Ql*CCvl + Qbody*CCvbody + Qkid*CCvkid)/Qtot
C = Sum(AClu,ACl,ACkid,ACbody,ACurine)
{calculated concentrations of TCOH}
CDart = CDvlu
CDvl = ADl/(Vl*PDl)
CDl = ADl/Vl
CDvlu = ADlu/(Vlu*PDlu)
CDvbody = ADbody/(Vbody*PDbody)
CDvkid = ADkid/(Vkid*PDkid)
CDvtot = (Ql*CDvl + Qbody*CDvbody + Qkid*CDvkid)/Qtot
D = Sum(ADlu,ADl,ADkid,ADbody,ADurine)
{calculated concentrations of TCOG}
CEart = CEvlu
CEvl = AEl/(Vl*PEl)
CEvlu = AElu/(Vlu*PElu)
CEvbody = AEbody/(Vbody*PEbody)
CEvkid = AEkid/(Vkid*PEkid)
CEkid = AEkid/Vkid
CEvtot = (Ql*CEvl + Qbody*CEvbody + Qkid*CDvkid)/Qtot
E = Sum(AElu,AEl,AEkid,AEbody,AEfec,AEurine)
{differential equations for TCE uptake, metabolism, and excretion}
d/dt(Astom) = -Astom*3.09 -Astom*2.18
d/dt(Agi) = Astom*2.18 - Agi*0.044
d/dt(Apu) = Qpu*(Cvipu - Cvpu)
d/dt(Abr) = Qbr*(Cart - Cvbr)
d/dt(Alu) = Apu + Abr
d/dt(Al) = Ql*(Cart - Cvl) - Vmaxl1*Cvl/(Km1 + Cvl) + Agi*0.044 + Astom*3.09
d/dt(Af) = Qf*(Cart - Cvf)
d/dt(Am) = Qm*(Cart - Cvm)
d/dt(Avrg) = Qvrg*(Cart - Cvvrg)
d/dt(Akid) = Qkid*(Cart - Cvkid)
{amount of TCE metabolized in liver}
d/dt(Ametl1) = Vmaxl1*Cvl/(Km1 + Cvl)
d/dt(AUCvtot) = Cvtot
d/dt(Aexh) = Cexh*Qalv
{differential equations for CH metabolism}
d/dt(ABlu) = Qtot*(CBvtot - CBvlu)
d/dt(ABl) = Ql*(CBart - CBvl) + Vmaxl1*Cvl/(Km1 + Cvl) - ABl*PTCA - ABl*PTCOH
d/dt(ABbody) = Qbody*(CBart - CBvbody)
d/dt(ABkid) = Qkid*(CBart - CBvkid) - ABkid*KUB
d/dt(ABurine) = ABkid*KUB

{AUCs for CH}
d/dt(AUCBlu) = CBlu
d/dt(AUCBvtot) = CBvtot
{differential equations for TCA}
d/dt(AClu) = Qtot*(CCvtot - CCvlu)
d/dt(ACl) = Ql*(CCart - CCvl) + ABl*PTCA + ADl*KTCA
d/dt(ACbody) = Qbody*(CCart - CCvbody)
d/dt(ACkid) = Qkid*(CCart - CCvkid) - ACkid*KUC
d/dt(ACurine) = ACkid*KUC
{AUCs for TCA}
d/dt(AUCCl) = CCl
d/dt(AUCCvtot) = CCvtot
{differential equations for TCOH}
d/dt(ADlu) = Qtot*(CDvtot - CDvlu)
d/dt(ADl) = Ql*(CDart - CDvl) + ABl*PTCOH - ADl*KTCA - 2.73E-3*CDvl/(Km2 + CDvl)
d/dt(ADbody) = Qbody*(CDart - CDvbody)
d/dt(ADkid) = Qkid*(CDart - CDvkid) - ADkid*KUD
d/dt(AUCDvtot) = CDvtot
d/dt(ADurine) = ADkid*KUD
{differential equations for TCOG}
d/dt(AElu) = Qtot*(CEvtot - CEvlu)
d/dt(AEl) = Ql*(CEart - CEvl) + 2.73E-3*CDvl/(Km2 + CDvl) - AEl*KFE
d/dt(AEbody) = Qbody*(CEart - CEvbody)
d/dt(AEkid) = Qkid*(CEart - CEvkid) - AEkid*KUE
d/dt(AEurine) = AEkid*KUE
d/dt(AEfec) = AEl*KFE
d/dt(AUCEkid) = CEkid
d/dt(AUCEvtot) = CEvtot

E.5.11 Model Code for Styrene/SO (Csanady et al*. 2003) 0-6 yr Child*

METHOD Stiff

STARTTIME = 0
STOPTIME= 48
DT = 0.001
{Styrene mmol}
init Aluc = 0 {conducting airways}
init Alua = 0 {alveoli}
init Alubld = 0 {lung blood}
init Aven = 0 {venous blood}
init Aart = 0 {arterial blood}

init Afat = 0
init Avrg = 0
init Amusc = 0
init Al = 0
init Amet1luc = 0
init Amet1lua = 0
init Amet1l = 0
{Styrene oxide, mmol}
init ABluc = 0
init ABlua = 0
init ABlubld = 0
init ABven = 0
init ABart = 0
init ABfat = 0
init ABvrg = 0
init ABmusc = 0
init ABler = 0
init ABlcy = 0
init ABmet2luc = 0
init ABmet2lua = 0
init ABmet2l = 0
init ABmet3luc = 0
init ABmet3lua = 0
init ABmet3l = 0
init AUCBluc = 0
init AUCBlua = 0
init AUCBl = 0
{Model parameters}
BW = (-1.9*Age^4 + 72.8*Age^3 - 813.1*Age^2 + 5535.6*Age + 4453.7)/1000 {kg, L}
Qalv = 0.82*Qtot {L/hr}
Qtot = 0.012*Age^3 - 1.2144*Age^2 + 40.324*Age + 44.414
tcap = 7.45E-6 {dm}
Scap = 115 {dm2/kg}
Dst = 4.4E-4 {dm2/hr}
Dso = 4.3E-4
{Flows, L/hr}
Qfat = 0.053*Qtot
Ql = 0.0795*Qtot
Qvrg = Qtot - (Qfat + Ql + Qmusc)
Qmusc = 0.03*Qtot
{Volumes, L}
Vart = 0.0178*BW
Vven = 0.0533*BW
Vlubld = 0.0079*BW

Vfat = 0.19*BW
Vlu = (-0.0346*Age^4 + 1.5069*Age^3 - 20.31*Age^2 + 123.99*Age + 59.213)/1000
Vluc = fs*Vlu
Vlua = (1-fs)*Vlu
Vl = (0.0072*Age^5 - 0.3975*Age^4 + 7.9052*Age^3 - 65.624*Age^2 + 262.02*Age + 157.52)/1000
Vvrg = BW - (Vfat + Vl + Vart + Vven + Vlubld + Vmusc + Vlu)
Vmusc = (-0.0623*Age^5 + 2.3433*Age^4 - 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2)/1000
{Partition coeffs styrene, dimensionless}
Pb = 70.0
Pfat = 93.8
Pl = 2.71
Plu = 1.46
Pvrg = 2.60
Pmusc = 1.96
{Partition coeffs styrene oxide, dimensionless}
PbB = 2370
PBfat = 6.1
PBl = 2.6
PBlu = 1.9
PBvrg = 2.6
PBmusc = 1.5
{Concentrations ST mmol/L}
Exposure = IF TIME < 24 THEN 1*(1E-3/24.45) ELSE 0
Age = 0.542
fs = 0.1
Cair = exposure
Cart = Aart/Vart
Cven = Aven/Vven
Cfat = Afat/Vfat
Cl = Al/Vl
Cvrg = Avrg/Vvrg
Cmusc = Amusc/Vmusc
Clubld = Alubld/Vlubld
Cluc = Aluc/(fs*Vlu)
Clua = Alua/((1-fs)*Vlu)
{Concentrations SO, mmol/L}
CBart = ABart/Vart
CBven = ABven/Vven
CBfat = ABfat/Vfat
CBvrg = ABvrg/Vvrg
CBmusc = ABmusc/Vmusc
CBlcy = ABlcy/Vl
CBvlcy = ABlcy/(Vl*Pl)
CBluc = ABluc/(fs*Vlu)

CBlua = ABlua/((1-fs)*Vlu)
CBlubld = ABlubld/Vlubld
Qendo = Vmaxl2*1E3*Vl/(Kml2app - Kml2eh)
a = CBlcy - Kml2eh + (Vmaxl1*1E3*Vl*Cl/(Qendo*(Pl*Kml1 + Cl))) - (Vmaxl2*1E3*Vl/Qendo)
CBendo = 0.5*(a + (a^2 + 4*Kml2eh*(CBlcy + Vmaxl1*1E3*Vl*Cl/Qendo*(Pl*Kml1 + Cl)))^0.5)
{GSH}
init GSHluc = fs*GSHlu0
init GSHlua = (1-fs)*GSHlu0
init GSHl = GSHl0
CGSHluc = GSHluc*fs/Vluc
CGSHlua = GSHlua*(1-fs)/Vlua
CGSHl = GSHl/Vl
fGSH = 0.75
GSHlu0 = 1.95*Vlu
GSHl0 = 5.9*Vl
{Biochemical parameters, mmol/hr/mL, mmol/L; 1 = P450, 2 = EH, 3 = GST}
Vmaxl1 = 0.002*(70/BW)^0.25
Kml1 = 0.01
Vmaxl2 = 0.0045*(70/BW)^0.25
Kml2eh = 0.001
Kml2app = 0.01
Vmaxl3 = 0.028*(70/BW)^0.25
Kml3G = 0.1
Kml3so = 2.5
Kdl = 0.2
Vmaxlu1 = 2.5E-6*(70/BW)^0.25
Kmlu1 = 0.0175
Vmaxlu2 = 6.73E-4*(70/BW)^0.25
Kmlu2 = 0.0156
Vmaxlu3 = 0.082*(70/BW)^0.25
Kmlu3G = 0.1
Kmlu3so = 2.5
Kdlu = 2.0
{Differential equations for styrene}
d/dt(Aluc) = Qalv*(Cair*fs + fs*(1 - fs)*(Clua/Pb) - (fs + fs*(1-fs))*Cluc/Pb) - Vmaxlu1*1E3*Vlu*fs*Cluc/(Kmlu1 + Cluc)
d/dt(Alua) = Qalv*(Cair*(1-fs) - (1-fs)*Clua/Pb) - Vmaxlu1*1E3*Vlu*(1-fs)*Clua/(Kmlu1 + Clua) - (Scap*Dst/tcap)*(Clua/Plu - Clubld)
d/dt(Alubld) = (Scap*Dst/tcap)*(Clua/Plu - Clubld) + Qtot*(Cven - Clubld)
d/dt(Aart) = Qtot*(Clubld - Cart)
d/dt(Afat) = Qfat*(Cart - Cfat/Pfat)
d/dt(Avrg) = Qvrg*(Cart - Cvrg/Pvrg)
d/dt(Amusc) = Qmusc*(Cart - Cmusc/Pmusc)
d/dt(Al) = Ql*(Cart - Cl/Pl) - Vmaxl1*1E3*Vl*Cl/(Pl*Kml1 + Cl)
d/dt(Aven) = (Qfat*Cfat/Pfat + Qvrg*Cvrg/Pvrg + Ql*Cl/Pl + Qmusc*Cmusc/Pmusc) - Qtot*Cven

d/dt(Amet1luc) = Vmaxlu1*1E3*Vlu*fs*Cluc/(Kmlu1 + Cluc)

d/dt(Amet1lua) = Vmaxlu1*1E3*Vlu*(1-fs)*Clua/(Kmlu1 + Clua)

d/dt(Amet1l) = Vmaxl1*1E3*Vl*Cl/(Pl*Kml1 + Cl)

{Differential equations for styrene oxide, B}

d/dt(ABluc) = Vmaxlu1*1E3*Vlu*(1-fs)*Cluc/(Kmlu1 + Cluc) - Vmaxlu2*1E3*Vlu*fs*CBluc/(Kmlu2 + CBluc) - Vmaxlu3*1E3*Vlu*fs*CBluc*CGSHluc/(Kmlu3so*CGSHluc + Kmlu3G*CBluc + CBluc*CGSHluc)

d/dt(ABlua) = Vmaxlu1*1E3*Vlu*(1-fs)*Clua/(Kmlu1 + Clua) - Vmaxlu2*1E3*Vlu*(1-fs)*CBlua/(Kmlu2 + CBlua) - Vmaxlu3*1E3*Vlu*(1-fs)*CBlua*CGSHlua/(Kmlu3so*CGSHlua + Kmlu3G*CBlua + CBlua*CGSHlua) - (Scap*Dso/tcap)*(CBlua/PBlu - CBlubld)

d/dt(ABlubld) = (Scap*Dso/tcap)*(CBlua/PBlu - CBlubld) + Qtot*(CBven - CBlubld)

d/dt(ABart) = Qtot*(CBlubld - CBart)

d/dt(ABfat) = Qfat*(CBart - CBfat/PBfat)

d/dt(ABvrg) = Qvrg*(CBart - CBvrg/PBvrg)

d/dt(ABmusc) = Qmusc*(CBart - CBmusc/PBmusc)

d/dt(ABlcy) = Ql*(CBart - CBvlcy) + Qendo*(CBendo - CBlcy) - Vmaxl3*1E3*Vl*CBlcy*CGSHl/(Kml3so*CGSHl + Kml3G*CBlcy + CBlcy*CGSHl)

d/dt (ABler) = Vmaxl1*1E3*Vl*Cl/(Pl*Kml1 + Cl) - Qendo*(CBendo - CBlcy) - Vmaxl2*CBendo*1E3*Vl/(Kml2eh + CBendo)

d/dt(ABven) = (Qfat*CBfat/PBfat + Qvrg*CBvrg/PBvrg + Ql*CBvlcy/PBl + Qmusc*CBmusc/PBmusc) - Qtot*CBven

d/dt(ABmet2luc) = Vmaxlu2*1E3*Vlu*fs*CBluc/(Kmlu2 + CBluc)

d/dt(ABmet2lua) = Vmaxlu2*1E3*Vlu*(1-fs)*CBlua/(Kmlu2 + CBlua)

d/dt(ABmet2l) = Vmaxl2*CBendo*1E3*Vl/(Kml2eh + CBendo)

d/dt(ABmet3luc) = Vmaxlu3*1E3*Vlu*fs*CBluc*CGSHluc/(Kmlu3so*CGSHluc + Kmlu3G*CBluc + CBluc*CGSHluc)

d/dt(ABmet3lua) = Vmaxlu3*1E3*Vlu*(1-fs)*CBlua*CGSHlua/(Kmlu3so*CGSHlua + Kmlu3G*CBlua + CBlua*CGSHlua)

d/dt(ABmet3l) = Vmaxl3*1E3*Vl*CBlcy*CGSHl/(Kml3so*CGSHl + Kml3G*CBlcy + CBlcy*CGSHl)

d/dt(AUCBluc) = CBluc

d/dt(AUCBlua) = CBlua

d/dt(AUCBl) = CBlcy

{differential equations GSH, no circadian term included}

d/dt(GSHluc) = fs*Kdlu*Vluc*(fGSH*1.95 - CGSHluc) - Vmaxlu3*1E3*Vlu*fs*CBluc*CGSHluc/(Kmlu3so*CGSHluc + Kmlu3G*CBluc + CBluc*CGSHluc)

d/dt(GSHlua) = (1-fs)*Kdlu*Vlua*(fGSH*1.95 - CGSHlua) - Vmaxlu3*1E3*Vlu*(1-fs)*CBlua*CGSHlua/(Kmlu3so*CGSHlua + Kmlu3G*CBlua + CBlua*CGSHlua)

d/dt(GSHl) = Kdl*Vl*(fGSH*5.9 - CGSHl) - Vmaxl3*1E3*Vl*CBlcy*CGSHl/(Kml3so*CGSHl + Kml3G*CBlcy + CBlcy*CGSHl)

E.5.12 Model Code for DCM 0-5 yr Child

METHOD Stiff

STARTTIME = 0
STOPTIME=48
DT = 0.001
{dichloromethane moles}
init Af = 0
init Al = 0
init Am = 0
init Avrg = 0
init Abr = 0
init Apu = 0
init Agi = 0
{moles dichloromethane metabolized by MFO pathway}
init Ametl1 = 0
init Ametpu1 = 0
init Ametbr1 = 0
{moles of dichloromethane metabolized by GST pathway}
init Ametl2 = 0
init Ametpu2 = 0
init Ametbr2 = 0
{tissue flows L/hr}
Qtot = 0.012*Age^3 - 1.2144*Age^2 + 40.324*Age + 44.414
Qalv = (17.875*Age) + 39.785
Qf = 0.0528*Qtot
Ql = 0.0795*Qtot
Qm = 0.0304*Qtot
Qvrg = 0.837*Qtot
Qpu = 0.93*Qtot
Qbr = 0.07*Qtot
{tissue volumes L}
Vf = (0.0165*Age^5 - 1.9784*Age^4 + 51.963*Age^3 - 459.38*Age^2 + 1566.8*Age + 1004.2)/1000
Vl = (0.0072*Age^5 - 0.3975*Age^4 + 7.9052*Age^3 - 65.624*Age^2 + 262.02*Age + 157.52)/1000
Vm = (-0.0623*Age^5 + 2.3433*Age^4 - 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2)/1000
Vvrg = BW - (Vf + Vl + Vm + Vlu)
Vlu = (-0.0346*Age^4 + 1.5069*Age^3 - 20.31*Age^2 + 123.99*Age + 59.213)/1000
Vpu = 0.9*Vlu
Vbr = 0.1*Vlu
BW = (-1.9*age^4 + 72.8*Age^3 - 813.1*Age^2 + 5535.6*Age + 4453.70)/1000
Age = 0
{blood/air and tissue/blood partition coefficients, dichloromethane}
Pb = 9.09

Pl = 0.824
Pf = 7.239
Pm = 1.09
Pvrg = 0.788
Ppu = 0.552
Pbr = 0.552
{dichloromethane oxidation metabolic parameters, mol/hr, mol/L}
Vmaxbr = 0.1*1.46E-3*Vmaxl
Vmaxpu = 0.9*1.46E-3*Vmaxl
Vmaxl = 8.58E-5*BW^0.7
Km = 8.7E-6
{dichloromethane GST conjugation /hr}
Kfl = 1.26*BW^-0.3
Kfpu = 0.9*0.242*Kfl
Kfbr = 0.1*0.242*Kfl
{uptake of DCM gfrom GI tract to liver, /hr}
KAl = 0.5
{exposure in ppm converted to moles/L}
Cair = IF TIME <= 6 THEN 10*(1E-6/25.45) ELSE 0
{calculated concentrations of dichloromethane}
Cart = (Qpu*Cvpu + Qbr*Cvbr)/Qtot
Cvf = Af/(Vf*Pf)
Cvl = Al/(Vl*Pl)
Cvm = Am/(Vm*Pm)
Cvvrg = Avrg/(Vvrg*Pvrg)
Cvpu = Apu/(Vpu*Ppu)
Cvbr = Abr/(Vbr*Pbr)
Cvtot = (Ql*Cvl + Qf*Cvf + Qm*Cvm + Qvrg*Cvvrg)/Qpu
Cvipu = (Qalv*Cair + Qpu*Cvtot)/((Qalv/Pb) + Qpu)
Cexh = Cvipu/Pb
{differential equations for dichloromethane uptake and metabolism}
d/dt(Agi) = - KAl*Agi
d/dt(Apu) = Qpu*(Cvipu - Cvpu) - Vmaxpu*Cvpu/(Km + Cvpu) - Kfpu*Apu
d/dt(Abr) = Qbr*(Cart - Cvbr) - Vmaxbr * Cvbr/(Km + Cvbr) - Kfbr*Abr
d/dt(Al) = Ql*(Cart - Cvl) - Vmaxl*Cvl/(Km + Cvl) - Kfl*Al + KAi*Agi
d/dt(Af) = Qf*(Cart - Cvf)
d/dt(Am) = Qm*(Cart - Cvm)
d/dt(Avrg) = Qvrg*(Cart - Cvvrg)
{amount of dichloromethane metabolized by MFO pathway in liver and lung}
d/dt(Ametl1) = Vmaxl*(Al/Vl)/(Km + (Al/Vl))
d/dt(Ametpu1) = Vmaxpu*(Apu/Vpu)/(Km + (Apu/Vpu))
d/dt(Ametbr1) = Vmaxbr*(Abr/Vbr)/(Km + (Abr/Vbr))
{amount of dichloromethane metabolized by GST pathway in liver and lung}
d/dt(Ametl2) = Kfl*Al

d/dt(Ametpu2) = Kfpu*Apu
d/dt(Ametbr2) = Kfbr*Abr
Ametpu2k = Ametpu2/BW
Ametbr2k = Ametbr2/BW

E.5.13 Model Code for Ethylene/Ethylene oxide 0-6 yr Child

METHOD Stiff

STARTTIME = 0
STOPTIME=48
DT = 0.001
{ethylene moles}
init Af = 0
Limit Af >= 0
init Al = 0
Limit Al >= 0
init Am = 0
Limit Am >= 0
init Avrg = 0
Limit Avrg >= 0
init Alubld = 0
Limit Alubld >= 0
init Aart = 0
Limit Aart >= 0
init Aven = 0
Limit Aven >= 0
{ethylene oxide moles}
init ABf = 0
Limit ABf >= 0
init ABl = 0
Limit ABl >= 0
init ABm = 0
Limit ABm >= 0
init ABvrg = 0
Limit ABvrg >= 0
init ABlubld = 0
Limit Ablubld >= 0
init ABart = 0
Limit Abart >= 0
init ABven = 0
Limit ABven >= 0

{adducts formed}
init Hbadd = 0
init DNAadd = 0
Khb = 4.5E-5
Kdna = 9.4E-5
Keldna = 0.0077
ter = 3024
{moles ethylene metabolized}
init Amet = 0
{moles of ethylene oxide metabolized}
init ABmet = 0
{area under the venous blood concn x time curve, ethylene}
init AUCvtot = 0
init AUCvl = 0
init AUCvlubld = 0
{area under the venous blood concn x time curve, ethylene oxide}
init AUCBvtot = 0
init AUCBvl = 0
init AUCBvlubld = 0
{tissue flows L/hr}
Qtot = 0.012*Age^3 - 1.2144*Age^2 + 40.324*Age + 44.414
Qalv = 0.82*Qtot
Qf = 0.053*Qtot
Ql = 0.0795*Qtot
Qm = 0.03*Qtot
Qvrg = Qtot - (Qf + Ql + Qm)
{tissue volumes, L}
BW = (-1.9*Age^4 + 72.8*Age^3 - 813.1*Age^2 + 5535.6*Age + 4453.7)/1000
Vf = (0.0165*Age^5 - 1.9784*Age^4 + 51.963*Age^3 - 459.38*Age^2 + 1566.8*Age + 1004.2)/1000
Vl = (0.0072*Age^5 - 0.3975*Age^4 + 7.9052*Age^3 - 65.624*Age^2 + 262.02*Age + 157.52)/1000
Vm = (-0.0623*Age^5 + 2.3433*Age^4 - 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2)/1000
Vvrg = BW - (Vf + Vl + Vm + Vart + Vven + Vlubld)
Vart = 0.0178*BW
Vven = 0.0533*BW
Vlubld = 0.0079*BW
t = TIME
{blood/air and tissue/blood partition coefficients, ethylene}
Pb = 0.22
Pl = 2.05
Pf = 8.73
Pm = 2.95
Pvrg = 2.18
{blood/air and tissue/blood partition coefficients, ethylene oxide}
PBb = 61

PBl = 0.89
PBf = 0.70
PBm = 1.08
PBvrg = 1.03
{ethylene oxidation metabolic parameters, clearance L/hr}
Clr = 74.9*(70/BW)^0.25
{ethylene oxide metabolic parameters, clearance L/hr}
CBlr = 1.53*(70/BW)^0.25
Feo = 0.8
{exposure in ppm converted to, mmoles/L}
Cair = IF TIME <= 24 THEN 1*(1E-3/25.45) ELSE 0
CBair = IF TIME <= 24 THEN 0.01*(1E-3/25.45) ELSE 0
Age = 0
{calculated concentrations of ethylene}
Cart = Aart/Vart
Cven = Aven/Vven
Clubld = Alubld/Vlubld
Cvlubld = Alubld/(Vlubld*Pb)
Cvf = Af/(Vf*Pf)
Cvl = Al/(Vl*Pl)
Cl = Al/Vl
Cvl = Al/(Vl*Pl)
Cvm = Am/(Vm*Pm)
Cvvrg = Avrg/(Vvrg*Pvrg)
Cvtot = (Ql*Cvl + Qf*Cvf + Qm*Cvm + Qvrg*Cvvrg)/Qtot
Cexh = Cvlubld/Pb
{calculated concentrations of ethylene oxide}
CBart = ABart/Vart
CBven = ABven/Vven
CBvf = ABf/(Vf*PBf)
CBl = ABl/Vl
CBvl = ABl/(Vl*PBl)
CBvm = ABm/(Vm*PBm)
CBlubld = ABlubld/Vlubld
CBvlubld = ABlubld/(Vlubld*Pb)
CBvvrg = ABvrg/(Vvrg*PBvrg)
CBvtot = (Ql*CBvl + Qf*CBvf + Qm*CBvm + Qvrg*CBvvrg)/Qtot
CBair = CBvtot/PB
Chb = Hbadd*(1- t/(2*ter)) {circulating Hb adducts}
{differential equations for ethylene uptake and metabolism}
d/dt(Alubld) = Qalv*(Cair - Cvlubld) + Qtot*(Cven - Cvlubld)
d/dt(Aart) = Qtot*(Clubld - Cart) + 4.71E-7*BW
d/dt(Aven) = (Ql*Cvl + Qf*Cvf + Qm*Cvm + Qvrg*Cvvrg) - Qtot*Cven
d/dt(Al) = Ql*(Cart - Cvl) - Clr*Cvl

d/dt(Af) = Qf*(Cart - Cvf)
d/dt(Am) = Qm*(Cart - Cvm)
d/dt(Avrg) = Qvrg*(Cart - Cvvrg)
{amount of ethylene metabolized in liver}
d/dt(Amet) = Clr*Cvl
{AUCs for ethylene}
d/dt(AUCvtot) = Cvtot
d/dt(AUCvl) = Cvl
d/dt(AUCvlubld) = Cvlubld
{differential equations for ethylene oxide metabolism}
d/dt(ABlubld) = Qalv*(CBair*Feo - CBvlubld) + Qtot*(CBven - CBvlubld)
d/dt(ABart) = Qtot*(CBlubld - CBart)
d/dt(ABven) = (Ql*CBvl + Qf*CBvf + Qm*CBvm + Qvrg*CBvvrg) - Qtot*CBven
d/dt(ABl) = Ql*(CBart - CBvl) + Clr*Cvl - CBlr*CBvl
d/dt(ABf) = Qf*(CBart - CBvf)
d/dt(ABm) = Qm*(CBart - CBvm)
d/dt(ABvrg) = Qvrg*(CBart - CBvvrg)
d/dt(Hbadd) = (Vart*CBart + Vven*CBven + Vlubld*CBlubld)*Khb
d/dt(DNAadd) = (Vart*CBart + Vven*CBven + Vlubld*CBlubld)*Kdna - Keldna*DNAadd
{AUCs for ethylene oxide}
d/dt(AUCBvtot) = CBvtot
d/dt(AUCBvl) = CBvl
d/dt(AUCBvlubld) = CBvlubld
{amounts of ethylene oxide metabolized in liver}
d/dt(ABmet) = CBlr*CBvl

E.5.14 Model Code for Styrene/SO RT Model of Csanady et al*. (2003) Adult*

METHOD Stiff

STARTTIME = 0
STOPTIME= 48
DT = 0.001
{Styrene mmol}
init Aluc = 0 {conducting airways}
init Alua = 0 {alveoli}
init Alubld = 0 {lung blood}
init Aven = 0 {venous blood}
init Aart = 0 {arterial blood}
init Afat = 0
init Avrg = 0
init Amusc = 0

init Al = 0
init Amet1luc = 0
init Amet1lua = 0
init Amet1lu = 0
init Amet1l = 0
{Styrene oxide, mmol}
init ABluc = 0
init ABlua = 0
init ABlubld = 0
init ABven = 0
init ABart = 0
init ABfat = 0
init ABvrg = 0
init ABmusc = 0
init ABler = 0
init ABlcy = 0
init ABmet2luc = 0
init ABmet2lua = 0
init ABmet2l = 0
init ABmet3luc = 0
init ABmet3lua = 0
init ABmet3l = 0
init AUCBluc = 0
init AUCBlua = 0
init AUCBl = 0
{Hb adduct, DNA Adduct}
Init Hbadd = 0
d/dt(Hbadd) = (Vart*CBart + Vven*CBven + Vlubld*CBlubld)*Kher
init DNAadd =0
d/dt(DNAadd) = (Vart*CBart + Vven*CBven + Vlubld*CBlubld)*Kfdna - Keldna*DNAadd
Kher = 4.5E-5
Kfdna = 3.7E-5
Keldna = 0.0077
{Model parameters}
BW = 70 {kg, L}
Qalv = 300 {L/hr}
Qtot = 372
tcap = 7.45E-6 {dm}
Scap = 115 {dm2/kg}
Dst = 4.4E-4 {dm2/hr}
Dso = 4.3E-4
{Flows, L/hr}
Qfat = 0.05*Qtot
Ql = 0.26*Qtot

Qvrg = 0.44*Qtot
Qmusc = 0.25*Qtot
{Volumes, L}
Vch = 3E3
Vart = 0.0178*BW
Vven = 0.0533*BW
Vlubld = 0.0079*BW
Vfat = 0.19*BW
Vlu = 0.0076*BW
Vluc = fs*Vlu
Vlua = (1-fs)*Vlu
Vl = 0.026*BW
Vvrg = 0.042*BW
Vmusc = 0.541*BW
{Partition coeffs styrene, dimensionless}
Pb = 70.0
Pfat = 93.8
Pl = 2.71
Plu = 1.46
Pvrg = 2.60
Pmusc = 1.96
{Partition coeffs styrene oxide, dimensionless}
PbB = 2370
PBfat = 6.1
PBl = 2.6
PBlu = 1.9
PBvrg = 2.6
PBmusc = 1.5
{Concentrations ST mmol/L}
Exposure = IF TIME < 24 THEN 1*(1E-3/24.45) ELSE 0
fs = 0.1
Cair = exposure
Cart = Aart/Vart
Cven = Aven/Vven
Cfat = Afat/Vfat
Cl = Al/Vl
Cvrg = Avrg/Vvrg
Cmusc = Amusc/Vmusc
Clubld = Alubld/Vlubld
Cluc = Aluc/(fs*Vlu)
Clua = Alua/((1-fs)*Vlu)
Cexalv = (fs*(2.0-fs)*(Cluc/Pb) + (1.0-fs)*(1.0-fs)*(Clua/Pb))/factor
Cexpul = (fs*(2.0-fs)*(Cluc/Pb) + (1.0-fs)*(1.0-fs)*(Clua/Pb))/factor + 1/3*Cairp
factor = 1

Cairp = Cair*(24.45/1E-3)
{Concentrations SO, mmol/L}
CBart = ABart/Vart
CBven = ABven/Vven
CBfat = ABfat/Vfat
CBvrg = ABvrg/Vvrg
CBmusc = ABmusc/Vmusc
CBlcy = ABlcy/Vl
CBvlcy = ABlcy/(Vl * Pl)
CBluc = ABluc/(fs*Vlu)
CBlua = ABlua/((1-fs)*Vlu)
CBlubld = ABlubld/Vlubld
Qendo = Vmaxl2*1E3*Vl/(Kml2app - Kml2eh)
a = CBlcy - Kml2eh + Vmaxl1*1E3*Vl*Cl/Qendo*(Pl*Kml1 + Cl) - Vmaxl2*1E3*Vl/Qendo
CBendo = 0.5*(a + (a^2 + 4*Kml2eh*(CBlcy + Vmaxl1*1E3*Vl*Cl/Qendo*(Pl*Kml1 + Cl)))^0.5)
{GSH}
init GSHluc = fs*GSHlu0
init GSHlua = (1-fs)*GSHlu0
init GSHl = GSHl0
CGSHluc = GSHluc*fs/Vluc
CGSHlua = GSHlua*(1-fs)/Vlua
CGSHl = GSHl/Vl
fGSH = 0.75
GSHlu0 = 1.95*Vlu
GSHl0 = 5.9*Vl
{Biochemical parameters, mmol/hr/mL, mmol/L; 1 = P450, 2 = EH, 3 = GST}
Vmaxl1 = 0.002
Kml1 = 0.01
Vmaxl2 = 0.0045
Kml2eh = 0.001
Kml2app = 0.01
Vmaxl3 = 0.028
Kml3G = 0.1
Kml3so = 2.5
Kdl = 0.2
Vmaxlu1 = 2.5E-6
Kmlu1 = 0.0175
Vmaxlu2 = 6.73E-4
Kmlu2 = 0.0156
Vmaxlu3 = 0.082
Kmlu3G = 0.1
Kmlu3so = 2.5
Kdlu = 2.0
{Differential equations for styrene}

d/dt(Aluc) = Qalv*(Cair*fs + fs*(1 - fs)*(Clua/Pb) - (fs + fs*(1-fs))*Cluc/Pb) - Vmaxlu1*1E3*Vlu*fs*Cluc/(Kmlu1 + Cluc)

d/dt(Alua) = Qalv*(Cair*(1-fs) - (1-fs)*Clua/Pb) - Vmaxlu1*1E3*Vlu*(1-fs)*Clua/(Kmlu1 + Clua) - (Scap*Dst/tcap)*(Clua/Plu - Clubld)

d/dt(Alubld) = (Scap*Dst/tcap)*(Clua/Plu - Clubld) + Qtot*(Cven - Clubld)

d/dt(Aart) = Qtot*(Clubld - Cart)

d/dt(Afat) = Qfat*(Cart - Cfat/Pfat)

d/dt(Avrg) = Qvrg*(Cart - Cvrg/Pvrg)

d/dt(Amusc) = Qmusc*(Cart - Cmusc/Pmusc)

d/dt(Al) = Ql*(Cart - Cl/Pl) - Vmaxl1*1E3*Vl*Cl/(Pl*Kml1 + Cl)

d/dt(Aven) = (Qfat*Cfat/Pfat + Qvrg*Cvrg/Pvrg + Ql*Cl/Pl + Qmusc*Cmusc/Pmusc) - Qtot*Cven

d/dt(Amet1luc) = Vmaxlu1*1E3*Vlu*fs*Cluc/(Kmlu1 + Cluc)

d/dt(Amet1lua) = Vmaxlu1*1E3*Vlu*(1-fs)*Clua/(Kmlu1 + Clua)

d/dt(Amet1lu) = Vmaxlu1*1E3*Vlu*fs*Cluc/(Kmlu1 + Cluc) + Vmaxlu1*1E3*Vlu*(1-fs)*Clua/(Kmlu1 + Clua)

d/dt(Amet1l) = Vmaxl1*1E3*Vl*Cl/(Pl*Kml1 + Cl)

{Differential equations for styrene oxide, B}

d/dt(ABluc) = Vmaxlu1*1E3*Vlu*(1-fs)*Cluc/(Kmlu1 + Cluc) - Vmaxlu2*1E3*Vlu*fs*CBluc/(Kmlu2 + CBluc) - Vmaxlu3*1E3*Vlu*fs*CBluc*CGSHluc/(Kmlu3so*CGSHluc + Kmlu3G*CBluc + CBluc*CGSHluc)

d/dt(ABlua) = Vmaxlu1*1E3*Vlu*(1-fs)*Clua/(Kmlu1 + Clua) - Vmaxlu2*1E3*Vlu*(1-fs)*CBlua/(Kmlu2 + CBlua) - Vmaxlu3*1E3*Vlu*(1-fs)*CBlua*CGSHlua/(Kmlu3so*CGSHlua + Kmlu3G*CBlua + CBlua*CGSHlua) - (Scap*Dso/tcap)*(CBlua/PBlu - CBlubld)

d/dt(ABlubld) = (Scap*Dso/tcap)*(CBlua/PBlu - CBlubld) + Qtot*(CBven - CBlubld)

d/dt(ABart) = Qtot*(CBlubld - CBart)

d/dt(ABfat) = Qfat*(CBart - CBfat/PBfat)

d/dt(ABvrg) = Qvrg*(CBart - CBvrg/PBvrg)

d/dt(ABmusc) = Qmusc*(CBart - CBmusc/PBmusc)

d/dt(ABlcy) = Ql*(CBart - CBvlcy) + Qendo*(CBendo - CBlcy) - Vmaxl3*1E3*Vl*CBlcy*CGSHl/(Kml3so*CGSHl + Kml3G*CBlcy + CBlcy*CGSHl)

d/dt(ABler) = Vmaxl1*1E3*Vl*Cl/(Pl*Kml1 + Cl) - Qendo*(CBendo - CBlcy) - Vmaxl2*1E3*Vl*CBendo/(Kml2eh + CBendo)

d/dt(ABven) = (Qfat*CBfat/PBfat + Qvrg*CBvrg/PBvrg + Ql*CBvlcy/PBl + Qmusc*CBmusc/PBmusc) - Qtot*CBven

d/dt(ABmet2luc) = Vmaxlu2*1E3*Vlu*fs*CBluc/(Kmlu2 + CBluc)

d/dt(ABmet2lua) = Vmaxlu2*1E3*Vlu*(1-fs)*CBlua/(Kmlu2 + CBlua)

d/dt(ABmet2l) = Vmaxl2*1E3*Vl*CBendo/(Kml2eh + CBendo)

d/dt(ABmet3luc) = Vmaxlu3*1E3*Vlu*fs*CBluc*CGSHluc/(Kmlu3so*CGSHluc + Kmlu3G*CBluc + CBluc*CGSHluc)

d/dt(ABmet3lua) = Vmaxlu3*1E3*Vlu*(1-fs)*CBlua*CGSHlua/(Kmlu3so*CGSHlua + Kmlu3G*CBlua + CBlua*CGSHlua)

d/dt(ABmet3l) = Vmaxl3*1E3*Vl*CBlcy*CGSHl/(Kml3so*CGSHl + Kml3G*CBlcy + CBlcy*CGSHl)

d/dt(AUCBluc) = CBluc

d/dt(AUCBlua) = CBlua

d/dt(AUCBl) = CBlcy

{differential equations GSH, no circadian term included}

d/dt(GSHluc) = fs*Kdlu*Vluc*(fGSH*1.95 - CGSHluc) - Vmaxlu3*1E3*Vlu*fs*CBluc*CGSHluc/(Kmlu3so*CGSHluc + Kmlu3G*CBluc + CBluc*CGSHluc)

d/dt(GSHlua) = (1-fs)*Kdlu*Vlua*(fGSH*1.95 - CGSHlua) - Vmaxlu3*1E3*Vlu*(1-fs)*CBlua*CGSHlua/(Kmlu3so*CGSHlua + Kmlu3G*CBlua + CBlua*CGSHlua)

d/dt(GSHl) = Kdl*Vl*(fGSH*5.9 - CGSHl) - Vmaxl3*1E3*Vl*CBlcy*CGSHl/(Kml3so*CGSHl + Kml3G*CBlcy + CBlcy*CGSHl)

E.5.15 Model Code for Carbon tetrachloride 0-6 yr Child

METHOD Stiff

STARTTIME = 0
STOPTIME=48
DT = 0.001
{CCl4 moles}
init Af = 0
init Al = 0
init Am = 0
init Avrg = 0
init Abr = 0
init Apu = 0
{moles CCl4 metabolized}
init Ametl = 0
init AUCvtot = 0
init AUCvl = 0
{tissue flows L/hr}
Qtot = 0.012*Age^3 - 1.2144*Age^2 + 40.324*Age + 44.414
Qalv = 0.82*Qtot
Qf = 0.053*Qtot
Ql = 0.0795*Qtot
Qm = 0.03*Qtot
Qvrg = Qtot -(Qf + Ql + Qm)
Qpu = 0.93*Qtot
Qbr = 0.07*Qtot
{tissue volumes L}
Vf = (0.0165*Age^5 - 1.9784*Age^4 + 51.963*Age^3 - 459.38*Age^2 + 1566.8*Age + 1004.2)/1000
Vl = (0.0072*Age^5 - 0.3975*Age^4 + 7.9052*Age^3 - 65.624*Age^2 + 262.02*Age + 157.52)/1000
Vm = (-0.0623*Age^5 + 2.3433*Age^4 - 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2)/1000
Vvrg = BW - (Vf + Vl + Vm + Vlu)
Vlu = (-0.0346*Age^4 + 1.5069*Age^3 - 20.31*Age^2 + 123.99*AGe + 59.213)/1000
Vpu = 0.9*Vlu
Vbr = 0.1*Vlu
BW = (-1.9*Age^4 + 72.8*Age^3 - 813.1*Age^2 + 5535.6*Age + 4453.7)/1000

{blood/air and tissue/blood partition coefficients, CCl4}
Pb = 4.52
Pl = 3.14
Pf = 79.4
Pm = 1.00
Pvrg = 1.00
Ppu = 1.00
Pbr = 1.00
{CCl4 oxidation metabolic parameters, mol/hr/mg protein, mol/L, mol/hr}
Vmax = 1.35E-7*(70/BW)^0.25
Vmaxl = Vmax*Vl*23.0*1E3
Km = 5.68E-5
{exposure in ppm converted to moles/L}
Cair = IF TIME <= 24 THEN 1*(1E-6/25.45) ELSE 0
Age = 5
{calculated concentrations of CCl4}
Cart = (Qpu*Cvpu + Qbr*Cvbr)/Qtot
Cvf = Af/(Vf*Pf)
Cvl = Al/(Vl*Pl)
Cvm = Am/(Vm*Pm)
Cvvrg = Avrg/(Vvrg*Pvrg)
Cvpu = Apu/(Vpu*Ppu)
Cvbr = Abr/(Vbr*Pbr)
Cvtot = (Ql*Cvl + Qf*Cvf + Qm*Cvm + Qvrg*Cvvrg)/Qpu
Cvipu = (Qalv*Cair + Qpu*Cvtot)/((Qalv/Pb) + Qpu)
Cexh = Cvipu/Pb
{differential equations for CCl4 uptake and metabolism}
d/dt(Apu) = Qpu*(Cvipu - Cvpu)
d/dt(Abr) = Qbr*(Cart - Cvbr)
d/dt(Al) = Ql*(Cart - Cvl) - Vmaxl*Cvl/(Km + Cvl)
d/dt(Af) = Qf*(Cart - Cvf)
d/dt(Am) = Qm*(Cart - Cvm)
d/dt(Avrg) = Qvrg*(Cart - Cvvrg)
{amount of CCl4 metabolized in liver}
d/dt(Ametl) = Vmaxl*Cvl/(Km + Cvl)
d/dt(AUCvtot) = Cvtot
d/dt(AUCvl) = Cvl

E.5.16 Model Code for Toluene 0-6 yr Child

METHOD Stiff

STARTTIME = 0
STOPTIME=48
DT = 0.001
{Toluene moles}
init Af = 0
init Al = 0
init Am = 0
init Avrg = 0
init Abr = 0
init Apu = 0
{moles toluene metabolized}
init Ametl = 0
init AUCvtot = 0
init AUCvl = 0
{tissue flows, L/hr}
Qtot = 0.012*Age^3 - 1.2144*Age^2 + 40.324*Age + 44.414
Qalv = 0.82*Qtot
Qf = 0.053*Qtot
Ql = 0.0795*Qtot
Qm = 0.03*Qtot
Qvrg = Qtot -(Qf + Ql + Qm)
Qpu = 0.93*Qtot
Qbr = 0.07*Qtot
{tissue volumes, L}
Vf = (0.0165*Age^5 - 1.9784*Age^4 + 51.963*Age^3 - 459.38*Age^2 + 1566.8*Age + 1004.2)/1000
Vl = (0.0072*Age^5 - 0.3975*Age^4 + 7.9052*Age^3 - 65.624*Age^2 + 262.02*Age + 157.52)/1000
Vm = (-0.0623*Age^5 + 2.3433*Age^4 - 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2)/1000
Vvrg = BW - (Vf + Vl + Vm + Vlu)
Vlu = (-0.0346*Age^4 + 1.5069*Age^3 - 20.31*Age^2 + 123.99*AGe + 59.213)/1000
Vpu = 0.9*Vlu
Vbr = 0.1*Vlu
BW = (-1.9*Age^4 + 72.8*Age^3 - 813.1*Age^2 + 5535.6*Age + 4453.7)/1000
{blood/air and tissue/blood partition coefficients, toluene}
Pb = 15.6
Pl = 2.98
Pf = 65.8
Pm = 1.37
Pvrg = 2.66
Ppu = 2.66
Pbr = 2.66

{toluene oxidation metabolic parameters, mol/hr, mol/L}
Vmaxl = 5.2E-5*BW*(70/BW)^0.25
Km = 5.97E-6
{exposure in ppm converted to moles/L}
Cair = IF TIME <= 24 THEN 1*(1E-6/25.45) ELSE 0
Age = 5
{calculated concentrations of toluene}
Cart = (Qpu*Cvpu + Qbr*Cvbr)/Qtot
Cvf = Af/(Vf*Pf)
Cvl = Al/(Vl*Pl)
Cvm = Am/(Vm*Pm)
Cvvrg = Avrg/(Vvrg*Pvrg)
Cvpu = Apu/(Vpu*Ppu)
Cvbr = Abr/(Vbr*Pbr)
Cvtot = (Ql*Cvl + Qf*Cvf + Qm*Cvm + Qvrg*Cvvrg)/Qpu
Cvipu = (Qalv*Cair + Qpu*Cvtot)/((Qalv/Pb) + Qpu)
Cexh = Cvipu/Pb
{differential equations for toluene uptake and metabolism}
d/dt(Apu) = Qpu*(Cvipu - Cvpu)
d/dt(Abr) = Qbr*(Cart - Cvbr)
d/dt(Al) = Ql*(Cart - Cvl) - Vmaxl*Cvl/(Km + Cvl)
d/dt(Af) = Qf*(Cart - Cvf)
d/dt(Am) = Qm*(Cart - Cvm)
d/dt(Avrg) = Qvrg*(Cart - Cvvrg)
{amount of toluene metabolized in liver and AUCs in blood and liver}
d/dt(Ametl) = Vmaxl*Cvl/(Km + Cvl)
d/dt(AUCvtot) = Cvtot
d/dt(AUCvl) = Cvl

E.5.17 Model Code for Xylene 0-6 Yr Child

METHOD Stiff

STARTTIME = 0
STOPTIME=48
DT = 0.001
{Xylene moles}
init Af = 0
init Al = 0
init Am = 0
init Avrg = 0
init Abr = 0

init Apu = 0
{moles xylene metabolized}
init Ametl = 0
init AUCvtot = 0
init AUCvl = 0
{tissue flows, L/hr}
Qtot = 0.012*Age^3 - 1.2144*Age^2 + 40.324*Age + 44.414
Qalv = 0.82*Qtot
Qf = 0.053*Qtot
Ql = 0.0795*Qtot
Qm = 0.03*Qtot
Qvrg = Qtot -(Qf + Ql + Qm)
Qpu = 0.93*Qtot
Qbr = 0.07*Qtot
{tissue volumes, L}
Vf = (0.0165*Age^5 - 1.9784*Age^4 + 51.963*Age^3 - 459.38*Age^2 + 1566.8*Age + 1004.2)/1000
Vl = (0.0072*Age^5 - 0.3975*Age^4 + 7.9052*Age^3 - 65.624*Age^2 + 262.02*Age + 157.52)/1000
Vm = (-0.0623*Age^5 + 2.3433*Age^4 - 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2)/1000
Vvrg = BW - (Vf + Vl + Vm + Vlu)
Vlu = (-0.0346*Age^4 + 1.5069*Age^3 - 20.31*Age^2 + 123.99*AGe + 59.213)/1000
Vpu = 0.9*Vlu
Vbr = 0.1*Vlu
BW = (-1.9*Age^4 + 72.8*Age^3 - 813.1*Age^2 + 5535.6*Age + 4453.7)/1000
{blood/air and tissue/blood partition coefficients, xylene}
Pb = 26.4
Pl = 3.02
Pf = 77.8
Pm = 3.00
Pvrg = 4.42
Ppu = 4.42
Pbr = 4.42
{Xylene oxidation metabolic parameters, mol/hr, mol/L}
Vmaxl = 7.9E-5*BW*(70/BW)^0.25
Km = 1.88E-6
{exposure in ppm converted to moles/L}
Cair = IF TIME <= 24 THEN 1*(1E-6/25.45) ELSE 0
Age = 5
{calculated concentrations of xylene}
Cart = (Qpu*Cvpu + Qbr*Cvbr)/Qtot
Cvf = Af/(Vf*Pf)
Cvl = Al/(Vl*Pl)
Cvm = Am/(Vm*Pm)
Cvvrg = Avrg/(Vvrg*Pvrg)
Cvpu = Apu/(Vpu*Ppu)

Cvbr = Abr/(Vbr*Pbr)
Cvtot = (Ql*Cvl + Qf*Cvf + Qm*Cvm + Qvrg*Cvvrg)/Qpu
Cvipu = (Qalv*Cair + Qpu*Cvtot)/((Qalv/Pb) + Qpu)
Cexh = Cvipu/Pb
{differential equations for xylene uptake and metabolism}
d/dt(Apu) = Qpu*(Cvipu - Cvpu)
d/dt(Abr) = Qbr*(Cart - Cvbr)
d/dt(Al) = Ql*(Cart - Cvl) - Vmaxl*Cvl/(Km + Cvl)
d/dt(Af) = Qf*(Cart - Cvf)
d/dt(Am) = Qm*(Cart - Cvm)
d/dt(Avrg) = Qvrg*(Cart - Cvvrg)
{amount of xylene metabolized in liver and AUCs in blood and liver}
d/dt(Ametl) = Vmaxl*Cvl/(Km + Cvl)
d/dt(AUCvtot) = Cvtot
d/dt(AUCvl) = Cvl

E.5.18 Model Code for Toluene-Xylene Mixed Exposure 0-6 Yr Child

METHOD Stiff

STARTTIME = 0
STOPTIME=48
DT = 0.001
{Toluene moles}
init Af = 0
Limit Af >= 0
init Al = 0
Limit Al >= 0
init Am = 0
Limit Am >= 0
init Avrg = 0
Limit Avrg >= 0
init Abr = 0
Limit Abr >= 0
init Apu = 0
Limit Apu >= 0
{Xylene moles}
init ABf = 0
Limit ABf >= 0
init ABl = 0
Limit ABl >= 0
init ABm = 0

Limit ABm >= 0
init ABvrg = 0
Limit ABvrg >= 0
init ABbr = 0
Limit ABbr >= 0
init ABpu = 0
Limit ABpu >= 0
{moles toluene metabolized}
init Ametl = 0
init AUCvtot = 0
init AUCvl = 0
{moles xylene metabolized}
init ABmetl = 0
init AUCBvtot = 0
init AUCBvl = 0
{tissue flows L/hr}
Qtot = 0.012*Age^3 - 1.2144*Age^2 + 40.324*Age + 44.414
Qalv = Qtot
Qf = 0.053*Qtot
Ql = 0.0795*Qtot
Qm = 0.03*Qtot
Qvrg = Qtot - (Qf + Ql + Qm)
Qpu = 0.93*Qtot
Qbr = 0.07*Qtot
{tissue volumes L}
Vf = (0.0165*Age^5 - 1.9784*Age^4 + 51.963*Age^3 - 459.38*Age^2 + 1566.8*Age + 1004.2)/1000
Vl = (0.0072*Age^5 - 0.3975*Age^4 + 7.9052*Age^3 - 65.624*Age^2 + 262.02*Age + 157.52)/1000
Vm = (-0.0623*Age^5 + 2.3433*Age^4 - 26.559*Age^3 + 144.75*Age^2 + 339.84*Age + 1648.2)/1000
Vvrg = BW - (Vf + Vl + Vm + Vlu)
Vlu = (-0.0346*Age^4 + 1.5069*Age^3 - 20.31*Age^2 + 123.99*AGe + 59.213)/1000
Vpu = 0.9*Vlu
Vbr = 0.1*Vlu
BW = (-1.9*Age^4 + 72.8*Age^3 - 813.1*Age^2 + 5535.6*Age + 4453.7)/1000
{blood/air and tissue/blood partition coefficients, toluene}
Pb = 15.6
Pl = 2.98
Pf = 65.8
Pm = 1.37
Pvrg = 2.66
Ppu = 2.66
Pbr = 2.66
{blood/air and tissue/blood partition coefficients, xylene}
PBb = 26.4
PBl = 3.02

PBf = 77.8
PBm = 3.00
PBvrg = 4.42
PBpu = 4.42
PBbr = 4.42
{toluene oxidation metabolic parameters, mol/hr, mol/L}
Vmaxl = 5.2E-5*BW*(70/BW)^0.25
Km = 5.97E-6
Ki = 3.8E-6
{xylene oxidation metabolic parameters, mol/hr, mol/L}
Vmaxl2 = 7.9E-5*BW*(70/BW)^0.25
Km2 = 1.88E-6
K2i = 5.6E-6
{toluene exposure in ppm converted to moles/L}
Cair = IF TIME <= 8 THEN 10*(1E-6/25.45) ELSE 0
{xylene exposure in ppm converted to moles/L}
CBair = IF TIME <= 8 THEN 1*(1E-6/25.45) ELSE 0
Age = 5
{calculated concentrations of toluene}
Cart = (Qpu*Cvpu + Qbr*Cvbr)/Qtot
Cvf = Af/(Vf*Pf)
Cvl = Al/(Vl*Pl)
Cvm = Am/(Vm*Pm)
Cvvrg = Avrg/(Vvrg*Pvrg)
Cvpu = Apu/(Vpu*Ppu)
Cvbr = Abr/(Vbr*Pbr)
Cvtot = (Ql*Cvl + Qf*Cvf + Qm*Cvm + Qvrg*Cvvrg)/Qpu
Cvipu = (Qalv*Cair + Qpu*Cvtot)/((Qalv/Pb) + Qpu)
Cexh = Cvipu/Pb
{calculated concentrations of xylene}
CBart = (Qpu*CBvpu + Qbr*CBvbr)/Qtot
CBvf = ABf/(Vf*PBf)
CBvl = ABl/(Vl*PBl)
CBvm = ABm/(Vm*PBm)
CBvvrg = ABvrg/(Vvrg*PBvrg)
CBvpu = ABpu/(Vpu*PBpu)
CBvbr = ABbr/(Vbr*PBbr)
CBvtot = (Ql*CBvl + Qf*CBvf + Qm*CBvm + Qvrg*CBvvrg)/Qpu
CBvipu = (Qalv*CBair + Qpu*CBvtot)/((Qalv/PBb) + Qpu)
CBexh = CBvipu/PBb
{differential equations for toluene uptake and metabolism}
d/dt(Apu) = Qpu*(Cvipu - Cvpu)
d/dt(Abr) = Qbr*(Cart - Cvbr)
d/dt(Al) = Ql*(Cart - Cvl) - Vmaxl*Cvl/(Km*(1 + CBvl/K2i) + Cvl)

d/dt(Af) = Qf*(Cart - Cvf)
d/dt(Am) = Qm*(Cart - Cvm)
d/dt(Avrg) = Qvrg*(Cart - Cvvrg)
{differential equations for xylene uptake and metabolism}
d/dt(ABpu) = Qpu*(CBvipu - CBvpu)
d/dt(ABbr) = Qbr*(CBart - CBvbr)
d/dt(ABl) = Ql*(CBart - CBvl) - Vmaxl2*CBvl/(Km2*(1 + Cvl/Ki) + CBvl)
d/dt(ABf) = Qf*(CBart - CBvf)
d/dt(ABm) = Qm*(CBart - CBvm)
d/dt(ABvrg) = Qvrg*(CBart - CBvvrg)
{amount of toluene metabolized in liver, AUCs in blood and liver}
d/dt(Ametl) = Vmaxl*Cvl/(Km*(1 + CBvl/K2i) + Cvl)
d/dt(AUCVtot) = Cvtot
d/dt(AUCvl) = Cvl
{amount of xylene metabolized in liver, AUCs in blood and liver}
d/dt(ABmetl) = Vmaxl2*CBvl/(Km2*(1 + Cvl/Ki) + CBvl)
d/dt(AUCBVtot) = CBvtot
d/dt(AUCBvl) = CBvl

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