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U.S. Human Health Risk Assessment Framework

Cochran Fellowship Program
Regulatory Framework for Agricultural Chemical Products
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Types of Human Health Risk Assessments Conducted for U.S.

- Handler (mixer, loader, applicator)
- Post-application agricultural worker
- Seed treatment workers (application, bagging, sewing, cleaning, etc.)
- Consumer dietary (food + water)
- Residential (handler and post-application, indoor and outdoor)
- Aggregate (chronic dietary + short-term residential)

Summary of Chronic Dietary Exposure and Risk			
Population Subgroup	cPAD (mg/kg/day)	Chronic	
		Exposure (mg/kg/day)	% cPAD
General U.S. Population	0.022	0.002923	14
All Infants (< 1 year old)		0.008474	40
Children 1-2 years old		0.010055	48
Children 3-5 years old		0.007369	35
Children 6-12 years old		0.004011	19
Youth 13-19 years old		0.002217	11
Adults 20-49 years old		0.002204	11
Adults 50+ years old		0.002007	10
Females 13-49 years old		0.001986	10

Data Needs for Human Health Risk Assessment

- Complete Toxicology Profile (Chemical specific)
 - ▶ Endpoints for consumer / residential (acute, chronic, incidental oral, etc.)
 - ▶ Endpoints for occupational workers (dermal, inhalation)
- Human Exposure Data (Generic)
 - ▶ Handler (occupational and residential)
 - ▶ Post-application (outdoor and indoor)
 - ▶ Food consumption (consumer survey data)
- Additional Information
 - ▶ Area treated or amount handled per day
 - ▶ Application rate and frequency
 - ▶ Label language (PPE requirements, REI, PHI)

40 CFR 158 Subpart K – Human Exposure Data Requirements

Human Exposure Studies**

Applicator Exposure

(Occupational and Residential)

Dermal indoor and outdoor

Inhalation indoor and outdoor

Biomonitoring

Post-application exposure

(Occupational and Residential)

Dislodgeable foliar residue

Turf Transferable residue

Soil residue dissipation

Dermal indoor and outdoor

Inhalation indoor and outdoor

Nondietary ingestion

** Studies involving human subjects must have approval by the Human Studies Review Board (HSRB) to meet scientific and ethical requirements before the study can be conducted and the results can be considered by EPA.

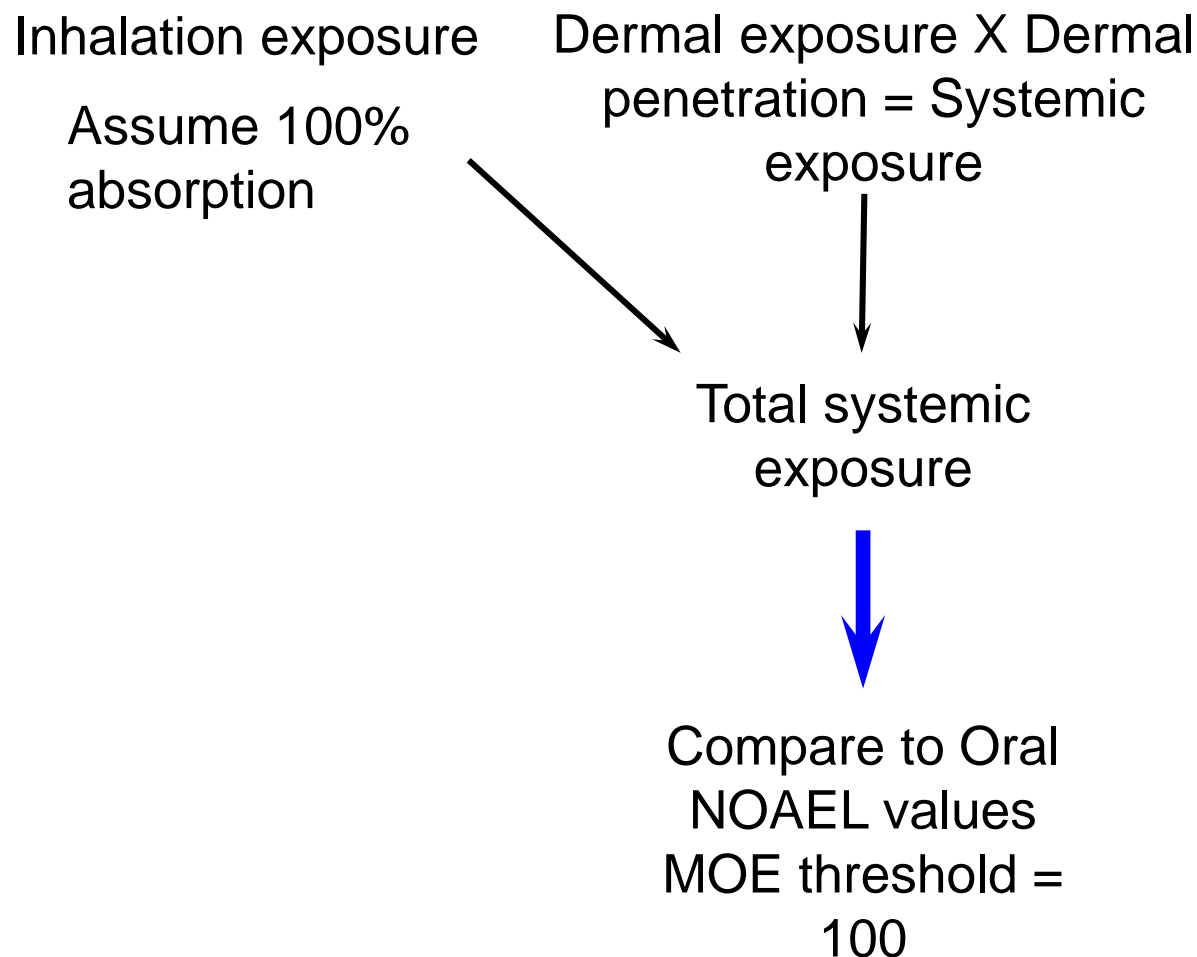
North American Task Forces on Human Exposure

- Task forces established in response to EPA Data Call-in
- Each Task Force is a consortium of companies with similar data development objectives
- Agricultural Reentry Exposure Task Force (ARTF, 1995)
 - Database of transfer coefficients for all crop/activity scenarios
 - Data allow development of default dislodgeable foliar residue (DFR)
- Outdoor Residential Exposure Task Force (ORETF, 1995)
 - Handler exposure for residential and professional operators
 - Post-application turf exposure [default turf transferrable residue (TTR)]
- Residential Exposure Joint Venture (REJV, 1997)
 - Use information on residential products
- Agricultural Handler Exposure Task Force (AHETF, 2001)
 - Dermal and inhalation exposure for mixing, loading, application (MLA)
 - Updated information to replace PHED database

Development and Use of Exposure Data

- Task Force data are developed and evaluated in collaboration with U.S. EPA, Canadian PMRA and California DPR
- TF conducts data collection and initial data analysis and recommendations with final evaluation and conclusions by Authorities
- Generic exposure data
 - ▶ The magnitude of exposure does not depend on the specific active ingredient used in the study, if all other conditions are similar
 - Transfer coefficients are not chemical-specific and apply to all active ingredients
 - MLA dermal and inhalation exposures are not chemical-specific
 - Data generated with a surrogate chemical can be used to estimate exposure to another active ingredient used in the same manner
- DFR/TTR studies can provide chemical-specific dissipation data

Determination of Systemic Dose for Comparison with Tox Endpoints



Dermal Absorption and Systemic Exposure

- If the dermal toxicity endpoint is based on a dermal dosing study, that endpoint is used for the risk assessment without adjustment
- If the NOAEL from a 28-day dermal study is at the limit dose of 1000 mg/kg bw/d and there are no developmental, reproductive, neurological or immunotoxicity concerns, EPA may choose not to assess risk from dermal exposures
- If the dermal toxicity endpoint is based on an oral dosing study, the endpoint is adjusted based on dermal absorption studies
 - EPA requires an *in vivo* rat dermal absorption study
 - EPA can refine the *in vivo* result with appropriate *in vitro* studies on rat and human skin (“Triple pack”)
- EPA does not currently use default dermal absorption values as they are used in the EU
- EPA is in the process of re-evaluating their policies on dermal absorption

Handler Exposure and Risk

- Exposure for mixer/loader and applicator may be evaluated for different workers or for one worker performing all activities - depends on scenario
 - Backpack mixing/loading/application of liquidsvs:
 - Open pour mixing/loading of liquids
 - Closed cab ground application of liquids
- Dermal and inhalation exposures may be combined if the toxicological endpoint is based on the same type of toxicity
- If the inhalation and dermal studies show different toxicological effects, the exposures are not combined
- Risk is calculated as a Margin of Exposure (MOE)
 - $MOE = NOAEL / Exposure$
 - Acceptable MOE can change based on safety factors, typically 100

Post-application Exposure and Risk

- Exposure for worker entering a treated field depends on the activity that the worker is performing (related to transfer coefficient)
- Initial restricted entry interval (REI) is based on the acute toxicity profile of the active ingredient or formulation (12 hours for Cat III or IV)
- Exposure (dermal) is calculated based on the Day 0 DFR and the TC
 - Default DFR from EPA analysis is about 25% of the application rate
 - Chemical-specific DFR may be used in place of the default value
- Risk is calculated as a Margin of Exposure (MOE)
 - $MOE = NOAEL / Exposure$
 - Acceptable MOE can vary based on safety factor (typically 100)
- If risk is unacceptable based on Day 0 DFR an REI may need to be established that is longer than the initial REI based on acute toxicity

Dietary Exposure and Risk

- Dietary exposure estimated using DEEM (Dietary Exposure Evaluation Model)
 - ▶ Food consumption data
 - ▶ Residues in crop commodities
 - ▶ Residues in animal commodities
 - ▶ Estimated or measured residues in drinking water
 - ▶ Toxicology endpoints for acute and chronic exposure (cancer if needed)
- U.S. EPA currently working with Industry to build a “cloud-based” replacement for DEEM since it will no longer be updated
- CARES NG (Cumulative and Aggregate Risk Evaluation System, Next Generation) will include capabilities for both dietary and residential assessment and facilitate aggregate risk assessments within the software



Dietary Information: Consumption Data

- The database for food consumption in the U.S. is based on the National Health and Nutrition Examination Survey (NHANES), What We Eat in America conducted by the CDC
- Foods accounting for largest intake by Americans include
 - Apples, bananas, beef, carrot, chicken, corn (field), corn (sweet), egg, grape, lettuce, milk, onion, orange, pork, potato, rice, soybean oil, sugar, tomato, wheat.

What's a Risk Cup?

- The “risk cup” is based on the toxicity endpoint used to evaluate different durations of chemical exposure (eg. acute, chronic and cancer risk).
- The NOAEL from the reference study is divided by the standard safety factor of 100 (or by a different SF) to derive a “Population Adjusted Dose” or PAD.
- The PAD defines the total level of exposure that would be acceptable without exceeding a “reasonable certainty of no harm” as defined under FQPA.
- The exposures filling the aggregate risk cup include dietary, drinking water and residential exposures (does not include bystander or worker).
- As the total exposure approaches 100% of the acceptable risk, refinements to the assessment are required or no new uses will be considered.

Dietary Exposure and Risk Refinements

- EPA starts with a Tier 1 risk assessment comprised of:
 - Tolerance level residues
 - Assumption that 100% of the crop is treated with a given chemical
 - Default processing factors
 - Highest modeled drinking water value
- If Tier 1 assessment is less than 100% of the risk cup, uses are accepted
- If Tier 1 is >100%, dietary exposure is refined using:
 - % market share for an active ingredient on specific crop(s)
 - Anticipated residues instead of tolerance levels
 - Empirical processing factors
 - USDA Pesticide Data Program – Market basket survey of residues
 - Probabilistic assessment based on statistical sampling methods
- With additional refinements, EPA increases the percentile of dietary exposure that is required to pass the risk assessment

Residential Exposure and Risk

- The process for estimating residential exposure is detailed in EPA's 2012 revision to the Residential SOPs
- Only selected population subgroups are evaluated and represent sensitive populations
- For products that can be applied by a resident (indoor and outdoor), a handler risk assessment is performed to estimate exposures via dermal and inhalation routes
- Post-application exposures (indoor and outdoor) are determined for adults and children
- For children age 1 to 2, exposures via dermal and oral routes (hand-to-mouth, object-to-mouth, etc.) are considered

Scenarios of Residential Exposure Assessed by EPA

Home garden

- Lawns/turf (residential, golf course, etc.)
- Garden plants
- Fruit, nut and ornamental trees
- Outdoor fogging and misting systems
- Insect repellents
- Painting and wood preservative treatments
- Pet treatment
- Impregnated materials
- Termiticides
- Indoor treatments
- Pick your own fruit

Pets

Indoor treatments

Aggregate Exposure (one chemical : multiple exposure pathways)

Risk cup < 100% full

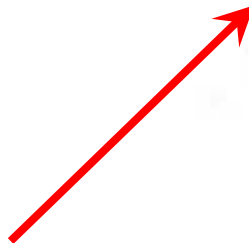
Water



Diet



Residential



Total exposure is determined and compared to toxicology endpoints

Aggregate Exposure and Risk

- Exposures considered for aggregate assessment include:
 - Chronic dietary exposure (food + drinking water)
 - Short-term residential exposure for co-occurring exposures
- Aggregate exposure does not include all possible sources of residential exposure since there is very low probability of same day occurrence
- Aggregate exposure considers scenario representing highest exposure
 - e.g. dermal and hand-to-mouth exposure for infant on turf
 - e.g. residential handler for adult mixing/loading and applying lawn care product to turf (can include both dermal and inhalation)
- Aggregate risk is calculated using an MOE approach considering oral, dermal and possibly inhalation exposures

Cancer Risk Assessment

- A cancer risk assessment is only conducted when the toxicology evaluation indicates a linear low-dose extrapolation ($q1^*$) is appropriate
- Cancer risk assessment for worker:
 - Uses Lifetime Average Daily Dose (LADD) – based on frequency of exposure every working year over the lifetime of a worker
 - Multiply LADD by $q1^*$ to estimate cancer risk
 - Acceptable cancer risk of 1×10^{-5} or lower for worker
- Cancer risk assessment for US Population
 - Multiply chronic dietary and drinking water exposure by $q1^*$
 - Acceptable cancer risk for general population is 1 to 3×10^{-6} or lower

Links to Web Pages on Risk Assessment

- Handler exposure data: <https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data>
- Post-Application exposure data: <https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure>
- Dietary exposure assessment: <https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/deem-fcidcalendex-software-installer#models>
- Residential exposure assessment: <https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide>
- Task Forces: <http://www.exposuretf.com/Home/tabid/54/Default.aspx>



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