

CORRECTION OF THE EPA'S 2010 IUR FOR CHLOROPRENE BASED ON PBPK MODELING RESULTS

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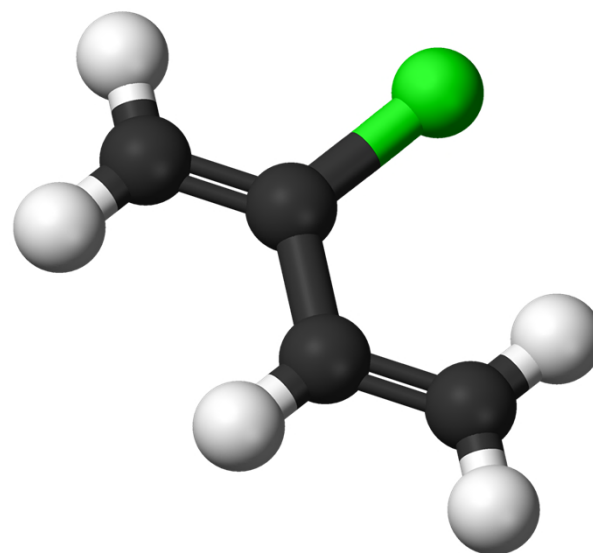
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INTRODUCTION

- On behalf of Denka Performance Elastomer (DPE) and Ramboll we thank EPA for continued collaboration and dialog regarding the use of the best available science to develop a health-based standard for chloroprene
- DPE representative – Patrick Walsh
- Ramboll team – Ken Mundt, Robinan Gentry, and Harvey Clewell (in person), Cynthia Van Landingham, Sonja Sax, and Jerry Campbell (on the phone)

OBJECTIVES

- Summarize the available evidence demonstrating the importance for using PBPK adjustments for estimating an IUR for chloroprene
- Describe efforts to update the PBPK model to address EPA's concerns raised in response to Denka's RFC and the proposed PBPK Workplan
- Present results of sensitivity analyses used to test the PBPK model
- Provide EPA with proposed conclusions based on model testing
- Discuss next steps

OVERVIEW

- Background
- Request for correction – summary of key points
- Summary of epidemiological evidence and Ramboll's "reality check"
- Summary of the scientific support for the validity of the chloroprene PBPK model
- PBPK workplan and EPA response
- Ramboll's implementation based on EPA comments on the chloroprene PBPK workplan
 - PBPK model summary
 - Sensitivity analyses and results
- Conclusions
- Next steps supporting EPA in its review and implementation of the chloroprene PBPK model

HISTORICAL BACKGROUND

- EPA published the IRIS Toxicological Review of Chloroprene* in 2010, with an inhalation unit risk (IUR) of **5×10^{-4} per $\mu\text{g}/\text{m}^3$**
- Denka Performance Elastomer (DPE) acquired the Neoprene production facility in LaPlace, Louisiana from DuPont on November 1, 2015
- The 2011 National Air Toxics Assessment (NATA), published in December 2015, identified DPE's facility as associated with **the highest offsite cancer risks** of any chemical facility in the US, based on the EPA IUR for chloroprene and 2011 emissions
- DPE retained Ramboll in March 2016 to evaluate the 2010 IRIS IUR

* U.S. Environmental Protection Agency, Washington, DC, EPA/635/R-09/010F, 2010

BACKGROUND: RAMBOLL'S CRITICAL REVIEW

- Ramboll evaluated the scientific evidence underlying the chloroprene IUR
- A weight of evidence evaluation was conducted (peer-reviewed publication is in progress)
- Ramboll derived an IUR for chloroprene that was **156 times lower** than EPA's value, using published PBPK model results to account for species differences
- In June 2017, DPE submitted a Request for Correction (RFC) of the chloroprene IUR
- In January 2018, EPA denied the request for correction, and Request for Reconsideration (RFR) is due July 25th
- In March 2018, DPE submitted a workplan to address the limitations and uncertainties raised by EPA related to the PBPK model to support the chloroprene IUR
- Ramboll implemented the recommendations from EPA in an updated PBPK model, which is presented here

SUMMARY OF REQUEST FOR CORRECTION OF THE 2010 IUR

- The DPE RFC requested that the IRIS chloroprene assessment be corrected including:
 - Replace the current chloroprene IUR with the value produced by Ramboll, or withdraw
 - Classify chloroprene as a “suggestive” human carcinogen rather than “likely” human carcinogen
- The scientific basis for the RFC included:
 - All lines of evidence point to pharmacokinetic differences across species, especially between the mouse and human
 - PBPK modeling identified as the best approach for correcting the IUR based on the large pharmacokinetic differences between the mouse and humans
 - A corrected IUR based on PBPK model output and standard EPA methods resulted in a value 156 times lower than the 2010 IRIS IUR
 - The highest quality epidemiological studies do not demonstrate a causal relationship between occupational exposures to chloroprene and cancer
- EPA denied the request for correction in January 2018 concluding that the 2010 Toxicological Review of Chloroprene complies with EPA’s Information Quality Guidelines and was subject to extensive peer review

EPIDEMIOLOGICAL EVIDENCE

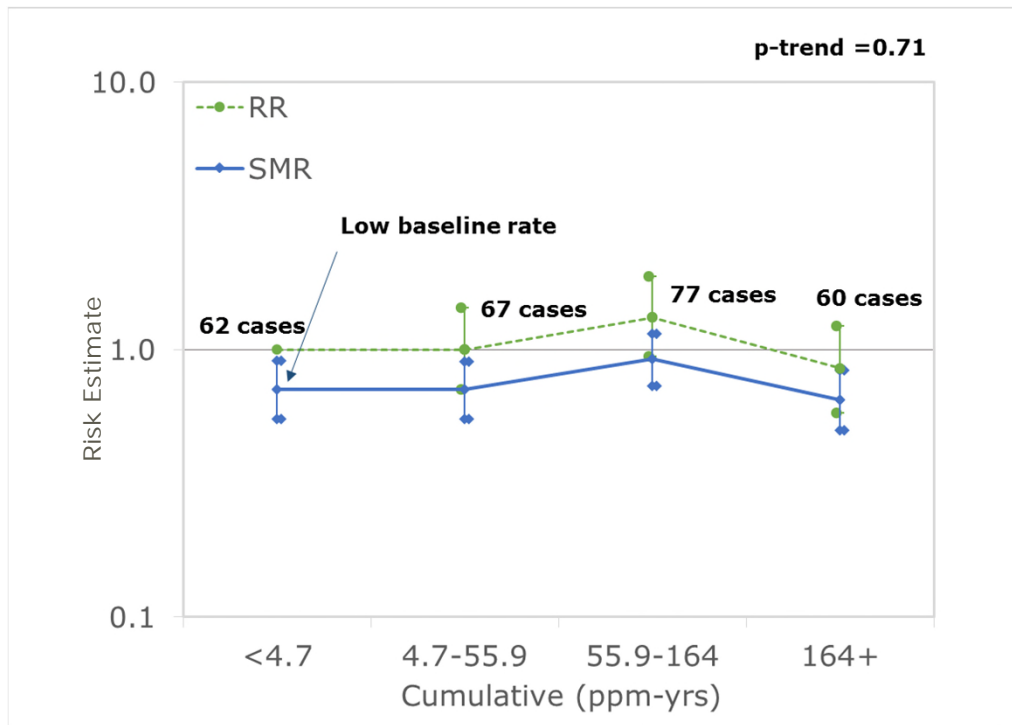
- Occupational cohort studies have been conducted around the world
 - U.S. and Western European cohorts (Pell 1978, Leet & Selevan 1982, Colonna & Leydevant 2001, Marsh et al. 2007 a,b)
 - Eastern European and Asian cohorts (Bulbulyan et al. 1998,1999, Li et al. 1989)
- US and Western European cohort studies are more robust
 - Pooled study (Marsh et al, 2007 a,b) is the largest and strongest
- Eastern European and Asian cohorts have significant limitations
 - Poor documentation of cohort enumeration and inadequate reference rates
 - Low statistical power and unstable relative risk estimates
 - Poor occupational exposure assessment, including identification and consideration of potentially consequential confounding factors

COMPARISON OF KEY CRITERIA ACROSS STUDIES

Key Criteria	US and Europe (Marsh <i>et al.</i> 2007)	Armenia (Bulbulyan <i>et al.</i> 1999)	Russia (Bulbulyan <i>et al.</i> 1998)	China (Li <i>et al.</i> 1989)
Sample Size	12,430	2,314	5,185	1,258
Follow-up	1949–2000	1979–1993	1979–1993	1969–1983
Exposure Assessment	Exposure modeling – 7 categories	Index (none, low, high)- before/after 1980	Index (none, med, high)- IH (inadequate) + job	High vs. low based on recall
Baseline rates	National, local plant area counties 1960–1994	Armenian rates 1980–1989	Moscow rates 1979–1993 or 1992–1993 (liver)	From “local area” 1973–1975 expected lung cancers: 0.4
Confounding	Used local rate comparisons; Low prevalence of other liver cancer risk factors	Alcohol use (high cirrhosis rates) and smoking prevalent	Alcohol use (high cirrhosis rates) and smoking; Co-exposure to VC	Hepatitis B and aflatoxin; Co-exposures to VC

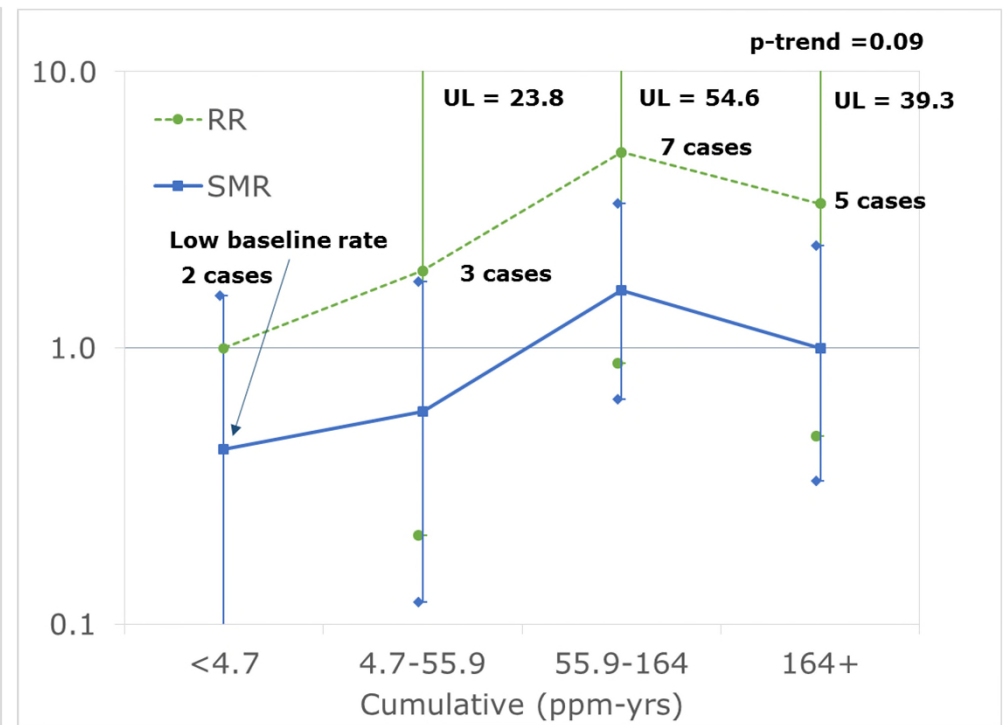
MARSH STUDY SHOWS NO INCREASED LUNG OR LIVER CANCER RISKS

Respiratory cancers RRs and SMRs by cumulative chloroprene exposure, Louisville plant



Source: Marsh 2007b

Liver cancers RRs and SMRs by cumulative chloroprene exposure, Louisville plant



Source: Marsh 2007b

“REALITY CHECK” EVALUATION

- Ramboll used the Louisville cohort from the Marsh et al. (2007) studies
 - Total of 5,468 workers exposed to chloroprene
 - Marsh calculated an SMR for lung and liver cancer for the cohort of 0.75 and 0.90 – indicating no excess cancer risk i.e., none of the total number of observed cancers were shown to be associated with chloroprene exposure in the cohort compared to local county cancer rates
- Ramboll performed the following analysis as a reality check for the 2010 IUR:
 - Calculated a lifetime exposure concentrations using 70 year exposure duration and exposures converted to $\mu\text{g}/\text{m}^3$ ($\text{ppm-years}/70 \text{ year} * 3620 \mu\text{g}/\text{m}^3 \text{ per ppm}$)
 - Median and mean exposure concentration = 18.35 and 80.35 ppm-years (highly skewed data)
 - Calculated the risk of an excess cancer for each worker by multiplying the 2010 IRIS IUR or Ramboll PBPK IUR by the lifetime exposure concentration
 - Calculated the total number of excess cancers for the Louisville worker population by multiplying the risk by 5,468 workers at risk from chloroprene exposure
 - Compared the estimated number of excess cancers to the TOTAL number of observed lung and liver cancers in the cohort

REALITY CHECK RESULTS

Source	Unit risk (per $\mu\text{g}/\text{m}^3$)	Excess Cancers Estimated based on Lifetime Exposure Concentration ($\mu\text{g}/\text{m}^3$) from Louisville cohort		Total number of Observed cancers in Louisville cohort
		Median	Mean	
EPA (2010) Multi-tumor, w/ADAF	5×10^{-4}	2,594	11,360	17 (liver) 266 (lung)
Ramboll (2018) lung tumor	3.2×10^{-6}	17	73	

REALITY CHECK CONCLUSIONS

- The 2010 IRIS IUR grossly overestimates cancer risk with numbers well above the total number of observed cancer cases
- An IUR corrected for pharmacokinetic differences yields an estimated number of cancers more in-line with the total number of observed cases
- Importantly, the IUR derived by Ramboll, though more realistic than the IRIS IUR, still generates a highly conservative upper-bound estimate, as the Marsh study did not find any statistically significant link between chloroprene exposure and cancer
- Ramboll maintains that the scientific evidence does not support a link between chloroprene exposure and cancer, even at the exposure levels described in the Marsh study, which are far greater than the exposure levels near the LaPlace facility

LOCAL COMMUNITY-LEVEL CANCER RATES

- Cancer incidence data from the Louisiana Tumor Registry for St. John the Baptist Parish (where DPE plant is located) and for the state of Louisiana
- Five most recent years

Cancer site	Parish Rate	State Rate	Ranking (1=lowest cancer rate)
All cancers	463.2	478.7	15/64
Respiratory cancers	60.1	70.5	7/64
Liver cancers	< 3 cases (too few to report)		Unknown*

*Unknown as as there were 28 parishes with too few liver cancer cases

Source: <https://statecancerprofiles.cancer.gov/incidencerates/index.php?stateFIPS=22&cancer=001&race=00&sex=0&age=001&type=incd&sortVariableName=rate&sortOrder=default#results>

EVIDENCE DEMONSTRATING THE NEED FOR A PBPK CORRECTION

- Studies conducted in B6C3F1 mice and Fischer rats (NTP, 1998), and in Wistar rats and Syrian hamsters (Trochimowicz et al., 1998) at chloroprene concentrations ranging from 10 to 80 ppm
 - Little consistency across species both in the number of tumors and in tumor location
 - No statistically significant increases in the incidence of tumors in Wistar rats and Syrian hamsters associated with chloroprene exposures, in particular ***no significant increase in the incidence of lung tumors***
 - Significant increases in the incidence of tumors seen primarily in mice and at the highest exposure levels
 - The most sensitive species/tumor site is the female mouse and the lung
- Lack of evidence of cancer in epidemiological studies of workers exposed to chloroprene
- Differences in tumor incidence can be explained by using PBPK modeling and the calculated internal dose of metabolized chloroprene (Allen et al. 2014)
- **All lines of evidence indicate that a PBPK correction is needed to arrive at a relevant IUR for humans**

SUMMARY OF ANIMAL DATA (HIMMELSTEIN ET AL. 2004, TABLE 4)

Species	Exposure concentration (ppm)	PBPK internal dose (mg/g)	Lung tumor incidence	Number of animals
Syrian Hamster (Trochimowicz et al., 1998)	0	0	0	100
	10	0.18	0	97
	50	0.88	0	97
Wistar rat (Trochimowicz et al., 1998)	0	0	0	97
	10	0.18	0	13
	50	0.89	0	100
Fischer rat (Melnick et al., 1999)	0	0	3	50
	12.8	0.22	3	50
	32	0.55	6	49
	80	1.37	9	50
B6C3F1 mouse (Melnick et al., 1999) RAMBOLL	0	0	15	50
	12.8	3.46	32	50
	32	5.3	40	50
	80	7.18	46	50

PHARMACOKINETIC CORRECTION OF THE CHLOROPRENE IUR

- The original chloroprene PBPK model was published by Himmelstein et al. (2004), which estimated a human equivalent concentration for 10% extra risk of 24 ppm continuous lifetime exposure (equivalent to an IUR of 1.2×10^{-6} per $\mu\text{g}/\text{m}^3$)
- New data were provided to EPA at the time of the review to check the validity of the model; however, EPA did not incorporate these data into the final IUR estimate
- The new data have now been published (Yang et al., 2012; Thomas et al., 2013)
- Allen et al. (2014) reported that an IUR that incorporates pharmacokinetic differences would be 250 times lower than the 2010 IRIS IUR
- Using the internal dose estimates from PBPK modeling in Yang et al. (2012), and EPA methodology consistent with other IRIS analyses, Ramboll derived an IUR of **3.2×10^{-6}** per $\mu\text{g}/\text{m}^3$ which is **156 times lower** than the 2010 IRIS IUR

RAMBOLL'S PBPK MODEL WORKPLAN

- EPA conducted a systematic review of literature published since the 2010 Toxicological Review and challenged the findings of the key publications that were included in the RFC to support the correction of the IUR using a PBPK model (e.g., Yang et al. 2012; Allen et al., 2014)
- In March 2018, Ramboll submitted a PBPK model workplan to address questions raised by EPA in the RFC including:
 - Availability of a useable version of the model (i.e., in an R platform or similar)
 - Justification for selected parameters in the in vivo/in vitro models
 - Sensitivity analyses
 - Ability to reproduce in vivo pharmacokinetic data
 - Estimation of uncertainty in the model using Markov Chain Monte Carlo (MCMC) analyses

SUMMARY OF SCIENTIFIC ISSUES/PBPK MODEL UNCERTAINTIES

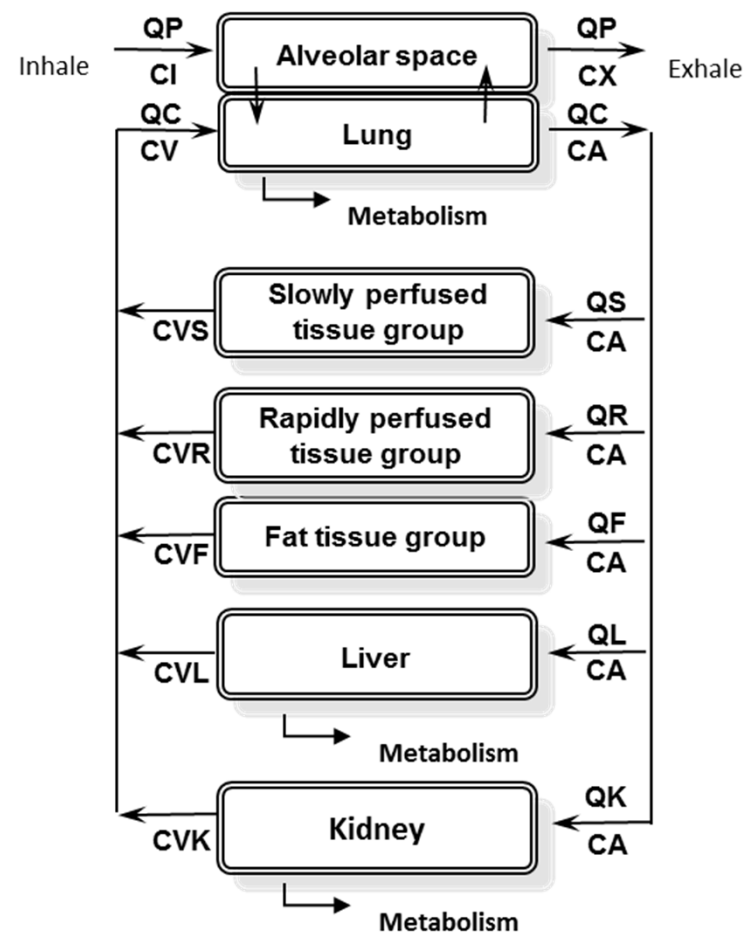
EPA provided comments on the workplan and raised several concerns regarding the PBPK model including:

- Proper documentation of the model and model parameters to allow EPA to review the PBPK model according its QAPP
- Single vs repeated exposures possibly due to respiratory depression or metabolic induction
- Estimates of parameters and consistency across tissues and genders
 - Scale-up of in vitro data
- Dose metrics
 - Uncertainty
 - Multi-tumor approach/whole body metabolism

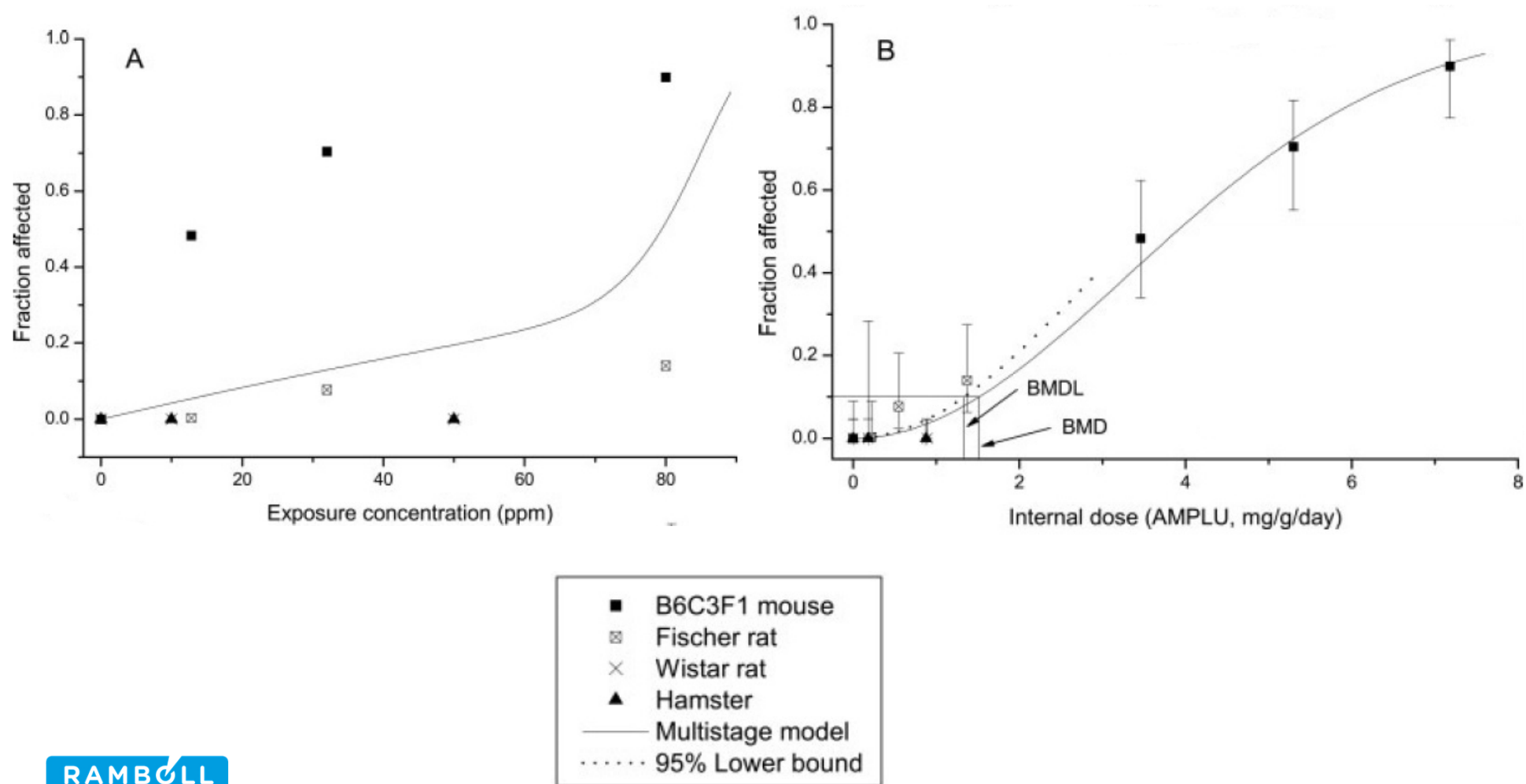
Ramboll has addressed each of these EPA concerns

UPDATED CHLOROPRENE PBPK MODEL

- Same structure used by Himmelstein et al. (2004b) and Yang et al. (2012)
- Parameters from Yang et al. (2012)
- Converted to R programming language
- R-scripts for running mouse validation study and dose metrics in mouse, rat and human
- Documentation provided for all parameters
- A manuscript documenting the model and in vivo validation data is under development for publication



SUMMARY OF ANIMAL DATA (HIMMELSTEIN ET AL. 2004, FIGURE 4)



MODEL TESTING AND VALIDATION ANALYSES

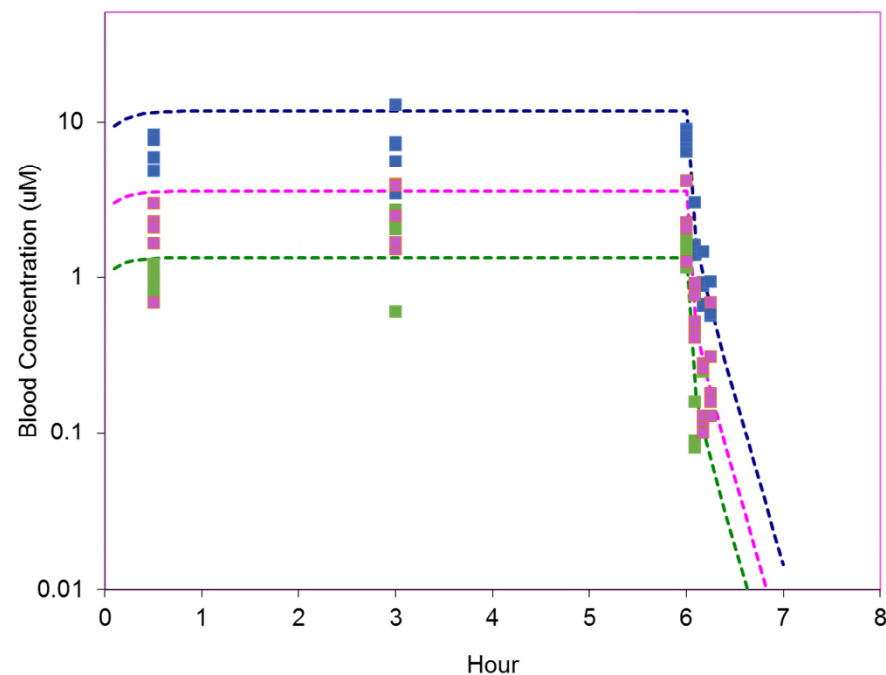
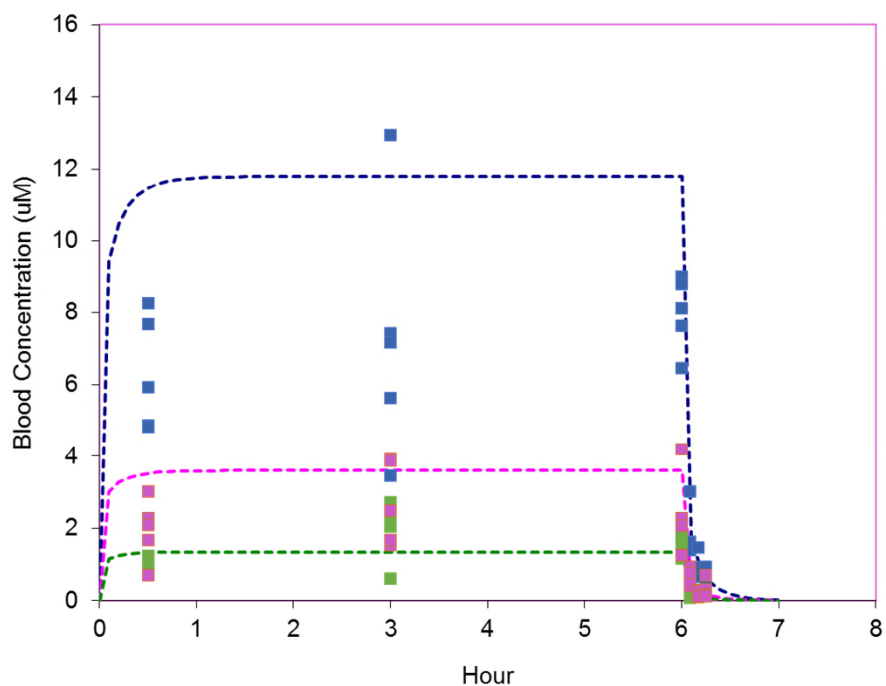
- EPA Concern: Single vs repeated end-exposure blood concentration differences possibly due to respiratory depression or metabolic induction
 - The chloroprene PBPK model was able to reproduce the blood concentrations reported in both the single and repeated exposure in vivo studies
 - Ramboll evaluated the minute ventilation data from the chloroprene single exposure study and the metabolism induction data from the repeated exposure study and determined that there was no evidence of reduced ventilation or induction of metabolism in response to chloroprene exposure
- EPA Concern: Estimates of parameters and consistency across tissues and genders
 - Ramboll conducted a sensitivity analysis on alternative parameter estimates and resulting dose metrics, results shown shortly
 - Ramboll investigated the impact of (a) using the deterministic estimates from Yang et al. (2012), and (b) assuming a fixed K_m across tissues and genders

MODEL TESTING AND VALIDATION ANALYSES (CONT.)

- EPA Concern: Scale-up of in vitro data
 - Ramboll is consulting with a metabolism expert, Dr. Miyoung Yoon, on the uncertainty associated with using in vitro metabolism data, the adequacy of the in vitro data underlying the metabolic parameters and the appropriateness of the scaling approach
- EPA Concern: EPA suggested the use of whole body metabolism and application of a total or multi-tumor approach
 - Ramboll investigated the use of whole body metabolism and total tumors by conducting statistical analyses to assess independence of tumors and evaluated the effects of applying a multi-tumor approach

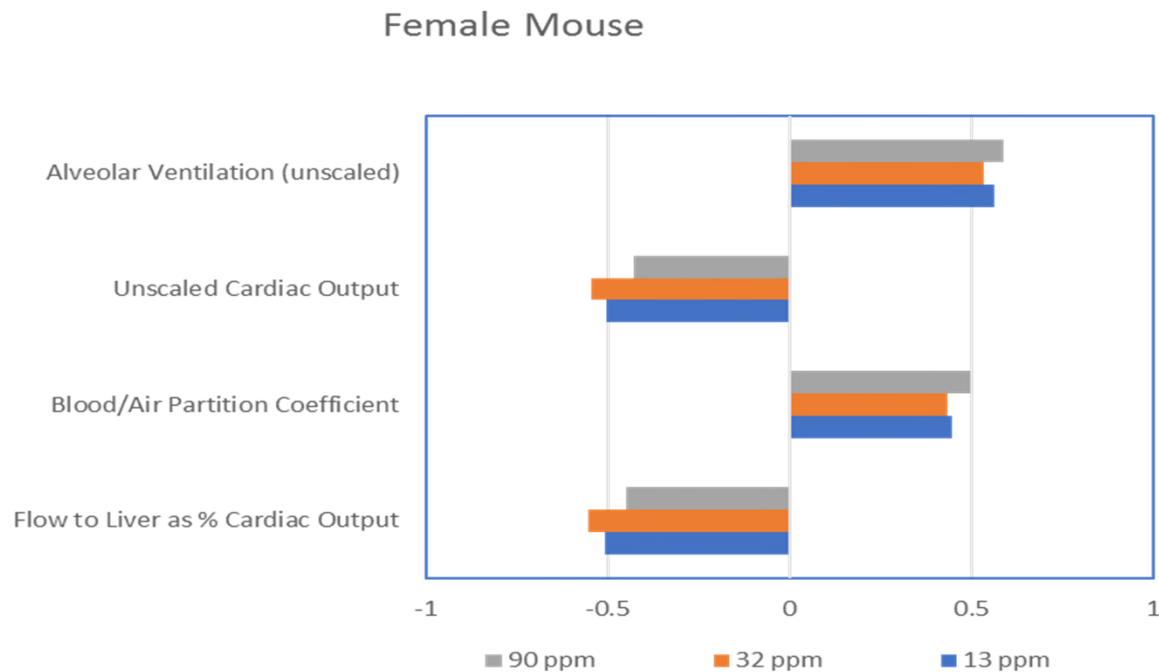
TESTING THE MODEL: SINGLE EXPOSURE

- 6-hour inhalation exposures of female mice to chloroprene (data from IISRP-12828-1388 2009)
- The model predictions fit the in vivo results very well (within a factor of 2 of the means of animal data)



RAMBOLL

MODEL PARAMETERS: SENSITIVITY OF BLOOD CONCENTRATION (CVLC) TO CHANGES IN THE MODEL PARAMETERS

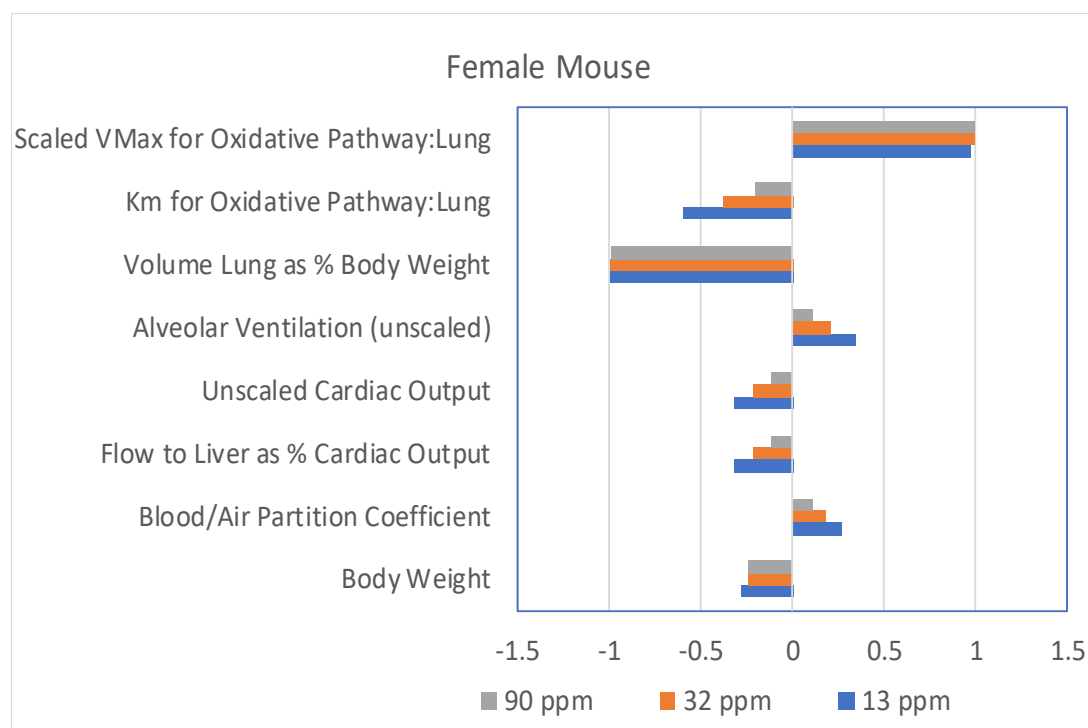
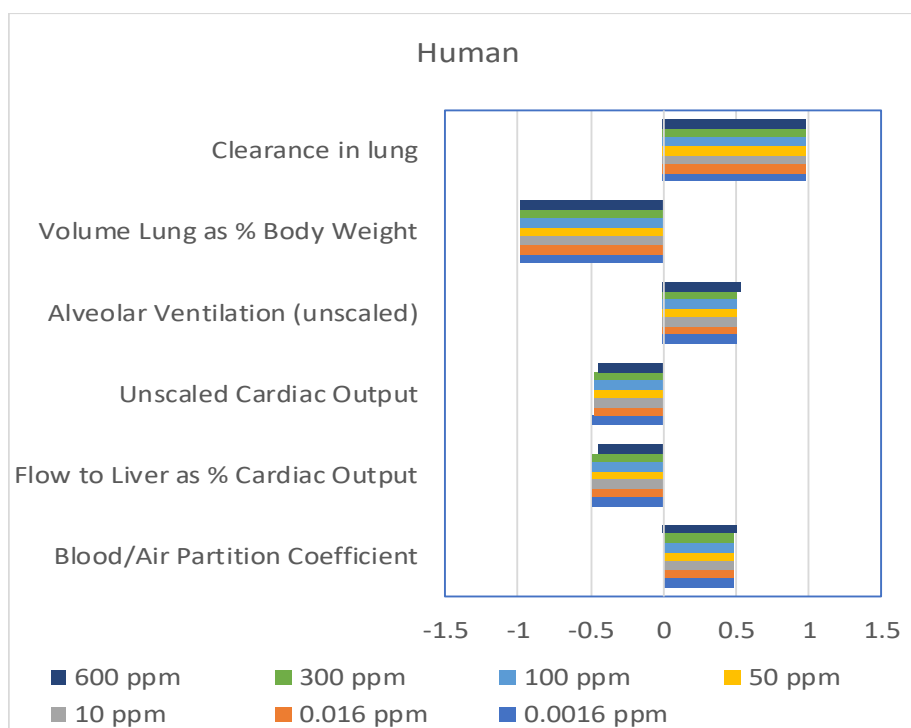


All sensitive parameters are either:

- directly measured (ventilation, blood/air partition) or
- obtained from physiological literature (cardiac output, liver blood flow)

MODEL PARAMETERS: SENSITIVITY ANALYSIS OF AMOUNT METABOLIZED IN THE LUNG DAILY PER GRAM OF TISSUE (AMPLU) TO CHANGES IN THE MODEL PARAMETERS

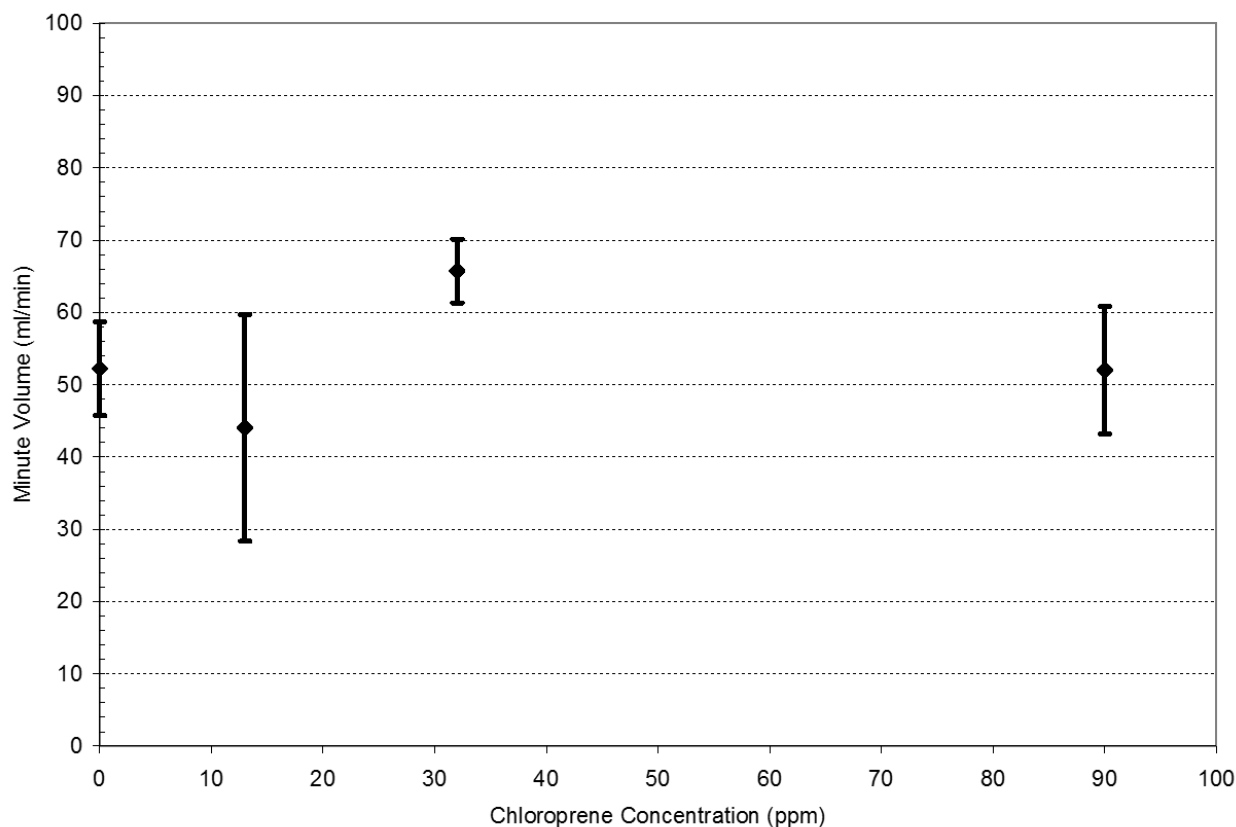
As expected, the lung dose metric is sensitive to the same parameters as the in vivo study, plus lung metabolism and lung volume



TESTING THE MODEL: SINGLE EXPOSURES

Minute ventilation during 6-hour inhalation exposures of female mice to chloroprene (IISRP-12828-1388, 2009)

- Plot: measured pulmonary ventilation (ml/min) as a function of chloroprene concentration
- Results show that minute volume is not associated with chloroprene concentrations
- This suggests that respiratory depression was not an issue
- Alveolar ventilation used in PBPK model ($Q_{PC} = 30 \text{ L/hr/kg}^{3/4}$) corresponds to average value



TESTING THE MODEL: REPEATED EXPOSURE

- In a separate study, end-exposure blood concentrations measured after 5 and 15 exposures were lower than those measured in the single exposure study
- However, after 15 days of inhalation exposure, no dose-dependent alterations were observed in total CYP content or CYP 1A2, 2B1/2, 2E1, 3A2 or 4A1/2/3 content (IISRP-12828-1406, 2009), indicating no induction of metabolism
- In addition, modeling a reduction in ventilation from measured value of 30 L/hr/kg^{**3/4} to 5 L/hr/kg^{**3/4} demonstrated that the observed differences between the single and repeated exposure data were not due to reduced ventilation

MODEL PARAMETERS: SCALE UP OF IN VITRO DATA

- EPA raised concerns regarding the methodology used in this analysis, and specifically the uncertainty associated with the scale-up of in vitro data (given the lack of in vivo human data)
- We are working with a metabolism expert (Miyoungh Yoon, PhD, ToxStrategies) to evaluate the scaling approach used in the chloroprene model and to provide an analysis of the uncertainties associated with the use of in vitro to in vivo extrapolation (IVIVE) approaches in PBPK modeling when human pharmacokinetic studies cannot be conducted
- The EPA office of pesticides currently considers PBPK models using IVIVE approaches to be of value for their pesticide risk assessments

DOSE METRICS: UNCERTAINTY ANALYSES

Species	ppm	Yang et al. (2012) Parameters (Table 2)	Yang et al. (2012) Deterministic Parameters	Assuming Fixed Km Across Tissues and Genders	Yang et al. (2012) Parameters (Table 2)	Yang et al. (2012) Deterministic Parameters	Assuming Fixed Km Across Tissues and Genders
		AMP			AMPLU		
Female Mouse	12.3	1.49	1.47	1.488	0.702	0.948	0.657
	32	3.91	3.89	3.924	1.61	1.571	0.866
	80	9.74	9.58	9.729	1.552	2.064	1.004
Male Mouse	12.3	1.2	1.1	1.27	3.79	5.0	3.04
	32	3.45	3.29	3.64	6.48	8.57	4.19
	80	9.3	9.09	9.61	8.62	11.28	4.91
Human	12.3	0.253	0.240	0.256	0.04	0.127	0.040
	32	0.657	0.624	0.670	0.105	0.330	0.055
	80	1.642	1.559	1.676	0.262	0.825	0.078

DOSE METRICS: UNCERTAINTY ANALYSIS

Source of Parameters for Calculating Internal Dose Metric	IUR at $\mu\text{g}/\text{m}^3$
Himmelstein et al. (2004)	1.2×10^{-6}
MCMC Parameter estimates from Yang et al. (2012) Table 2	3.2×10^{-6}
Deterministic parameter estimates from Yang et al. (2012) Table 3	1.9×10^{-5}
Re-estimated parameters with Km fixed across tissues and genders	1.9×10^{-5}

- Higher risk estimates compared to those obtained with the parameters in Table 2 of Yang et al. (2012), due to higher estimate of lung metabolism using deterministic approach (0.16) compared to mean of stochastic (MCMC) approach (0.05)
- For fixed Km approach, risks at concentrations above ~1 ppm cannot be inferred from the IUR due to saturation of lung metabolism, resulting in lower potency

DOSE METRICS: MULTI-TUMOR APPROACH

- Comparison of incidence from the NTP study of lung: alveolar/bronchiolar adenoma with all tumors of relevance in the female mouse from the IRIS 2010 assessment
- Combined incidence was determined by counting an individual animal if it had any of the tumors of interest
- For time-to-tumor dose-response modeling, any observation of a hemangioma prior to terminal sacrifice was considered “fatal”, based on the histopathological conclusions in the NTP report

Dose Level (ppm)	Metabolized in Lung (average daily μ mole metabolized/per g of lung tissue)	Lung: alveolar/bronchiolar adenoma	Total Metabolized (average daily μ mole metabolized/per kg of BW)	Combined Incidence
0	0	4/50	0	28/50
12.3	0.74	28/50*	8.20	42/50*
32	1.18	34/50	20.29	46/50
80	1.56	42/50	49.66	47/50

- One animal in this group was not examined microscopically and is included with an unknown context.

DOSE METRICS: MULTI-TUMOR APPROACH

- Analysis of the female mice tumor data from the NTP (1988) using a tetrachoric correlation estimation
- Evidence for lack of independence (95% confidence that correlations are significantly different from zero, i.e. p-value < 0.05) for endpoints from different sites
- IUR calculated for multi-tumor using total metabolized = 2.7×10^{-6}

Correlated Endpoint	Second Endpoint	Correlation Coefficient	P-value	# with lung tumors/ Total # with second endpoint
Lung: alveolar/bronchiolar adenoma and/or carcinoma	All organs: hemangio-sarcomas and/or hemangiomas	0.26992	0.0374	25/36
	Mammary gland: carcinoma and/or adenoacanthoma	0.30095	0.0242	23/32
	Forestomach: squamous cell papilloma and/or carcinoma	0.9990	0.0123	5/5
	Liver: hepatocellular adenoma and/or carcinoma	0.28582	0.0091	61/96
	Skin: sarcoma	0.38219	0.0023	30/40
	Harderian gland: adenoma and/or carcinoma	0.13109	0.3965	12/19
	Zymbal gland: carcinoma	0.95663	0.0533	3/3

SUMMARY

- ***PBPK modeling is the best approach for correcting the IUR because of large pharmacokinetic differences demonstrated between the mouse and humans***
- In the RFC Ramboll relied on published data to arrive at an updated IUR
- Based on comments from EPA, Ramboll has obtained all the model code, updated the model in an R platform and worked on addressing EPA concerns regarding the model
- Ramboll now has a working PBPK model for chloroprene that EPA can run and verify and that simulates the in vivo exposure data in the mouse
- Ramboll has tested the validity of the PBPK model and addressed EPA concerns

SUMMARY (CONT.)

- Ramboll will provide the model code, as well as documentation to facilitate EPA review consistent with its QAPP for the data and parameters relied upon in the PBPK model
- According to the QAPP:
 - If a PBPK model is being used as published in the peer-reviewed scientific literature, with only minor modification or corrections, then it is assumed that model was selected by the process described in the IRIS Handbook (i.e., by discussion and agreement among the PKWG, chemical managers, and other NCEA management personnel as appropriate), and no additional peer review (beyond that of the Toxicological Review) necessary
- Nevertheless, Ramboll plans to publish the updated model and associated analyses

CONCLUSIONS

- The Ramboll team appreciates the detailed comments provided by EPA, which were helpful in improving the PBPK model
- Based on sensitivity analyses, Ramboll has shown that the impact of the uncertainties in the PBPK model is relatively small, less than a factor of five
- A validated PBPK model now has been developed and documented, and a publication documenting the model and sensitivity analysis is being prepared
- Use of the PBPK correction in the derivation of the IUR results in a value that passes the 'reality check' and comparable to IURs for compounds known to be human carcinogens
- The corrected IUR provides a conservative risk number that will inform protective occupational and environmental exposure limits and is 156 times lower than the 2010 IUR

KEY POINTS

- The use of best available scientific methods as well as EPA policy dictate the need to use PBPK modeling to address pharmacokinetic differences in order to obtain the most valid risk value
- Based on our re-evaluation and testing of the PBPK model, incorporating EPA's comments, we now have a validated model for chloroprene
- The validated model confirms the findings in Yang et al. (2012) and the updated Ramboll IUR of 3.2×10^{-6} per $\mu\text{g}/\text{m}^3$, which demonstrates that the 2010 IUR overestimates human risk from chloroprene exposure by over 100 fold

NEXT STEPS TOWARD UPDATING THE IUR FOR CHLOROPRENE

- What is the best process for delivering Ramboll's PBPK model to EPA?
- Would scheduling an in-person meeting with Ramboll and EPA experts facilitate open communication between Ramboll and EPA and facilitate progress toward the most scientifically sound outcome?
- Ramboll has prepared a manuscript for publication on critically reviewing and integrating the evidence on chloroprene carcinogenicity, including the derivation of an IUR using our updated PBPK model to correct for interspecies differences, as well as other more minor corrections
- What is the process and timetable for EPA's review of the revised PBPK model? Is there anything Ramboll can do to facilitate the process?
- DPE will submit an RFR to EPA by the July 25th deadline, and we look forward to continued open communication and collaboration

THANK YOU

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