Susceptible Populations Workshop
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CHEMICAL HAZARDS SUSCEPTIBLE POPULATIONS DISCUSSION

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DEFINITION: A Susceptible Population is a group of individuals that have an identifiable common characteristic for which the rate/magnitude of response or type of health outcome differs (or could reasonably be expected to differ) from that of a reference population.

This definition includes:

(1) Qualitative or quantitative differences in response arising from a given exposure.
(2) It may or may not include differences arising from different exposures. *(All agreed differing exposures must be included in a risk assessment but did not agree on whether groups with high exposure should be classified as susceptible populations or not.)*

What questions should a risk assessor ask to identify relevant susceptible populations for a given chemical hazard?

- Does the chemical have a known harmful effect?
- Is there a known Mode of Action (MOA) that implicates particular sensitive populations?
- Have there been reports of illness in exposed populations/individuals?
- Is there an activation/deactivation step that may involve a susceptible population?
- Are there likely to be interactions with other common exposures (e.g., Tylenol/alcohol)?
- Are there known groups with expected high exposure or unique exposure patterns?
- What are the chemical's characteristics? (Will it bioaccumulate? Persist? Sequester in animal tissue or the environment? Lipophilicity?)
- Are there indicators in available hazard data pointing to possible susceptible populations/life-stages?
- Is the MOA unique or will it interact with background disease process (and perhaps augment them)?
- How will the chemical be used?

What data are needed to define/characterize a susceptible population? Susceptibility?

- Need to start from context of risk assessment

Context = new product

- See list of questions for Risk Assessor above
- Characteristics of the potentially exposed population
    - Demographics
    - Lifestyle

- Culture
- Genetics
- Metabolism differences
- Dietary habits
- Nutritional status
- Health status or Disease characteristics e.g., diabetes/sugar substitutes, allergies/proteins, liver disease/vibrio, immune compromised/listeria, pregnancy (developmental, maternal), drug interactions
- Drug exposure
- Other co-exposures
- Life-stage
- Geography
- Occupation
- Socioeconomic status

Context = known susceptible population

- Characterize the population—see list above
  - Health status
  - Diseases status
  - Diet
  - Geologic location
  - demographics

What are the challenges to doing a risk assessment (RA) that incorporates susceptible populations?

- Lack of resources
- Uncertainty as to how the data will be used
- Level of effort
- Data
- Animal models don't address question of concern
- Human subjects protection for rare/unusual conditions
- Exposure data
  - Biomonitoring
  - Ultimate uses
  - Data for population subgroups, especially early ages and higher age group
  - Can't monitor for new substances or unknown metabolites
  - Behavior/lifestyle information
- Lack of up-to-date information (e.g., consumption)
- Epidemiological studies
  - Longitudinal
  - Specific targeted exposure data vs. identifying associations
  - *Resource: hospital discharge data*
- Much data is not of sufficient quality to inform risk assessments
- MOA information that can feed into analyses
  - Toxicity pathways
  - How they change with life-stages

- Ways to use toxicological/genomic data to inform susceptibility
- How representative are genomic/screening studies of susceptible populations?
- Can gene arrays or other screening techniques be developed in such a way that they can be fed into risk assessments and or identification or characterization of susceptible populations?
- How do we define the baseline for comparison?
- Epidemiological studies –potential for confounding co-exposures
- Burden of proof required re: effects/associations
- Basic lack of knowledge
    - Windows of vulnerability
    - Critical toxicity pathways
    - Paradoxical dose-response curves
    - Defining adversity
        - Connection between molecular or genotoxic changes to effects of concern
        - Clear connection between assay results and disease outcomes
- Delayed sequelae
    - How do we identify?
    - Delayed effects of early life exposure

What do we need to overcome the challenges?

- Exposure models vs. toxicokinetic models vs. toxicodynamic models
- Dose models
- Increased accessibility and better standardization of models
    - More transparency of model parameters and assumptions
    - More consistent terminology
- Model Parameterization
    - Exposure – OK
    - Kinetics – Fair amount of data
    - Polymorphisms – some data
    - Dynamics- "Black box"

- Toxicology testing methods that better address susceptible populations
    - Life-stages
    - Genetics
    - Disease states
    - Can we make better use of available disease models in understanding disease/chemical interactions?
        - Knockout mice (for example)
        - Humanized mice
- Better data regarding how consumer products are used.
    - What chemicals were used in what products
- Better matching of cross-sectional survey data with long-term outcomes

How do we improve considerations of susceptibility in RA?

- Check box method unlikely to work

- Incorporate all available information
- Identify tests/pathways most relevant to issue of concern
- Protect known sensitive groups
- Descriptive data versus numerical data
- Risk Management options for susceptible populations
    - Warn group via labels?
- *Resource – Center for Disease Control & Prevention (CDC): National Environmental Public Health Tracking Program*

Top Risk Assessment Issues/Improvements

- Value of animal models in identifying susceptible factors
- Increased collection of biomonitoring data for early life stages
- Identifying interactions between chemicals and other factors as they impact susceptibility (including non-chemical stressors)
- What toxicity pathways are most predictive/correlated with susceptibility?
- What are pharmacokinetic and pharmacodynamic differences between susceptible population and reference population?
- Identifying surveillance systems we can use to track disease in populations

How are susceptible populations addressed in each of our agencies?

- Food & Drug Administration (FDA): case-by-case basis, often include assessments for identifiable populations associated with use of that food (e.g., children for BPA, adults taking Coumadin for Olestra, diabetics for artificial sweeteners)
- Start with exposure assessment in pre-market assessments
    - Office of Food Additive Safety (OFAS) reviews new food additive petitions for direct and indirect food additives pre-market. (Indirect additives include industrial compounds that are not supposed to be in foods, 85% of these will result in <50 ppb exposure). OFAS has 120 days respond to petition.
        - Exposure to the additive is calculated based on the proposed use of the additive and the intended use level.
        - Exposure is calculated for the general population as well as any other population that should be considered (e.g., children)
        - Don't always know ultimate use of food additive, so simply use-type and foods involved. No standard way to address.
- CDC: gather information, ask about identifiable populations and look for susceptible populations from these data, ID populations, and develop target educational programs.
    - Effort for chemicals and toxins, priority to be proactive is increasing
    - Info from outbreaks—then ask about characteristics of the people who involved
    - Routine surveys—through National Center for Health Statistics (NCHS)
    - National surveillance for lead
    - Blood & urine samples from National Health & Nutrition Examination Survey (NHANES) –200 chemicals, trying to measure health outcomes, food exposures, trying to make correlations with diet, susceptible populations

- United States Department of Agriculture (USDA)**:** lot of work on the microbial side. Chemical work building back up. Right now focus is on testing for residues rather than risk assessment because we do not set regulatory limits.
    - Lot of work on microbial side, Food Safety & Inspection Service (FSIS) has big testing program, Agricultural Research Service (ARS) has huge sampling and research question. ARS is moving to genomics.
    - USDA National residue program that addresses chemicals: annual sampling of meats for vet drugs, pesticide residues. Have not tied that to outbreaks yet. USDA testing for adulterated foods based on regulations from FDA and others.
    - Problem is finding residues for which there are no levels set (by FDA/Center for Food Safety & Applied Nutrition). USDA is exploring whether they can establish levels for which there is not regulatory level (e.g., Cd, dioxin). Have trigger levels and alert FDA to ID sources of chemicals to address through compliance. Susceptible populations pop up but just starting with chemicals. Farm bill, catfish now on USDA, and environmental chemicals will be most important rather than microbial contamination. May be able to set levels in catfish now that it is their responsibility.
- States (Connecticut and regional work): Body burden chemicals—looking at susceptible populations, e.g., females of child-bearing age
    - When looking at fish—looking at earlier life-stages as well as pregnancy (for PCBs).
    - Thought about trans-generational susceptibility
    - It also starts with question: who is exposed? Looking at identifiable populations (children, pregnant women).
    - Generally, we don't have access to data.
    - States working to come up with watch lists for chemicals (looking at Toxic Substances Control Act (TSCA)).

Additional Questions Raised

- How do you communicate susceptibility?
- What do you do with information on susceptibility once you have it?
- Can we make a common framework for addressing susceptible populations in risk assessments?

<u>Where do we go from here?</u>

(1) Continue the conversation (through additional meetings organized by IRAC membership.) Can we develop a common framework?

(2) Create databases for the following (& possible post on *FoodRisk.org*)

- case studies that have addressed risk assessment for susceptible populations
- characterization of susceptible populations
    - disease-food connections
    - risk assessments that have included consideration of susceptible populations (Good starting point: Rebecca's talk, identified 9 such risk assessments)
    - ILSI (International Life Sciences Institute) has workgroup on thresholds, 4 working groups,--Steve Baldwin will have copy Steve Taylor

- Groups that have very high intakes, e.g., Vit. A