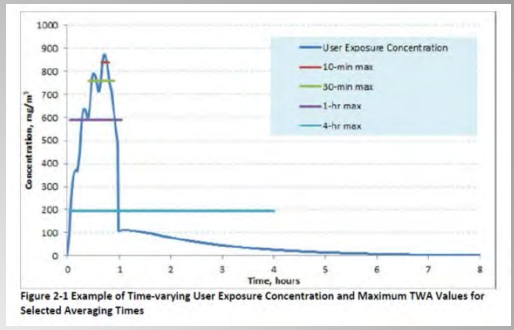


Figure 2-1 Example of Time-varying User Exposure Concentration and Maximum TWA Values for Selected Averaging Times

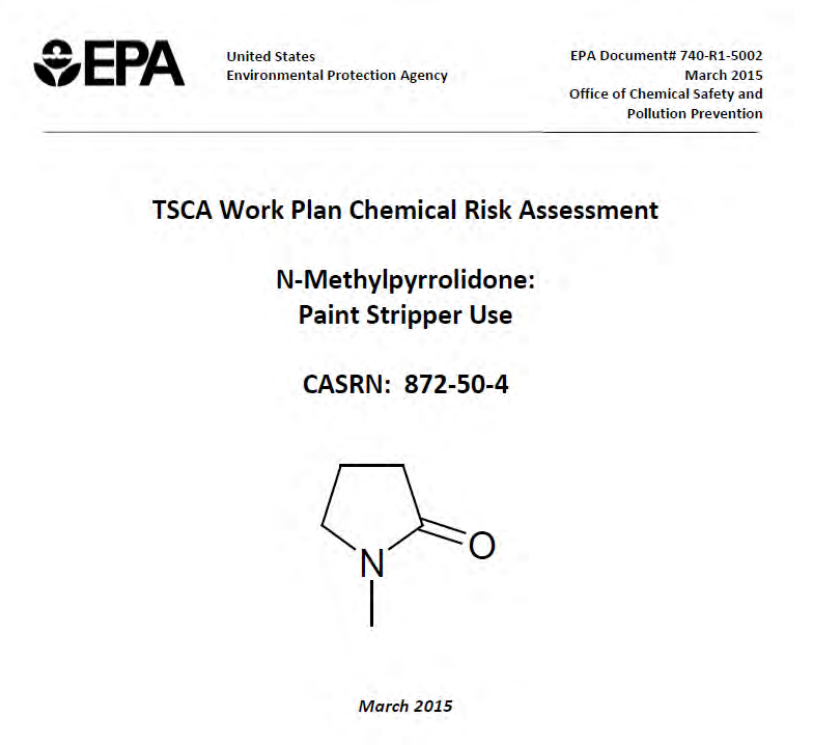
Temporality Best Practices:
Case Study with N-Methylpyrrolidone

Gary Ginsberg

Connecticut Dept of Public Health

NMP Furniture Stripping Case Study

- USEPA OPPTS Action Plan RA – NMP and DCM
  - NMP assessment completed March 2015
    - http://www.epa.gov/sites/production/files/2015-11/documents/nmp_ra_3_23_15_final.pdf



EPA

United States
Environmental Protection Agency

EPA Document# 740-R1-5002
March 2015
Office of Chemical Safety and
Pollution Prevention

TSCA Work Plan Chemical Risk Assessment

N-Methylpyrrolidone:
Paint Stripper Use

CASRN: 872-50-4

March 2015

NMP RA Highlights

- MOE approach to evaluate acute & chronic risk
  - Different toxicity endpoint picked from same studies
- Adult exposure and risk (developmental)
  - Applicator and bystander exposures
  - Worker and DYIer (Consumer) exposures
- Multiple pathway exposure
  - Inhalation + Dermal
  - PBPK model to combine pathways
  - Relate human internal dose to rodent internal dose

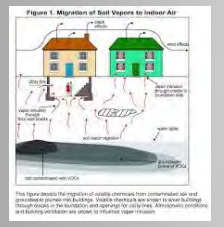
Vulnerable Life Stages and Unique Exposure Patterns Present a Temporal Challenge to Risk Assessment

Life Stages






Exposure Patterns





Tox Testing

LD_{50} Adult	Repeat Dose Adult	Repeat Dose Prenatal	Repeat Dose Postnatal	Long Term Reproduction	Chronic Adult

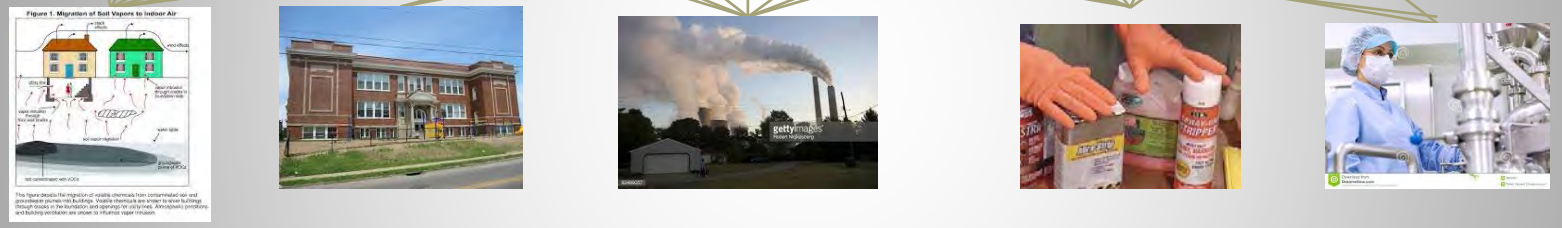
Risk Assessment

How do we apply tox/epi to exposure scenarios and critical windows of vulnerability

Vulnerable Life Stages and Unique Exposure Patterns Present a Temporal Challenge to Risk Assessment

Life Stages

Exposure Patterns



Tox Testing

LD_{50} Adult	Repeat Dose Adult	Repeat Dose Prenatal	Repeat Dose Postnatal	Long Term Reproduction	Chronic Adult

Risk Assessment

How do we apply tox/epi to exposure scenarios and critical windows of vulnerability

Vulnerable Life Stages and Unique Exposure Patterns Present a Temporal Challenge to Risk Assessment

Life Stages

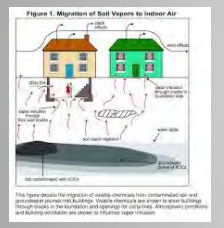





Acute POD

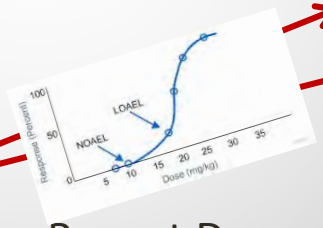
Chronic POD

Exposure Patterns





Tox Testing



LD_{50} Adult	Repeat Dose Adult	Repeat Dose Prenatal	Repeat Dose Postnatal	Long Term Reproduction	Chronic Adult

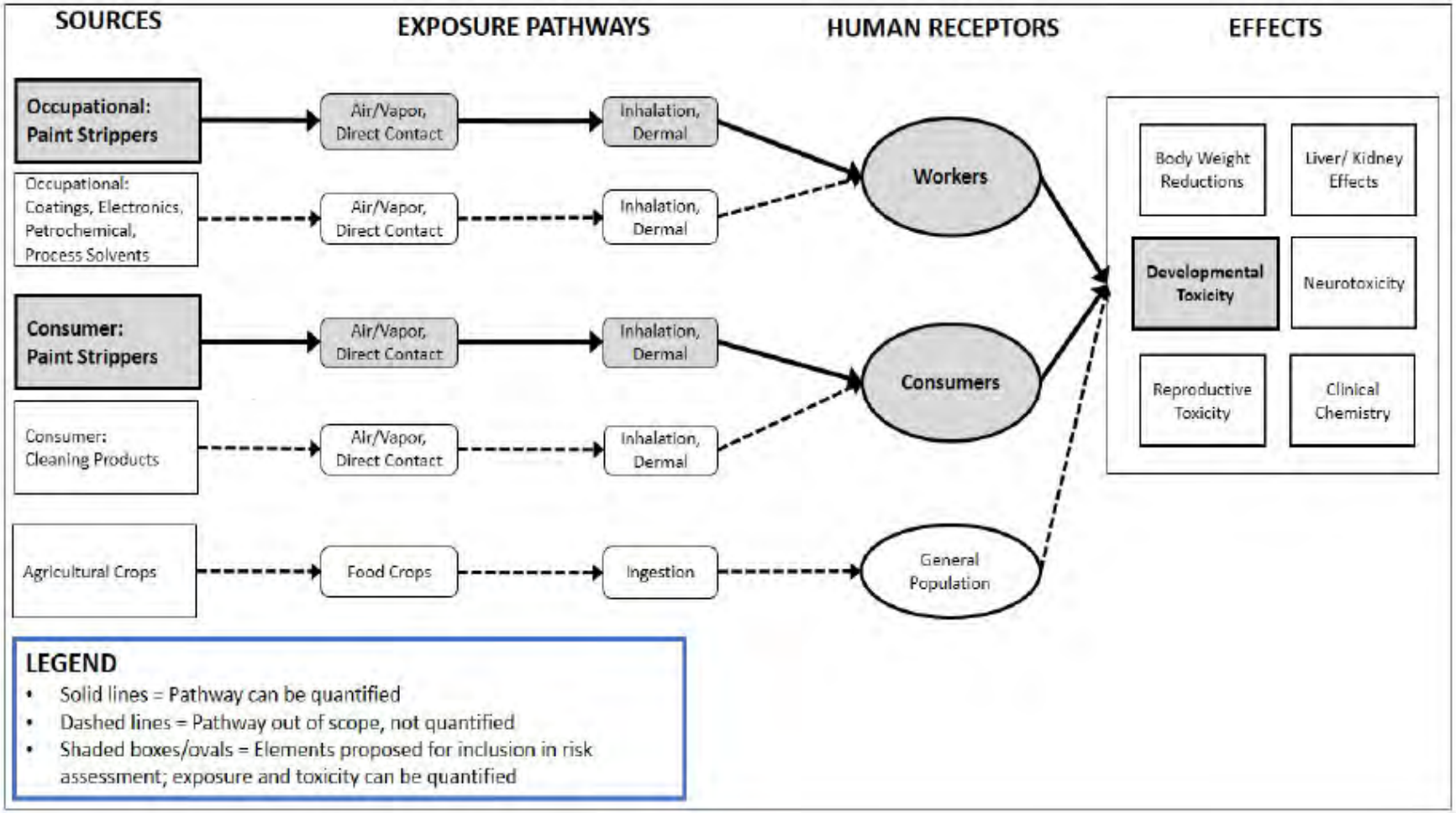
Risk Assessment

How do we apply tox/epi to exposure scenarios and critical windows of vulnerability

Potential Acute Tox Endpoints

- Acute tox testing – LD_{50} studies
  - Oral: 3605 – 7725 mg/kg/d
  - Inh LC_{50} - > 5100 mg/m3
- Neurotoxicity testing
  - Inhalation/gestation – high dose, limited testing
  - 3 month dietary study – foot splay at high doses
    - Not progressive between 4 and 12 weeks
- Developmental testing
  - Inhalation, oral, dermal studies available
    - Consistent findings of fetal and maternal effects
  - ***Developmental endpts chosen for both acute and chronic***

NMP Analysis Plan, March 2015



NMP Exposures

- Worker exposure – Acute and Chronic
  - 3 different stripping scenarios – L,M,H
  - 3 different graffitti cleaning scenarios – L,M,H
  - Concentrations from NMP occupational literature
  - Dermal penetration modeled
  - PBPK modeling to estimate Cmax and AUC to relate to tox endpoints
  - Subscenarios for different levels of protection
    - Gloves, respirators

NMP Exposures

- Consumer – Acute
- Inhalation + Dermal
- 1994 Chamber study of NMP in stripping application
- MCCEM model used to estimate air concs in different zones of house
  - Workshop
  - Bathroom
  - Bystander – rest of house
- Scenarios cover various exposure patterns
  - Application / Wait / Scrape / Repeat
- Model sensitivity analysis to establish scenarios

MCCEM Results for Consumer/Applicator Air Concentrations

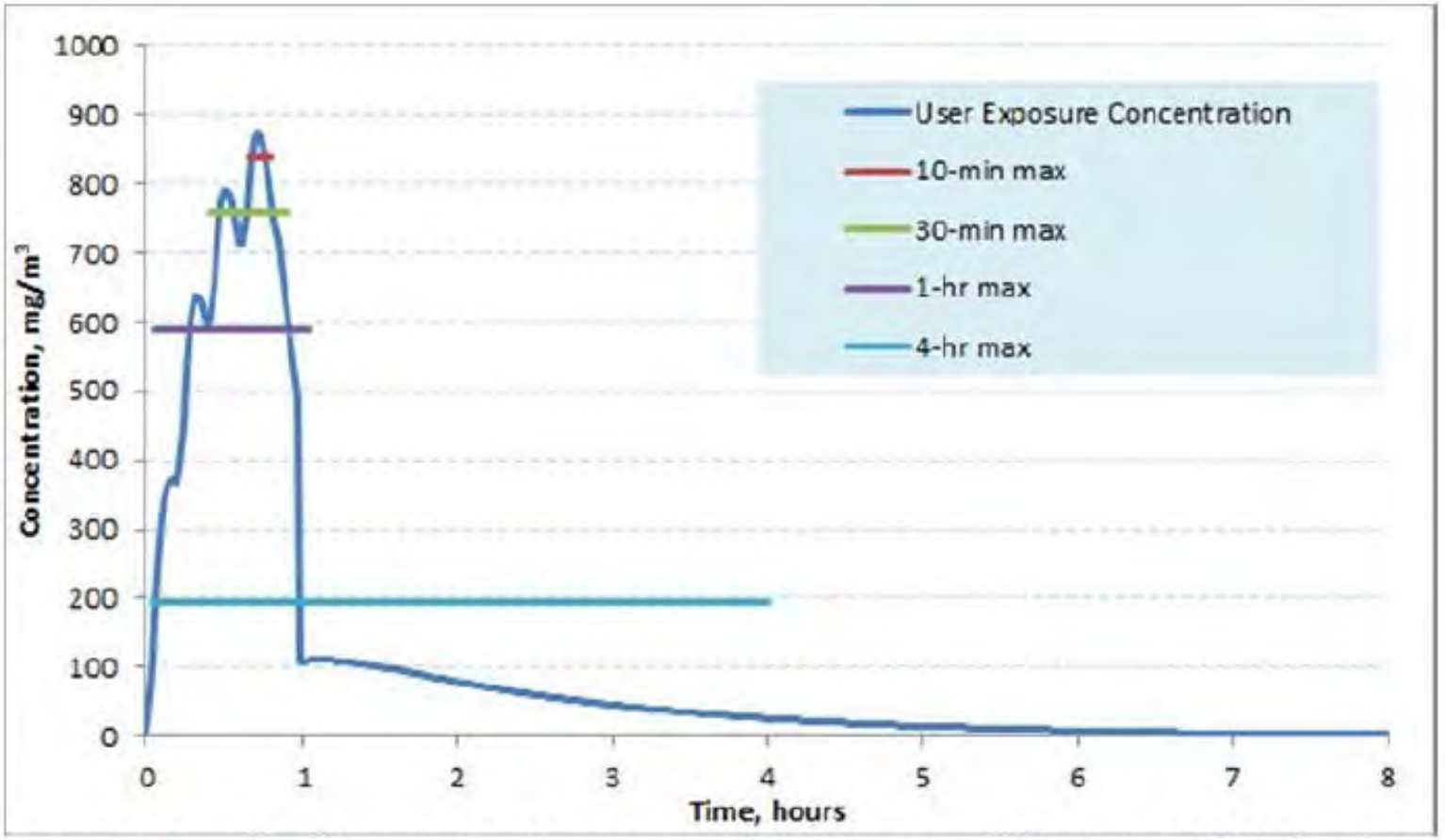


Figure 2-1 Example of Time-varying User Exposure Concentration and Maximum TWA Values for Selected Averaging Times

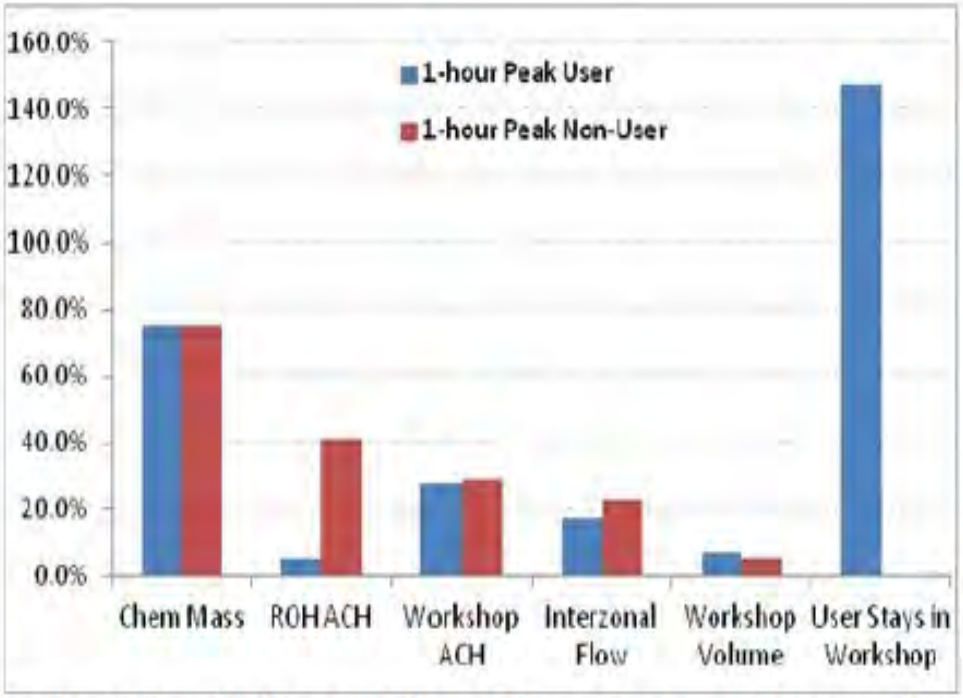
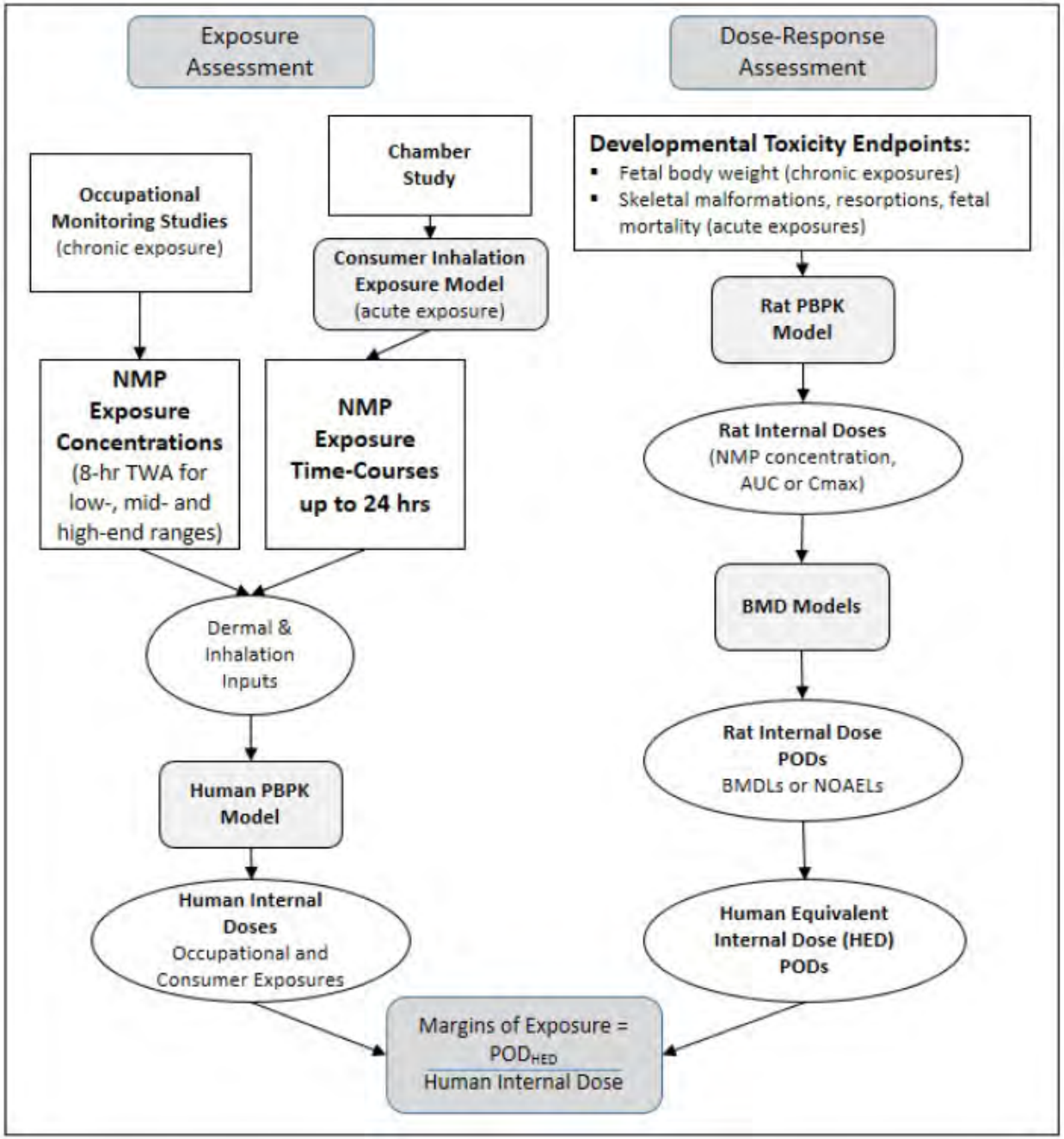


Figure 2-3 Model Sensitivity Results (Percent Change from Base-case Response) for Peak 1-hr TWA for Consumer User and Non-user



Rat and Human PBPK models used to estimate Cmax and AUCs

- Pregnant women
- First order metab, exhalation
- Dermal uptake dependent upon NMP conc in product

NMP Hazard Assessment

- Acute POD based upon one developmental endpoint
  - ***fetal resorptions/mortality***
- Chronic POD based upon a different developmental endpoint
  - ***decreased fetal body weight***
- Both endpoints from the same group of studies
- Logic:
  - Resorptions/mortality may occur from one dose during gestation
  - Body wt effect more likely to require repeat dosing

Analysis of Developmental Test Results for Establishing Acute RfD

- RIVM – Dutch Public Health Agency
  - (Van Raaij et al. 2003)
  - Desire to derive acute RfDs
    - LD_{50}s not suitable
    - How useful are developmental studies?
    - Haber's Law a possibility: C x T=K or C^x x T=K – CalOEHHA for some endpts
  - Consider devel studies for candidate endpoints
    - Certain malformations only require one day of dosing during critical window

RIVM – Van Raijj 2003

- Compared fetotoxicity endpoints for single dose vs multi-dose developmental studies
  - 20 chemicals in database
  - 10-15 chemicals for most endpoints
  - Ratio of NOAEL from 1x to LOAEL for multi-dose
    - Ratio < 1 – overlapping dose response, single dose as potent as multi – useful endpt for acute RA
    - Ratio >> 1 – single dose less potent

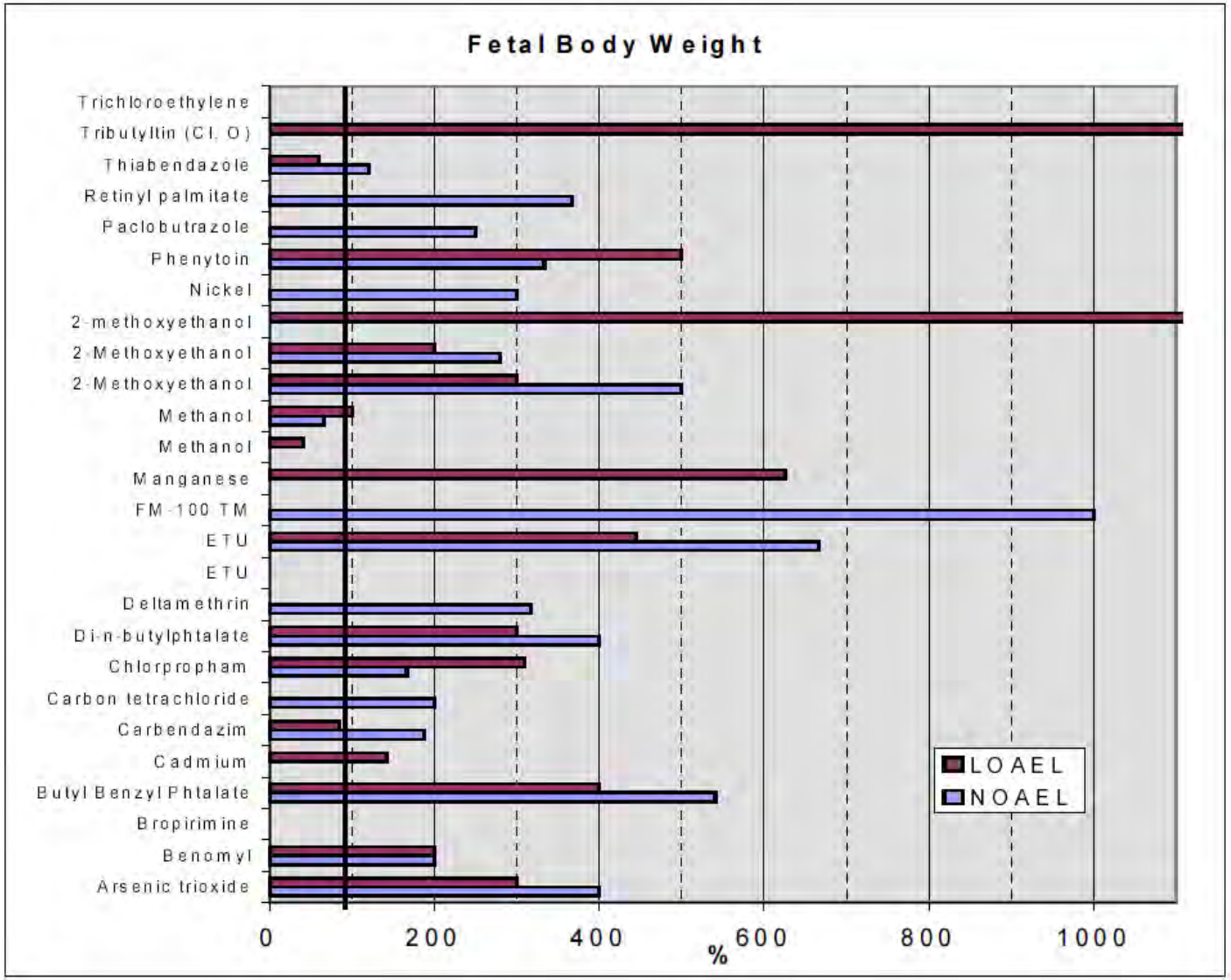


Figure 5. Single dose and repeated dose comparison for fetal body weight. Results represent the $NOAEL_{single}$ and $LOAEL_{single}$ values expressed as percentage of the corresponding NOAEL and LOAEL values from repeated dose experiments. The solid line marks the 100% (i.e. no difference)

Table 4. NLR results for fetal body weight.

Substance	**NLR-value**
Carbendazim, Methanol, Thiabendazole	NLR < 1
Benomyl, Cadmium, Chlorpropham, 2-ME (oral-mice).	1 ≤ NLR < 2
Arsenic trioxide, BBP, DBP, ETU (oral-hamster), 2-ME (oral-rat), Phenytoin,	2 ≤ NLR < 3
FM-100, 2-ME (derm-rat)	NLR ≥ 3

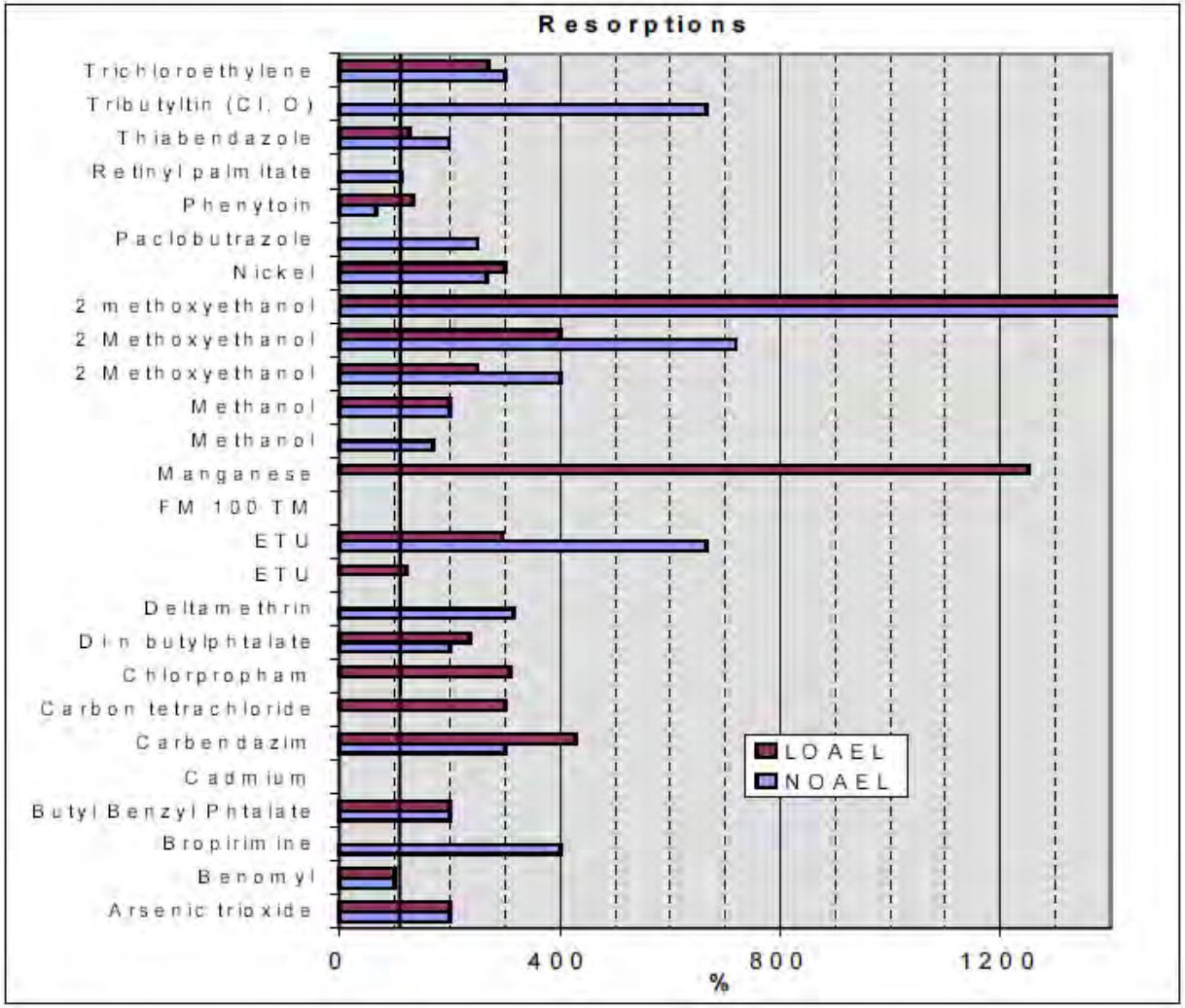


Figure 4. Single dose and repeated dose comparison for resorptions. Results represent the $NOAEL_{single}$ and $LOAEL_{single}$ values expressed as percentage of the corresponding NOAEL and LOAEL values from repeated dose experiments. The solid line marks the 100% (i.e. no difference)

Table 3. NLR results for resorptions

Substance	**NLR-value**
Benomyl, phenytoin	$NLR < 1$
Arsenic trioxide, BBP, Carbendazim, Chlorpropham, DBP, Methanol (oral-rat), Methanol (inhal-mice), Thiabendazole	$1 \leq NLR < 2$
Bropirimine, ETU (oral-hamster), 2-ME (oral-rat), Nickel, Trichloroethylene	$2 \leq NLR < 3$
2-ME (oral-mice), 2-ME (derm-rat),	$NLR \geq 3$

Summary of Van Raiij 2003 RIVM Report

Endpoint	NLR <2	Recommend for Acute RA?
Maternal Toxicity	4/15	No
Fetal Weight	7/15	No
Malformations/ Variants	8/15	Yes
Specific Malforms Hydronephrosis Cleft palate	 2/3 4/5	 Yes Yes
Resorptions	10/17	Yes

Conclusion: use of a guidelines (repeat dose) developmental NOAEL to estimate acute (single day) NOAEL is conservative but reasonable approach in some cases

Other Acute Guidelines

- ATSDR acute MRLs – 1-14 day basis
  - Developmental endpoints used
- California OEHHA acute RELs – 1 hr basis
  - Developmental endpoints used
    - Older approach – acute REL from devel dose/response
      - » time frame for REL matches the hrs/day of exposure
        - E.g., a gestation study of 4 hrs/day x 13 days
        - Derive a 4 hr REL – a single day may have produced the effect
    - Since 2008 – all acute RELs are 1 hr basis
      - » no time adjustment – even 1 hr of exposure might produce the effect

Other Possible Acute Endpoints

- Solecki et al. 2005, Acute RfDs for Pesticides
  - Hematotox: metHb, hemolytic anemia
  - Immunotox, if conceivable from one exposure
  - Acute neurotox, including acetylcholinesterase inhibition
  - Liver/kidney tox
    - If seen in single dose or early in repeat studies
  - Endocrine effects
    - If seen in single dose or early in repeat studies

NMP Developmental Data for Acute and Chronic Endpoint Selection

Table 3-3 NMP Studies with Evidence for Developmental Toxicity

	Study	Fetal Weight GD 20 - PND 1	Pup Weight PND 4	Pup Weight PND 21	Fetal Mortality (multiple metrics[a])	Pup Mortality PND 4	Pup Mortality PND 21	Incomplete Ossification	Skeletal Malformations
ORAL STUDIES	Sitarek et al., 2012	--	↓	↓	↑	↑	↑	NA	NA
	Sitarek et al., 2008	NA	NA	NA	--	↑	--	NA	NA
	NMP Producers Group, 1999a		↓	↓	↑	↑	↑		
	NMP Producers Group, 1999b		↓	↓	↑	↑	↑		
	Saillenfait et al., 2002	↓	NA	NA	↑	NA	NA	↑	↑
	Exxon, 1992	↓							
INHALATION STUDIES	Saillenfait et al., 2003	↓	NA	NA	--	NA	NA	--	--
	Hass et al.,1995	↓	NA	NA	↑	NA	NA	↑	--
	Hass et al., 1994	↓	↓	↓	--	--	--	NA	NA
	DuPont, 1990	↓	↓	↓	↑[b]	--	--	↑	↑
	Lee et al., 1987	--	NA		--	NA		--	--
DERMAL STUDIES	Becci et al., 1982	↓	NA	NA	↑	NA	NA	↑	↑

Notes:
↓ indicates decrease, ↑ indicates increase, -- indicates no change
[a] May be based on resorptions, post-implantation loss, dead pups at birth or decreased live pups at birth
[b] Statistically significant increase for p = 0.1
NA = Not Assessed
Blank = Data not publicly available

NMP Dose Response Analysis for Chronic Endpoint

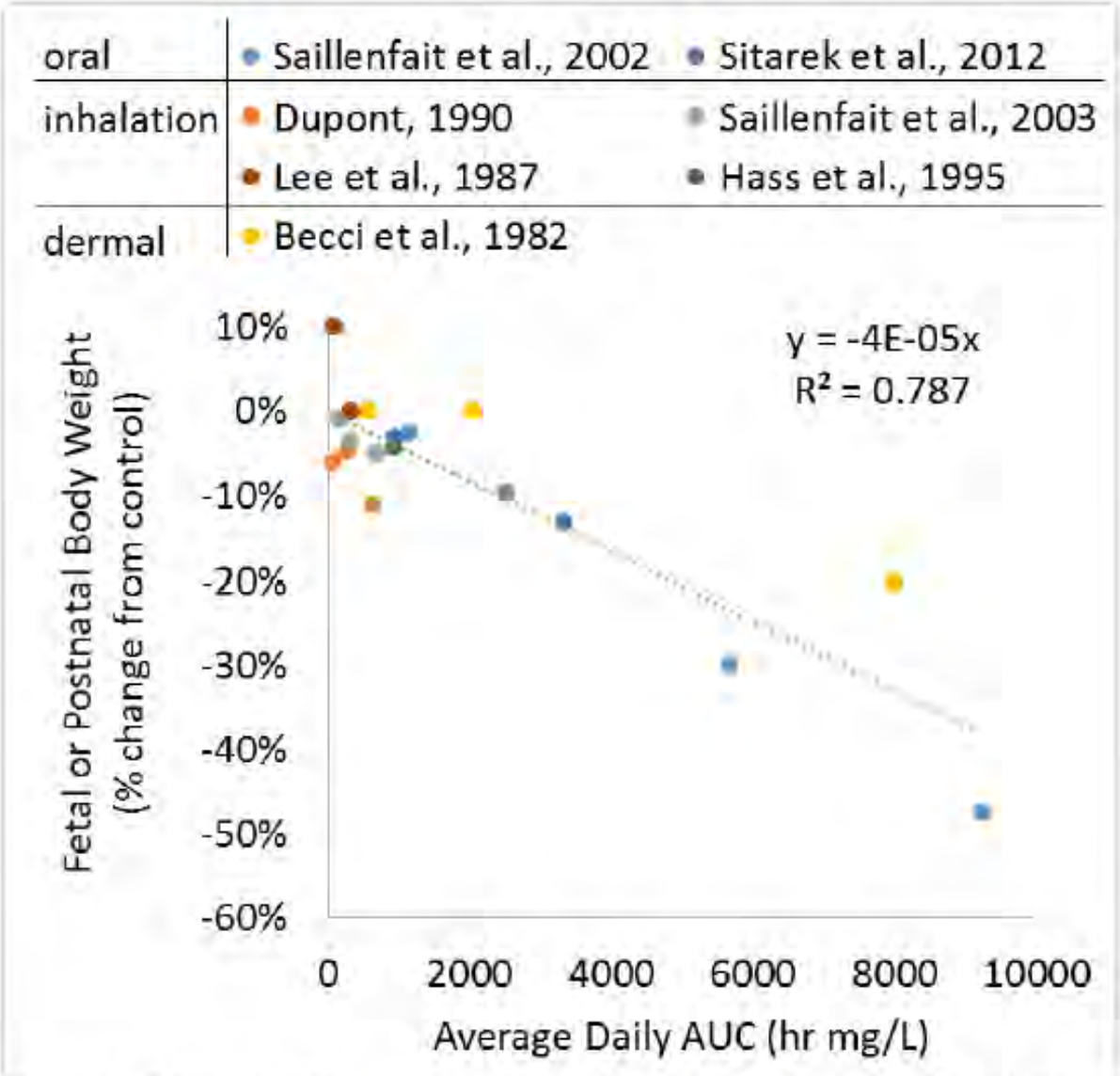


Figure 3-4 Analysis of Fit: Average Daily AUC vs Fetal or Postnatal Body Weight

NMP Dose Response Analysis for Acute Exposure

Table 3-4 Summary of Derivation of the PODs for Fetal Resorptions and Fetal Mortality Following Acute Exposure to NMP

Endpoint and reference (exposure duration/route)	Dose Metric	Model[a]	BMR	BMD Internal dose	BMDL Internal dose	POD	
						Internal dose	Equivalent administered dose (route)[a]
Resorptions							
Saillenfait et al. 2002 and 2003 (GD 6-20, oral and inhalation)	C_{max} (mg/L)	Hill	1% RD	429	216	**216**	218 mg/kg bw/day (oral)
	AUC (hr mg/L)	Power	1% RD	3343	2128	**2128**	217 mg/kg bw/day (oral)
Becci et al., 1982 (GD 6-15, dermal)	NOAEL = 237 mg/kg bw/day					662	237 mg/kg bw/day (dermal) 612 mg/kg bw/day (oral)[b]
Fetal Mortality							
Sitarek et al., 2012 (GD1-PND1, oral)	C_{max} (mg/L)	No model selected[c]	1% RD	N/A	N/A	N/A	264 mg/kg bw/day (oral)
	NOAEL = 450 mg/kg bw/day					265	

NMP Acute RA - Consumer

- Fetal Resorption Endpoint
- Exposure – Cmax for consumer scenarios
- MOE = Cmax Resorption/Cmax Consumer
  - Assumes that resorption risk is reflected by peak exposure on any of the dosing days
    - Intensity of exposure rather than total exposure
  - Does not say that one hour of peak exposure can cause resorptions
  - MOEs judge whether 1 day exposure a devel risk
    - MOE < 30 did not occur in any scenario
    - MOE of approx 30 occurred in bathtub refinishing scenario

NMP Chronic RA - Worker

- Fetal Body Wt Endpoint
- Exposure – AUC for worker scenarios - 8 hr basis
- MOE = AUC BWt Effect/AUC Worker Exp
  - Assumes that body wt risk is reflected by avg exp on a day of exposure on any of the dosing days
    - Total avg exposure assumed to relate to toxic endpoint
  - MOEs used to judge whether 1 day of exposure can be a developmental risk
  - Yes, MOE < 30 occurred in numerous (>1 hr) scenarios

NMP Acute Risk Worker

- MOE < 30 for a number of scenarios
  - Gloves makes a difference
  - NMP formulation makes a difference
  - Hours/day makes a difference
    - 4 and 8 hr scenarios had elevated risk

Temporality Uncertainties in NMP RA

- Extrapolation of developmental tox POD (Cmax) to a single day of consumer exposure
  - How well does the Cmax relate to resorptions in animal studies?
  - How likely is it that Cmax on one day of consumer use relates to resorptions?
  - Is there a basis for using other averaging times for this endpoint?
    - Oral animal studies and human exposure both have a distinct Cmax
- Extrapolation of developmental POD to chronic endpoint
  - No subchronic to chronic UF used since fetal development considered most vulnerable
  - Would chronic exposure lead to lower POD?
    - Unlikely since NMP t½ is short (2.5 hrs)

Implications of NMP RA

- Level of Concern/Urgency
  - High: Fetal death - severe endpoint
    - Fetal growth an important repeat dose endpoint
    - 1% BMR used making it less likely that an effect will occur near target MOE
- Temporal Issues
  - Will momentary exceedance of Cmax be a fetal health concern?
  - Does it take an hour, a day or longer at Cmax?
  - Would AUC for pd of exposure be a reasonable dose metric for acute?
- Advice to pregnant women handling NMP
  - Protective clothing especially gloves
  - Ventilation / Use outdoors
  - Limited time handling NMP
  - Alternative stripping methods – green chemistry solutions
- EPA considering regulatory options

Lessons Learned:
Temporality Issues in Setting Tox Values

- Consider whether effects may occur after a single dose
  - Van Raaij Assessment – certain developmental endpts appropriate for acute RA
  - Other endpoints
    - Narcosis, other acute CNS, irritation effects
    - These effects may or may not progress with repeat dosing
    - Solecki review for other endpoints – hematotox, immunotox
  - Dose response from chronic and acute studies may not be that diff if:
    - Chemical has short t½
    - If effect rapidly reversing
  - Some endpoints are obviously non-acute
    - Cancer
    - Body weight effects
    - Long t½ chemicals
- Application of an RfD or POD
  - Might it apply to short term and chronic? If so
  - Same RfD for both acute and chronic?
  - Or different UFs from same POD?
  - Or separate tox values for acute vs chronic from one study
    - NMP example

Lessons Learned
Utility of PBPK

- Temporality of exposure scenario
  - Model useful to capture differences in exposure pattern in animal tox vs human scenario
  - PBPK model useful to capture different averaging times relevant to acute vs chronic POD
  - Model sensitivity analysis can help pick exposure scenarios
  - Model may be able to determine which parameter (AUC vs Cmax) better correlates to outcome

Implications of RfD/POD that is Applicable to Short Term Exposures

- Risk assessment focuses less on TWA exposures (LADD) and more on peak exposures possible on a single day
  - Important to consider exposure assessment in more detail
    - Take a distributional approach to better understand temporal and interpersonal variability

Implications of RfD/POD that is Applicable to Short Term Exposures

- Potentially more urgent to mitigate exposure
  - Depends upon severity of endpoint and likelihood after one or few exposure periods
    - E.g. Developmental Effects
      - Critical windows of vulnerability
      - Irreversible effect if exposure during this window
      - How long is the vulnerability window?

Related Temporality Examples

- E.G. – OctaBDE (-153) RfD:
  - Critical study in mice single dose on PND 10
  - Neurodevelopmental effects in adults
  - Extrapolation from single dose to chronic RfD – 3x
  - Should that also be considered an acute RfD?
- E.G. – Target Blood Lead (Pb)
  - How long can young children have > 5 ug/dl?
  - IEUBK model allows seasonal averaging
  - Lead/copper rule allows rolling 4 quarter average
- E.G. – Mercury – short term (fishing season exposure)
  - Evaluation of risk from single fish meal during pregnancy

Development of a Single Fish Meal Advisory for meHg

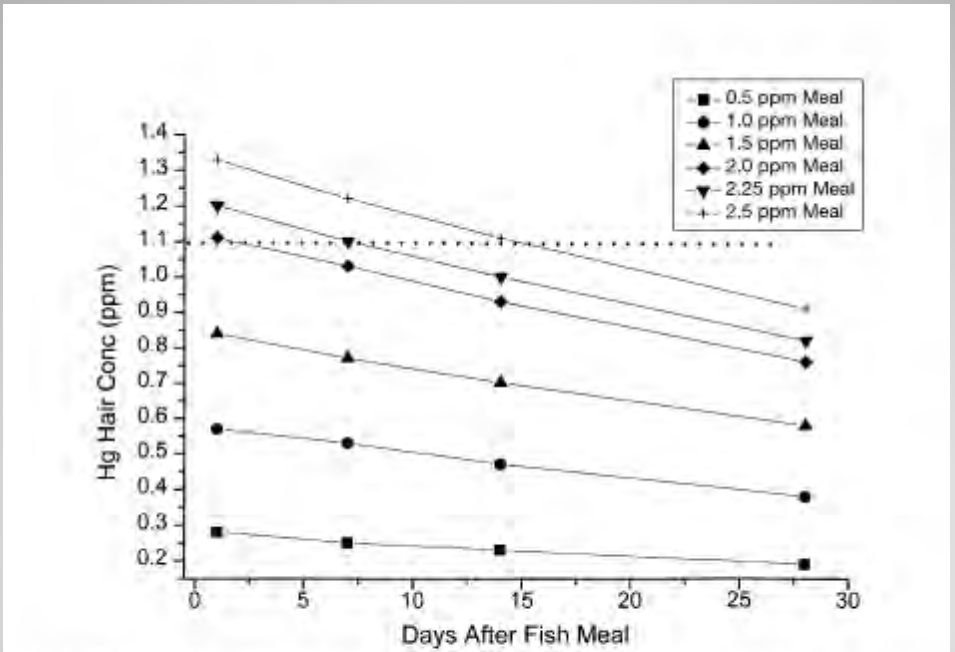


Fig. 4. Modeled Hg hair concentrations after a single fish meal.

- TK model used to predict internal dose and hair concentration
- Compare back to hair concentration assoc/with USEPA RfD
- Fish concentration > 2 ppm – Do Not Eat advice

Ginsberg and Toal, Risk Analysis, 2000

Possible Panel Questions

1. Do we need to review temporality issues with existing RfDs?
   - Consider application to non-chronic scenarios?
   - Type of effect, reversibility of effect, chemical t½
2. What are the cases we might need non-chronic RfDs?
   - Windows of exposure vulnerability
   - Windows of toxicokinetic vulnerability
   - Windows of toxicodynamic vulnerability
3. What types of risk assessments and regulations may need an acute focus?
   - Drinking water regs?
   - Air toxics regs?
   - Fish consumption advisories?

Possible Panel Questions

4. What data do we need for temporality issues with new RfDs/PODs?
   - More lifestage specific tox studies?
     Human vs rodent windows of vulnerability
   - Tox studies that better match human exposure scenarios?
     Focus on windows of exposure vulnerability?
   - More PBPK models?
5. Is there value to a temporality database?
   - Searchable by endpoints, chemicals to understand relationships between acute and chronic exposure
6. How do we bring these issues into epidemiology studies
   - E.G. meHg exposure characterized in different hair segments to document exposure profile during pregnancy