HED Comments on the Brazil Anvisa Tox Requirements

General comments:

- EPA-OPP appreciates the opportunity to provide public comments on the (add title). Our website contains information on the US statutes which govern pesticide registration and the EPA-OPP approach to regulating pesticides (http://www2.epa.gov/pesticides).
- Overall, the toxicology testing requirements for conventional pesticides are largely consistent with those of EPA with some differences.
- We also suggest you look at our Pesticide Science and Assessing Pesticide Risks webpage (http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks) that provides the most up to date information on our science policies and risk assessment approaches for human and ecological health. EPA-OPP's strategic vision for implementing the NAS vision for Toxicity Testing in the 21st Century can also be found at this site. We are working diligently in many areas such as alternative (ie*, in vitro, in silico*) acute toxicity testing, physiologically-based pharmacokinetic models (PBPK), read across, and adverse outcome pathways (AOPs) to implement this vision and would be glad to discuss these areas of advancing science.
- The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) authorizes EPA to register pesticides and require supporting studies to meet statutory safety standards as stipulated under 40 Code of Federal Regulations (CFR) Part 158. There is flexibility, however, in implementing Part 158. Additional data can be required, alternative approaches can be accepted, and studies can be waived. The 2007 NAS report on Toxicity Testing in the 21st Century describes a new vision for toxicity testing. EPA's Office of Pesticide Programs has developed a Strategic Direction for New Pesticide Testing and Assessment Approaches (http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/strategic-vision-adopting-21st-century-science) which describes OPP's approach to implementing the NAS vision. One component of OPP's strategic vision describes the need for improved approaches to more traditional toxicity tests to minimize the number of animals used while expanding the amount of information obtained. OPP's document on *Guiding Principles for Data Requirements* notes the importance of only requiring data that inform regulatory decision making and avoid unnecessary use of time and resources, data generation costs, and animal testing (http://www2.epa.gov/sites/production/files/2015-04/documents/data-require-guide-principle.pdf). Waiving studies, when such data offer little or no additional scientific information or public health protection, is an important component of the guiding principles for data requirements. As such, staff ca on focus on the information most relevant to a particular assessment and still ensure there is sufficient information for regulatory decisions that are protective of public health and the environment. For

example, OPP has specific guidance for waiving some types of studies: 1) *Guidance for Waiving or Bridging of Mammalian Acute Toxicity Tests for Pesticides and Pesticide Products (Acute Oral, Acute Dermal, Acute Inhalation, Primary Eye, Primary Dermal, and Dermal Sensitization)* and *2) Part 158 Toxicology Data Requirements: Guidance for Neurotoxicity Battery, Subchronic Inhalation, Subchronic Dermal and Immunotoxicity Studies.* In recent years, EPA-OPP has waived numerous studies using a weight of evidence approach considering hazard, mode of action, physical chemical properties, and exposure profile. We would be happy to discuss these guidances and our experience waiving studies.

Chapter III: Toxicological Evaluation

Determination of mutagenicity-

The document doesn't go into much detail about how they evaluate for mutagenicity and carcinogenicity. Focuses mainly on the classification scheme. Therefore, we have added information to give them insight on how are evaluations are done. When evaluating chemicals for mutagenic activity, the Agency uses a weight of evidence approach based on the following factors: (1) the genetic endpoints (e.g., gene mutations, structural or numerical chromosomal aberrations) detected by the test systems, (2) the sensitivity and predictive value of the test systems for various classes of chemical compounds, (3) the number of different test systems used for detecting each genetic endpoint, (4) the consistency of the results obtained in different test systems and different species, (5) the aspects of the dose-response relationship, and (6) whether the tests are conducted in accordance with appropriate test protocols agreed upon by experts in the field. In general, for all three endpoints (i.e., point mutations and numerical and structural aberrations), the Agency will place greater weight on tests conducted in germ cells than in somatic cells, on tests performed in vivo rather than in vitro, in eukaryotes rather than prokaryotes, and in mammalian species rather than in sub mammalian species.

Carcinogenicity-

The Agency's carcinogenicity evaluation and classification are based on weight-of-evidence considerations in accordance with the Agency's 2005 Guideline for Carcinogen Risk Assessment. The cancer guidelines emphasize the importance of weighing all available evidence in reaching conclusions about the human carcinogenic potential of agents. This is accomplished in a single integrative step after assessing all of the individual lines of evidence. Evidence considered includes tumor findings, or lack thereof, in humans and laboratory animals; an agent's chemical and physical properties; its structure-activity relationships (SARs) as compared with other carcinogenic agents; and studies addressing potential carcinogenic processes and mode(s) of action, either *in vivo* or *in vitro*. Data from epidemiological studies are generally preferred for characterizing human cancer hazard and risk. However, all of the information discussed above could provide valuable insights into the possible mode(s) of action and

likelihood of human cancer hazard and risk. When evaluating carcinogenicity studies, the following observations add significance to the tumor findings: tumors in multiple species, strains or both sexes; dose-related increases; progression of lesions from preneoplastic to benign to malignant; proportion of malignant tumors; reduced latency of neoplastic lesions; and both biological and statistical significance of the findings. The historical control incidence is also considered when evaluating tumor incidence.

Article 30, Paragraph 1: We are unclear about this. Does this paragraph mean that if there's already a product that acts on a certain pest then competing chemistries would not be registered? How will Brazil manage resistance issues?

Chapter IV: Toxicological Classification Criteria

Hazard Identification and Dose-Response Evaluation, Paragraph 1. Some clarification is requested: how Brazil will decide on the endpoint of "higher relevance"? Will mode of action (MOA)/human relevance analyses be conducted? What if MOA data are not available?

Hazard Identification and Dose-Response Evaluation, Article 58, Paragraph 2. Some clarification is requested on what effects are referred to. For instance, changes in hematology or urinalysis may be considered acute if they haven't been assessed after a single exposure? It is important to take into consideration the biological processes that may lead to an apical endpoint and whether or not those processes might be affected after a single exposure

Toxicological relevant Metabolites.

For residues and degradates of concern, The Agency compares the available toxicity data for the parent and metabolite to determine relative toxicity. Acute lethality studies, a subchronic oral study, and genotoxicity studies are recommended for metabolites of concern.

Chapter VIII Risk Evaluation/Section 1(Paragraph 3)

Uncertainty Factors: The Agency also uses uncertainty factors (UF) to account for missing data and lack of an acceptable NOAEL. Data derived UF and reduction of UF are also appropriate if the data are supportive.

(Paragraph 1)

Acute dietary Assessment: The Agency considers endpoints relevant for acute dietary exposure if they are treatment related, observed after a single dose exposure, or could be attributed to a single dose based on etiology.

(Paragraph 5)

Acceptable Operator Exposure Level. When assessing exposure to occupational workers, the Agency regulates on systemic toxicity and not local dermal effects. For inhalation toxicity, both portal of entry and systemic effects are considered and risk assessments are based on the most sensitive effects. We note that the document has no discussion of inhalation in this section when discussing aeol.

Subsection 1 (Chronic Dietary Exposure)

The Agency estimates drinking concentrations based on application rates, and the % crop treated. The drinking water estimate is included in the dietary assessment to establish the RfD. Some clarification is requested on how 20% contribution of drinking water was derived.

Paragraph 4: Some clarification is requested on whether Brazil is concerned with veterinarian drugs entering the food supply and what data support this?

Annex I Section 4: Toxicological and toxicokinetics studies.

Subchronic mouse study: The US does not require a 2nd subrchronic rodent study and believe this requirement is not necessary and provides duplicative information since there are typically subchronic timepoints in the chronic/cancer testing.

11 - Considerations on ADME studies after exposure via different routes.. Some clarification is requested on how Brazil will handle chemicals that impact the integrity of the skin.

More information regarding the complementary studies you require. Is the immuntoxicty study a requirement or a study that is triggered based on the available data. Are the mechanism studies related to non-cancer or cancer findings? Also, are there criteria for waiving toxicity studies?