Estimating Human Exposures And Comparison To Doses Used In Testing

Symposium - Opportunities and Challenges in Using the Kinetically Derived Maximum Dose Concept to Refine Risk Assessment

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Goals

- Describe exposure estimates in different chemical space using modeling and monitoring data across various scenarios of interest with consideration of variability and uncertainty

- Provide basis for understanding how KMD compares to exposure

Overview

- KMD and Exposure
- General Background
- Fit For Purpose
- Detailed Example U.S. EPA – Pesticide Approaches
- Other Examples For Consideration
  - OSHA Industrial Monitoring Data Summary
  - U.S. EPA ChemSTEER Modeling Example
  - SHEDS
  - SEEM3 Expocast
  - EU Modeled Upper Bound Exposure
- Conclusions

KMD and Exposure

- Exposure assessments serve a wide range of purposes and can vary in scope and content depending upon data availability (i.e., data rich or lacking data).

- Fit for purpose approaches support scope of assessments and therefore potential relevance to KMD. Examples include:
  - data rich chemical review
  - data poor new chemicals
  - large scale emergency response

- Key is to augment confidence in using KMD with an understanding of exposure patterns, levels, uncertainty and variability.

General Background

- Many established resources available globally for exposure assessment. Examples include:
  - U.S. Exposure Assessment Guidelines
  - U.S. Exposure Monitoring Guidelines
  - U.S. Exposure Models – ChemSTEER, SHEDS, SEEM, etc.
  - REACH Exposure Assessment Guidance
  - EU Exposure Assessment Models
  - Monitoring Data – OSHA, Pesticides, National Surveillance, Air, Water
  - OECD Test Guidance - Dosimetry
- Peer reviewed and long-standing use in regulatory framework
- Information curation and data availability

Exposure Assessment Is Fit For Purpose

- Problem formulation determines scope of exposure assessment

- In regulatory sense, range of exposures related to anticipated use of a chemical are considered with associated uncertainty and variability
  - Intent to provide protective estimates
  - Informed consideration of exposure co-occurrence and aggregation

- Typically used to support risk management approaches for commerce

- There are exceptions and other considerations, but animal testing should be tailored for those situations

- An overview of various approaches follows

EPA Pesticide Exposure Assessment

- Peer reviewed, monitoring based methods using a scenario approach
- Directly applicable to licensing/product labeling
- Current approaches use statistical sampling design, protective adjustments for variable data and sampling issues
- Occupational
  - https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data
- Residential
  - https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

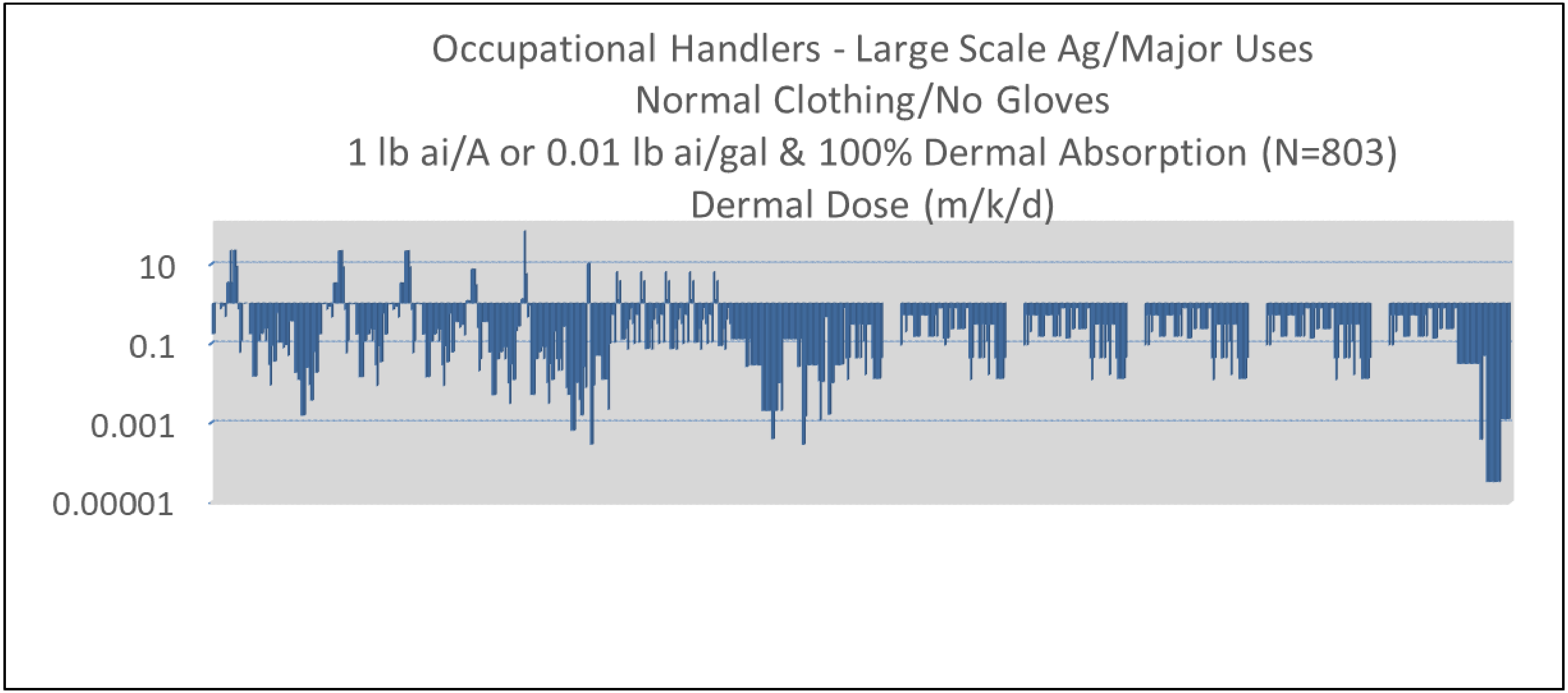



Pesticide Exposure Example

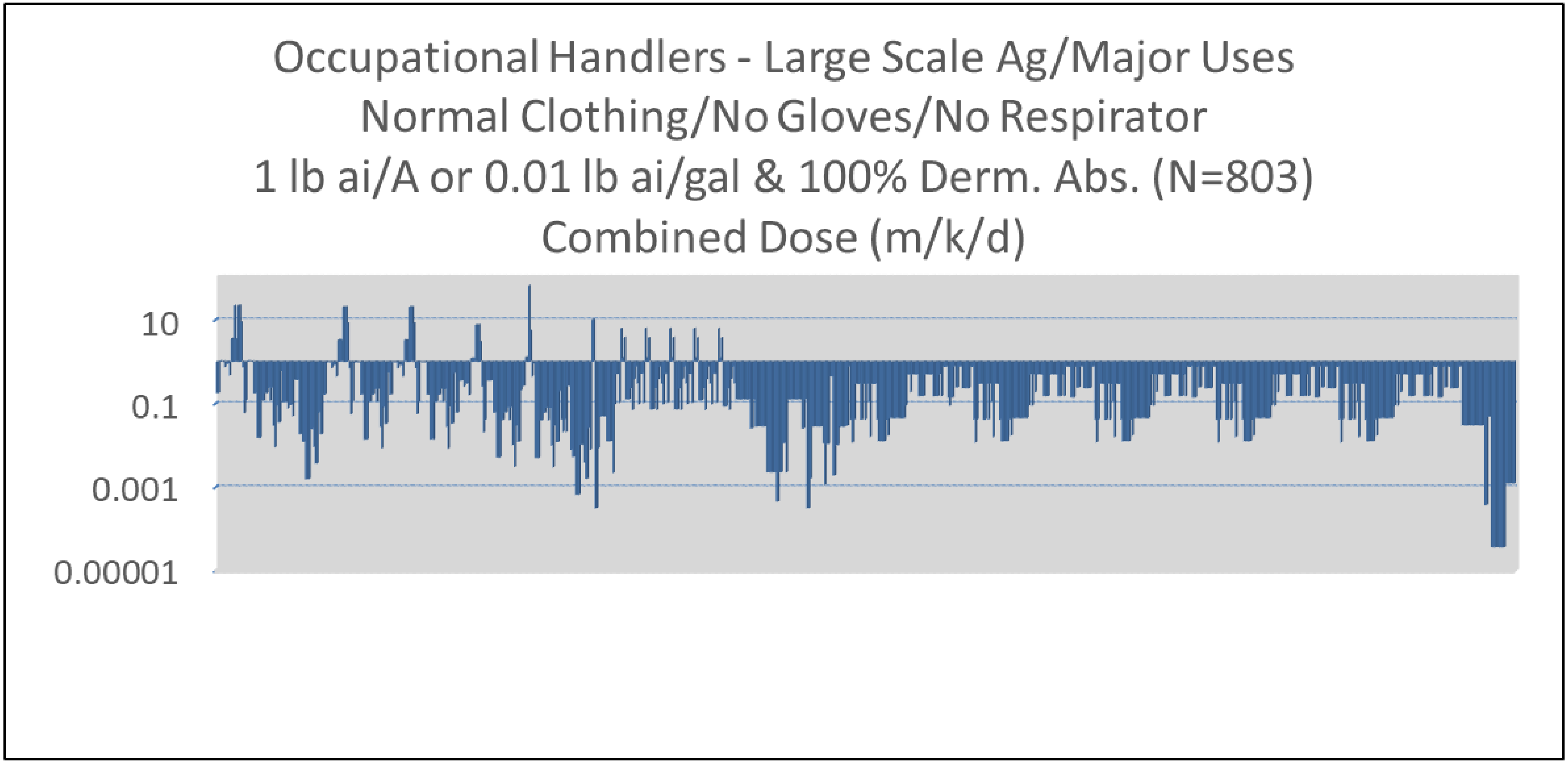
- In this case study, non-dietary exposures are considered
- Estimated exposure (mg/kg/day) across many scenarios
  - Use patterns across all common residential and occupational scenarios
  - Application rate (i.e., 1 lb ai/acre)
  - Occupational - normal work clothing, no respirators, 803 scenarios
  - Residential – shorts/short sleeved shirts, no respirators, 120 scenarios
- Exposures are normalized by body weight to calculate dose
  - Dermal and combined dermal and inhalation are presented
- Highest dose level configuration used for this exercise, input was selected as 100% dermal absorption
- Occupational handler summary results

Stat	Dermal (mkd)	Inhalation (mkd)	Combined (mkd)
Max	66.4	0.840	66.6
Mean	0.78	0.011	0.739
Std Dev.	3.459	0.057	3.370

Occupational Pesticide Dermal Exposure

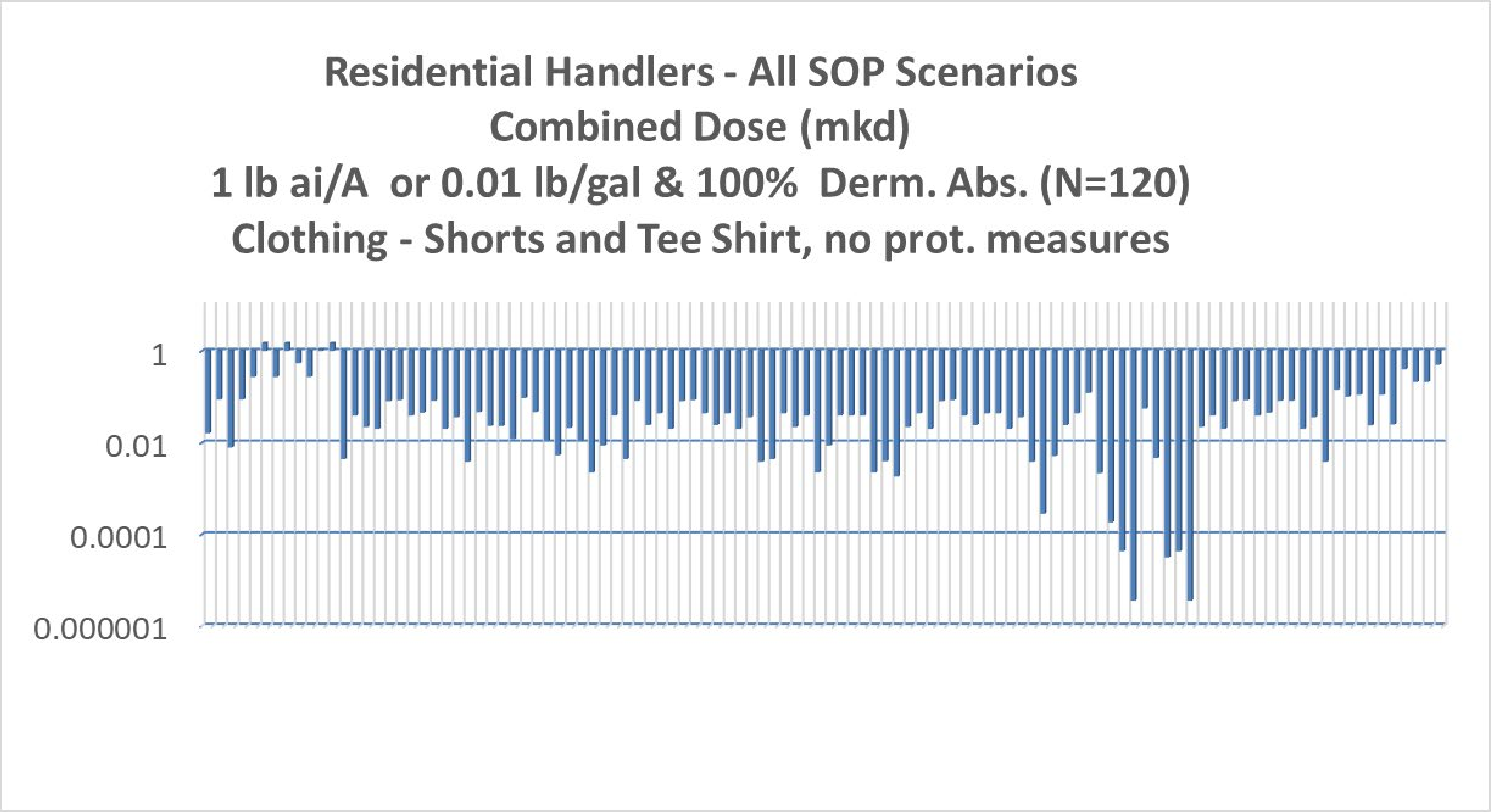


Occupational Pesticide Dermal & Inhalation Exposure



Note: Pattern is similar to dermal only. Inhalation is a minor contributor.

Consumer Pesticide Dermal & Inhalation Exposure



Pesticide Hazard Assessment

- Multiple routes considered in non-dietary exposure
  - Occupational – Dermal and Inhalation
  - Consumer (Residential) – Dermal, Inhalation, Oral
- Broad range of hazard domains
  - Most sensitive endpoints selected
  - Route-specific studies typically available but sometimes oral with absorption data used because of nature of endpoint
  - Different durations of exposure – key focus is subchronic given usage
- Data predominantly generated using GLP and standard protocols based on EPA or OECD guidance
- Typical points of departure (NOAELs, LOAELs, etc.) would be anticipated to be much lower than KMD levels

Pesticide NOAEL & LOAEL Summary For Dermal Exposure

Stat	NOAELS	LOAELS
Dermal Administration (N= 217, 204)		
Min	0.05	0.203
Max	1000	4000
Mean	130.15	383.6
Oral Administration (N= 411, 454)		
Min	0.002	0.01
Max	1000	1900
Mean	34.54	87.7

- Data for all conventional chemicals (durations, routes, etc.)
- KMD values generally anticipated to be much higher
- Exposures used for regulatory purposes generally much lower
- Exposures under normal use conditions do not approach KMD
    - High acute toxicity chemicals addressed through other prescriptive means (min. PPE, no consumer use, etc.)

Occupational Safety and Health Administration (OSHA) Data

- 2,303,043 observations, 1984-present
  - Data available at https://www.osha.gov/opengov/healthsamples.html
  - Data collected by OSHA compliance officers
  - Data on personal, area, and bulk samples for various airborne contaminants
  - Inspection sampling results included once the case is closed

- 26 different descriptors per sample. The samples cover:
  - 60 different "states" (includes various US territories)
  - 1140 different substances
  - Many industries as indicated by 1001 different Standard Industrial Classification (SIC, pre-1997) codes and 1040 different North American Industrial Classification System (NAICS) codes

Establishment Name	City	State	ZIP	SIC	NAICS	Date Sampled	Time Sampled	Substance	Sample Result	Units
BATTERY RECYCLING INC.	VAN WERT	OH	45891		423930	2012-JAN-31	448	Lead, Inorganic (as Pb)	0.0485974	M
BATTERY RECYCLING INC.	VAN WERT	OH	45891		423930	2012-JAN-31	445	Lead, Inorganic (as Pb)	0.0292245	M
BATTERY RECYCLING INC.	VAN WERT	OH	45891		423930	2012-JAN-31	447	Lead, Inorganic (as Pb)	0.0620832	M

OSHA Summary Information

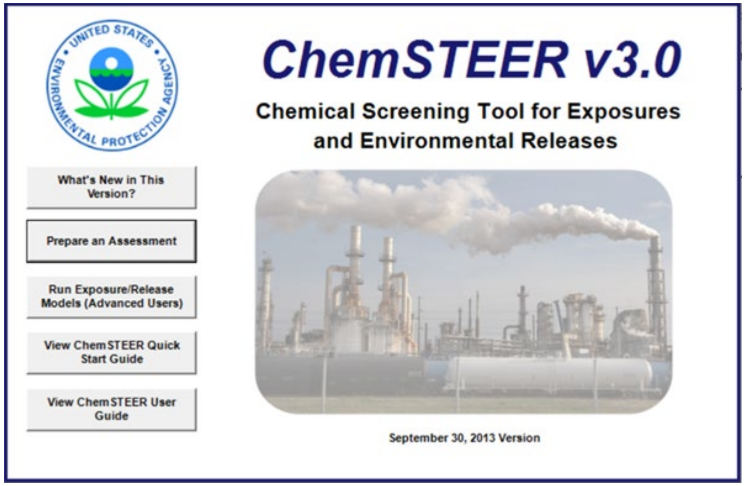
- Millions of observations collected by OSHA have been organized based on the 1140 chemical substances. Examples include:

2000 - present Compound	CASRN	Samples	Fraction Detected	75% Conc	97.5% Conc	Max Conc	Units	Number of NAICS Industries
4-Methyl-2-pentanone	108-10-1	326	0.67	18.30	445.62	2157.25	mg/m3	12
Caprolactam	105-60-2	68	0.82	6.72	57.85	57.85	mg/m3	1
Carbaryl	63-25-2	3	0.67	2.01	3.69	3.88	mg/m3	2
Toluene	108-88-3	1925	0.73	42.52	648.73	10627.53	mg/m3	19

1984 - 1999 Compound	CASRN	Samples	Fraction Detected	75% Conc	97.5% Conc	Max Conc	Units	Number of NAICS Industries
4-Methyl-2-pentanone	108-10-1	817	0.83	59.40	820.98	819312.88	mg/m3	11
Caprolactam	105-60-2	112	0.71	1.00	49.40	49.40	mg/m3	3
Carbaryl	63-25-2	12	0.33	0.39	18.77	21.00	mg/m3	5
Toluene	108-88-3	3685	0.94	160.13	1533.61	3335165.03	mg/m3	18

NAICS: North American Industrial Classification System

Example Assessment Using ChemSTEER



KEY TOOL USED

- Publicly available, peer reviewed
- ORD High throughput values presented
- Used in many types of evaluations

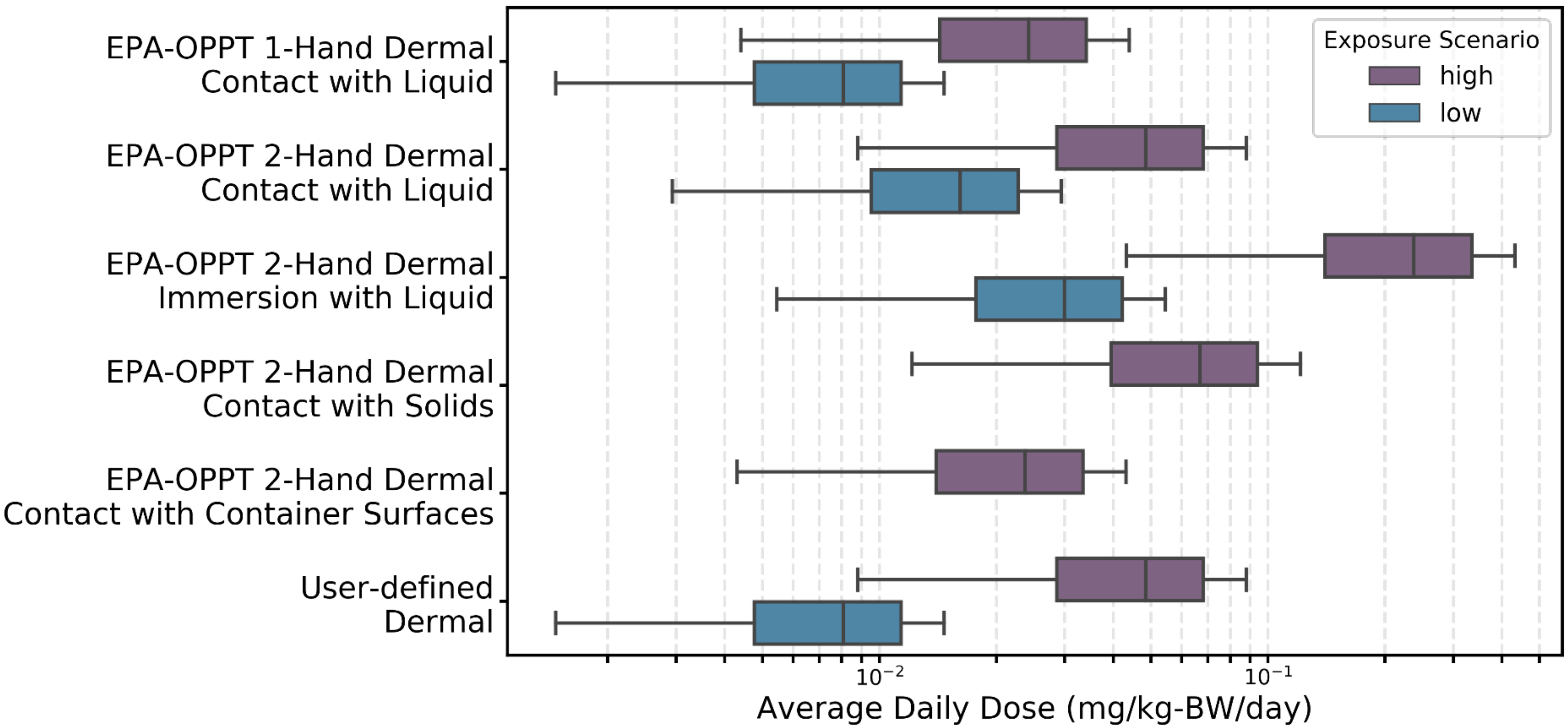
DERMAL MODELS

- 1-hand dermal contact with liquid
- 2-hand dermal contact with liquid
- 2-hand dermal immersion in liquid
- Direct 2-hand dermal contact with solids
- 2-hand dermal contact with container surfaces
- User defined

INHALATION MODELS

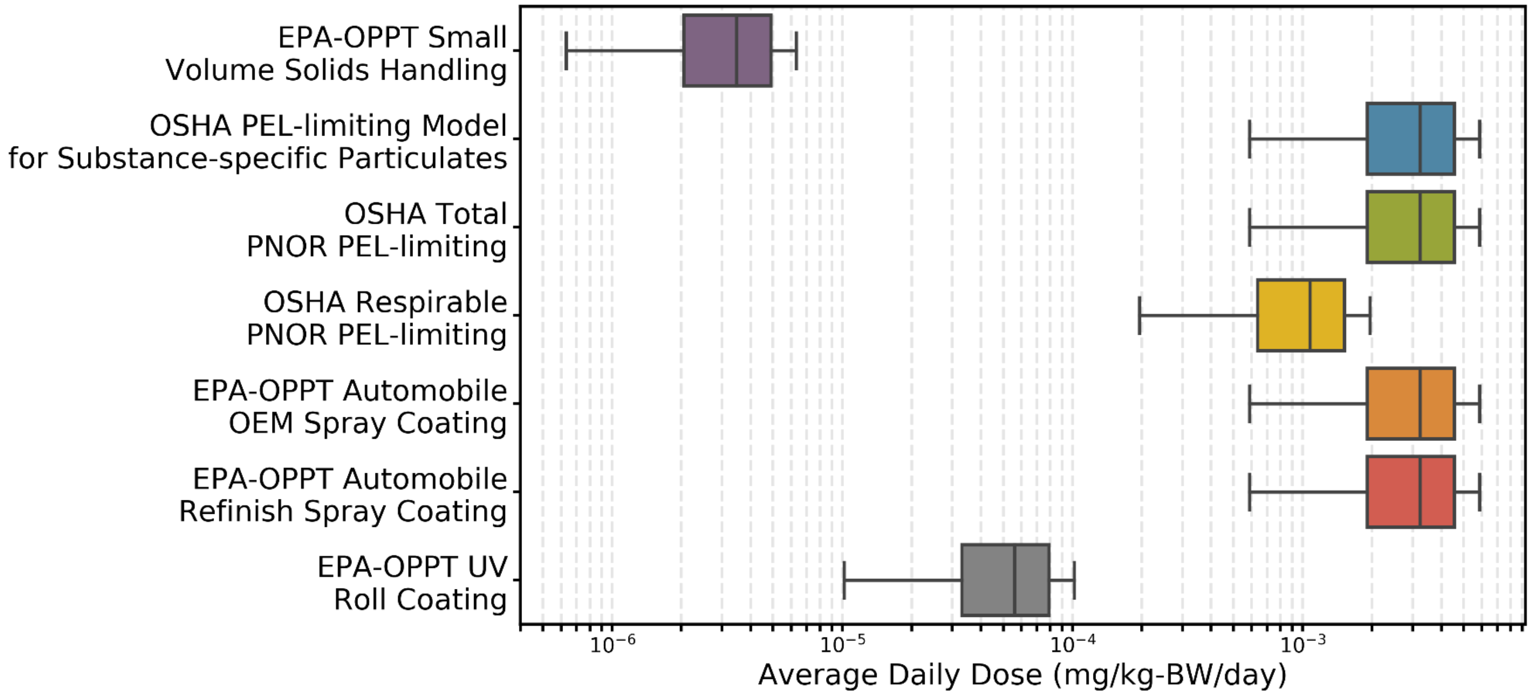
- Small volumes handling
- Mass balance
- PEL-limiting for substance specific particulates
- PEL-limiting for substance specific vapors
- Total PNOR PEL-limiting
- Automobile OEM Spray Coating
- Automobile Refinish Spray Coating
- Automobile Spray Coating
- UV Roll Coating
- User defined

ChemSTEER Dermal Average Daily Dose



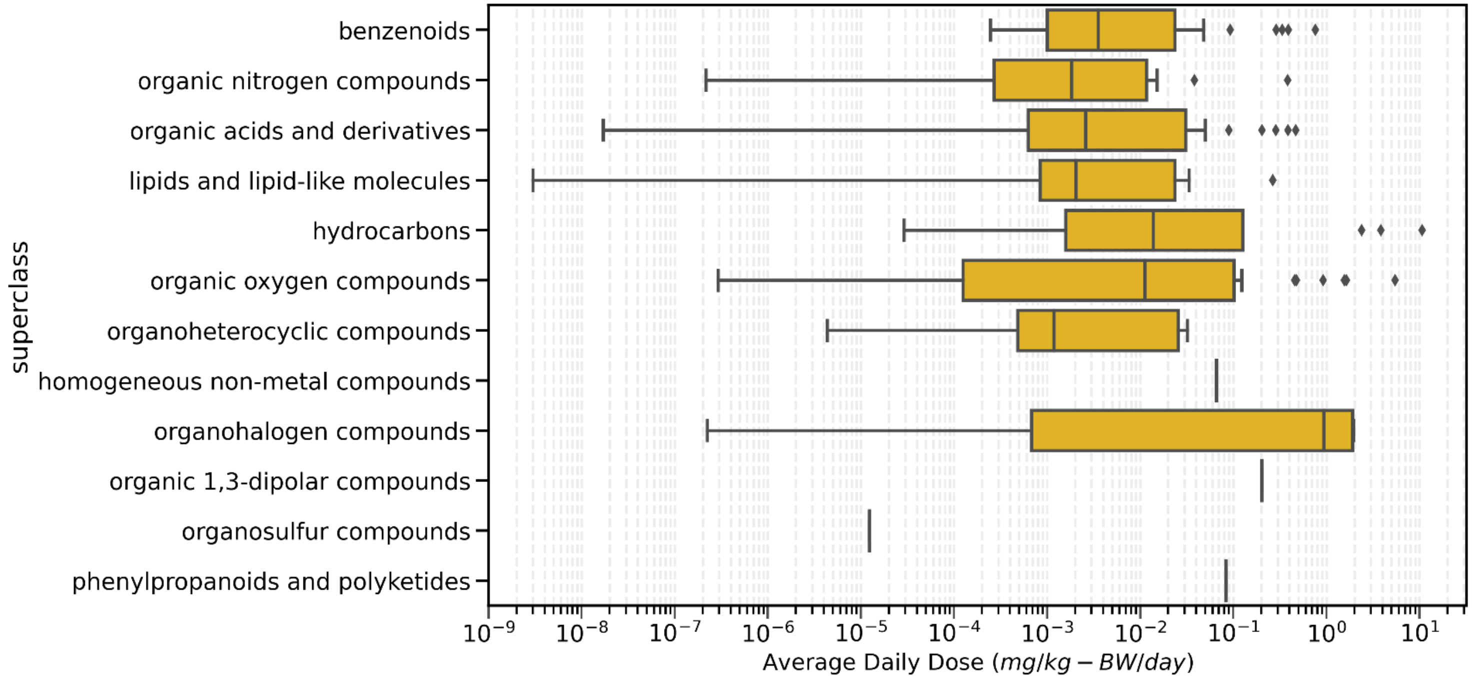
- All 6 dermal models are chemical agnostic, there are no chemical-dependent parameters for these models
- Models have only one required input: weight fraction of compound in liquid or solid
- Two possible exposure scenarios in model: **low** and **high**, the default for all is **high**
- Other parameters that can be changed, but have default values are:
  - Surface area of skin in contact with liquid or solid (default: 535 cm^2)
  - Quantity of liquid or solid that remains on skin after contact (low: 0.7 mg/cm^2, high: 2.1 mg/cm^2)
  - Frequency of contact event occurring per worker per day (1 event/day/worker)
- The average daily does for all six models was computed using a weight fraction of 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0

ChemSTEER Inhalation Average Daily Dose



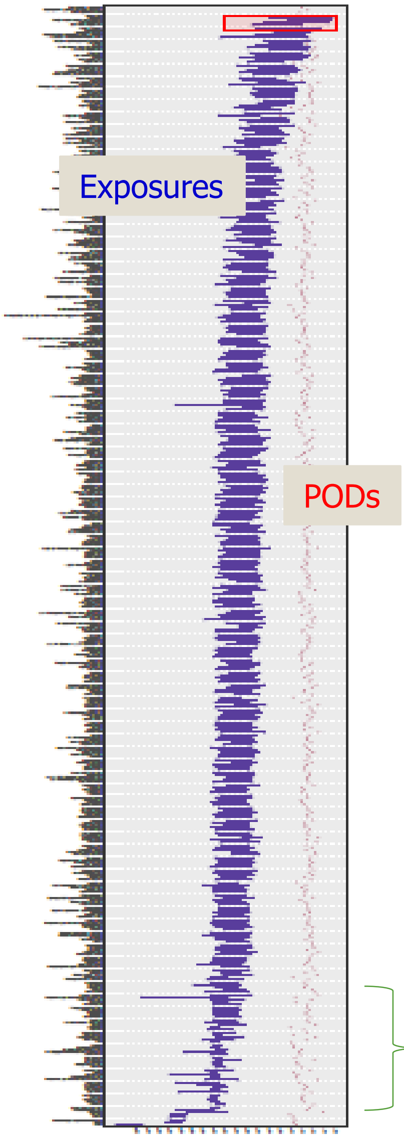
- There are 9 chemical agnostic inhalation models
  - Seven of these models require information on the weight fraction of the substance in a particulate
  - Two of these models require the concentration of the substance in the air
- No consistent scenarios across all models; each model can have very different parameters
- The average daily dose for the 7 chemical-agnostic, particulate models was computed using a weight fraction of 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0

SHEDS High Throughput Consumer Exposures

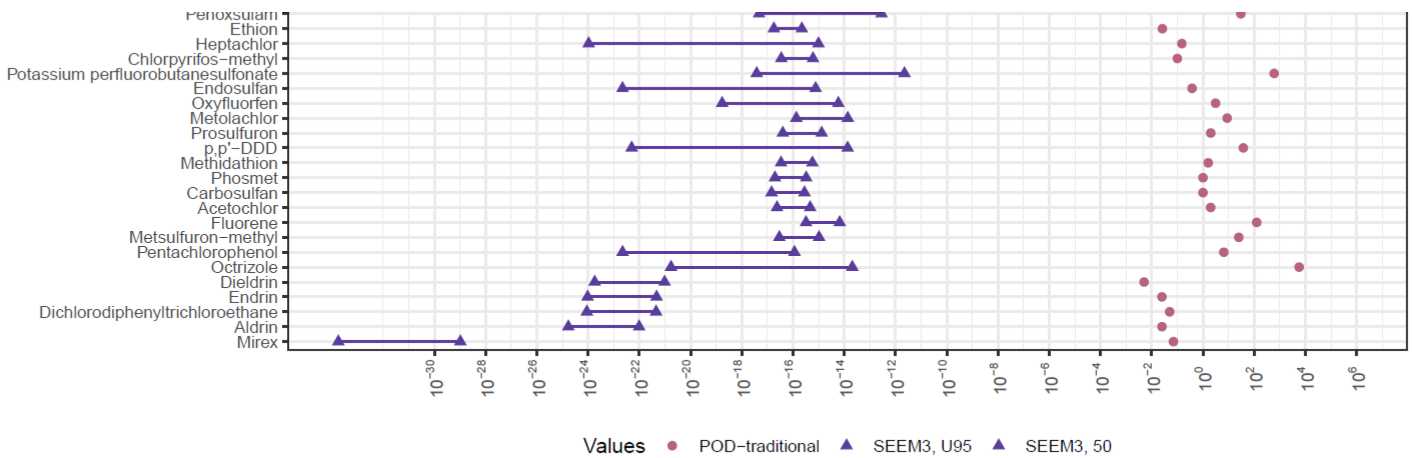


- SHEDS-HT (high-throughput stochastic human exposure and dose) model estimates daily exposures for the general population using publicly available consumer product composition data. The exposure estimates shown here aggregate inhalation, dermal, and dietary ingestion (where available) routes.
- SHEDS-HT is a conservative model in that if a compound is reported in any product within a consumer product category, it is assumed to be in all products in the category.
- The chemicals for which SHEDS-HT was run were classified into a chemical taxonomy, ClassyFire, and are aggregated by the superclasses in this taxonomy.

SEEM3 - EXPOCAST

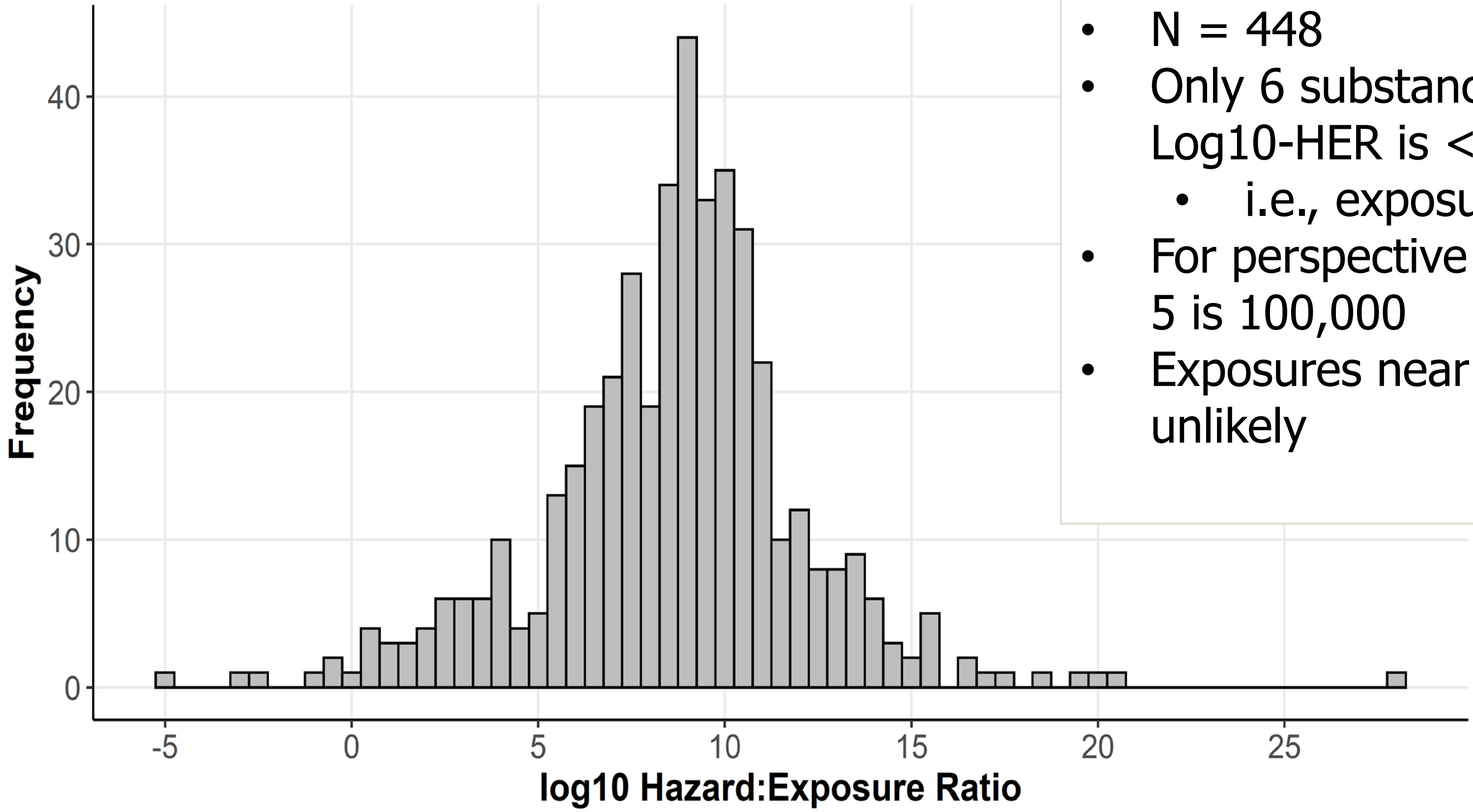


- 448 Chemicals included based on Paul-Friedman et al, 2019
  - Based on availability of ExpoCast, ToxCast, HTTK, and ToxValDB data
  - Many pesticides in this list, but other functional uses available also
- Expocast SEEM3 outputs are median and 95th percentile values for total population
- Animal study data from ToxValDB used to calculate points of departure (5th %tile of all NOAEL/LOAEL values per chemical); oral admin only.



Unpublished work, adapted from Paul Friedman et al. 2019 to include ExpoCast SEEM3

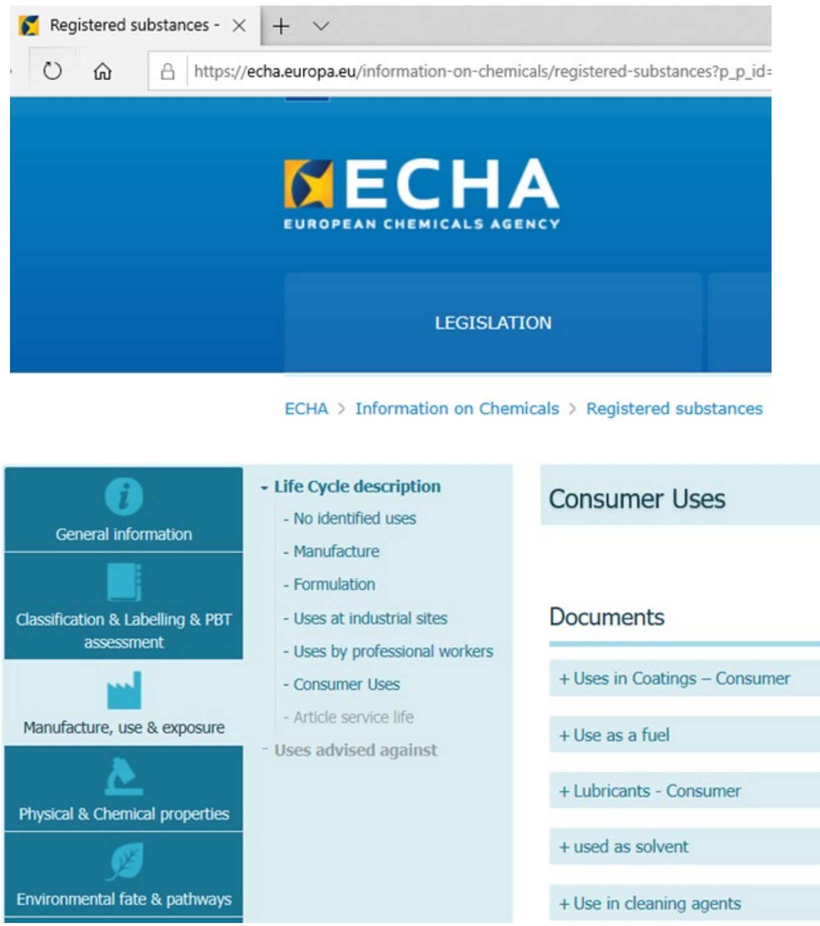
SEEM 3 – EXPOCAST Quantifying Hazard/Exposure Ratios (HERs)



- N = 448
- Only 6 substances where Log10-HER is <0
  - i.e., exposure > POD
- For perspective a log10 = 5 is 100,000
- Exposures near KMD unlikely

Unpublished work, adapted from Paul Friedman et al. 2019 to include ExpoCast SEEM3

REACH Exposure Resources



<u>Registered Substances Database</u>

- Does not have the exposure estimation info publicly available
- Includes substance use information along its life cycle stages
- https://echa.europa.eu/information-on-chemicals/registered-substances

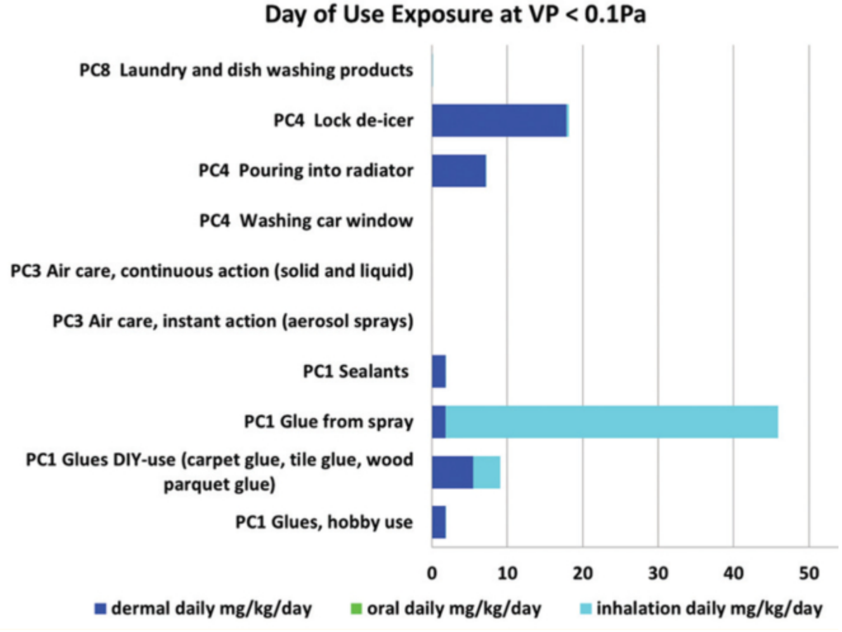
<u>Guidance on Chemical Safety Assessment</u>

- ECHA Guidance Guidance on Information Requirements and Chemical Safety Assessment
- See Chapters 14 (Occupational) and 15 (Consumer) for more detailed information
- https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment

Assessing Upper Bound Exposure based on EU Models

- Exposure bands were developed based on screening level EU models (e.g., ECETOC TRA, EGRET) with defaults to understand the upper bound exposure levels under HESI Risk21 project.
- With minimal info (e.g., pchem properties, use info), exposure level can be looked up quickly in exposure bands.
- When queried from REACH registered substances database for substance specific info, their exposure levels can be reconstructed conservatively.

Exposure Bands for Consumer



Using exposure bands for rapid decision making in the RISK21 tiered exposure assessment (2017) [*https://pubmed.ncbi.nlm.nih.gov/28266262/*](https://pubmed.ncbi.nlm.nih.gov/28266262/)

Conclusions

- Exposure assessments are quite varied
- Fit for purpose approaches based on data availability and scope/needs
- Many rigorous tools are globally available
- Exposures are not thought to approach KMD levels in typical chemical lifecycle
- KMD consideration is potential approach for a variety of settings

Conclusions

- U.S. examples illustrate exposures under normal conditions of use do not generally approach anticipated KMD levels
- Uncertainty and variability are accounted for in selection process, study design, data analysis, etc.
- Next steps
  - Frame issue for consideration across disciplines
  - Provide realistic basis for future decision making on the KMD topic