WPHA
Western Plant Health Association

January 22, 2014

Ms. Cynthia Oshita
Office of Environmental Health Hazard Assessment
P.O. Box 4010, MS-19B
Sacramento, California 95812-4010

RE: Request for Comment on DART Data Tabulations

Dear Ms. Oshita:

Western Plant Health Association (WPHA) appreciates the opportunity to comment on the proposed tables for tabulating epidemiological and animal data for hazard identification documents for review by the Developmental and Reproductive Toxicant Identification Committee (DART IC). WPHA represents the interests of crop protection and fertilizer manufacturers, agricultural biotechnology providers, and agricultural retailers and distributors in California, Arizona, and Hawaii. Our members comprise more than ninety percent of all the companies marketing crop production and fertilizer products in these states.

We applaud the Office of Health Hazard Assessment (OEHHA) for working to improve the process of evaluating multiple studies for review by DART IC and believe the proposed templates provide an excellent start to encourage both comprehensive and consistent recording of information from multiple publications. This systematic approach captures not only standard characteristics of the test chemical but includes key details of experimental design required for a more robust analysis.

Equally important, the proposed templates serve as a foundation upon which the members of OEHHA's scientific panel and other interested parties can assess study quality and data reliability. Inclusion of these criteria will add to the clarity and transparency of the processes.

As confirmed by Dr. Woodruff at the DART IC meeting in November 2013, there are well established authorities and institutional programs that have implemented analogous tools used to extract and compare relevant scientific information. We concur with Dr. Woodruff and encourage OEHHA to consider these tools as guidance for development of the tables.

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Notable proposals by Klimisch et al. (1997) and Adami et al. (2011) provide strong evidence to support a weight-of-evidence approach that incorporates quality assessment (references enclosed). Likewise, the National Toxicology Program's (NTP) systematic review methodology evaluates the reliability and quality of all available information and evaluates the weight of evidence for what findings are observed or not observed.

The software-based tool "ToxRTool" (**Tox**icological data **R**eliability Assessment **Tool**) developed by the European Commission should also be referenced as it was designed to provide more detailed criteria for assigning data quality than in Klimisch's design. This tool uniquely allows for assignment of an additional fourth category for personal judgment. If personal judgment differs from the tool outcome, the evaluator is requested to document why.

The difficulty with study summary templates lies primarily with determining the optimal columns for inclusion. We believe the overall process would be more informative if the study data were recorded in more than one table and if those tables had more columns. A recent review by Rhomberg et al. (2013, reference enclosed) provides an extensive discussion on systematic approaches for reviewing data. The process of recording data into tables can be time consuming but if the tables are highly detailed, the data evaluation can be more transparent.

There are a number of elements in the currently proposed templates that we support. These elements provide the reviewer important information about each study to improve the systematic process of evaluating the consistency across populations. With respect to the **developmental and reproductive toxicity templates,** these include:

1. The test material source, purity, and preparation for each study. This is required to compare treatment and response across studies such as dose and relative potency, and to judge the relevance of study findings to the chemical being considered for listing. For example, the purity may range from 1% active ingredient to > 99% or may be unknown, making its relevance uncertain. In assessments such as those required under Proposition 65, clear identification of the test materials, including the controls, is crucial.

2. The sample size and the number and selection of dose levels to support the reliability of the relationship between dose and response that are a basic tenet of toxicology. For example, a reported finding based on a small sample at a single dose is generally less reliable than a dose-related finding or absence of a finding with a larger sample size.

3. Reference to other endpoints that were measured such as body weight changes. This will help establish whether effects on developmental or reproductive endpoints are associated with maternal and systemic toxicity or other corresponding effects. We support the listing of endpoints that were measured but not affected for reference to other findings in the same study or in other studies. We would emphasize that this should not be limited to endpoints that are relatively specific to development or reproduction.

With respect to criteria in the **epidemiology** template, we support inclusion of:

1. The study design

2. Sample size

3. Exposure measurement and methods

4. Comments (potential biases, errors, omissions, confounding factors, etc.)

While we are encouraged by the draft templates, additional components could improve the integrity of the system. Examples of these suggested draft templates are included in the appendix to this letter. With respect to the **epidemiology** template, **we suggest**:

1. Creation of a separate table for exposure determination. Information on exposure in epidemiology studies can differ vastly from study to study. The approach can vary from inferred exposure from a geographic location (such as a residence), questionnaire based information on use or consumption, and biomonitoring data such as from urine or blood. The frequency of exposure can be episodic or chronic. The situation can be avocational, occupational, or dietary. Since epidemiology studies rarely estimate an internal "dose" it is more important to devote specific columns in a table to compare and contrast the available data.

2. Differentiating "publication" from "study." Results from epidemiology studies often appear in multiple publications and meetings. It is useful to be able to identify results from a single population so that the findings are not considered as independent observations. Similarly, the strengths and weaknesses can be recognized across the multiple reports.

3. Population characteristic – age, location, year of collection. These data allow the reviewer to compare studies more systematically.

4. Results section should be aligned so that the reader can determine the sample size for each analysis and covariates included in each. These can vary significantly within a single publication.

5. Other considerations include recognition of supplementary data and tables as well as "data not shown." As with a separate table for exposure, it may be necessary to create separate tables for outcomes of interest. This is a unique complication of epidemiology data in which cohort studies can evaluate multiple health outcomes as the population ages.

With respect to the **developmental and reproductive toxicology** templates, covering animal studies, we suggest:

1. Ensuring that the test articles are clearly described and compared to the compound being considered by the OEHHA advisory panel. For studies using formulated test materials, the identity of the test material used in the controls is also needed.

2. Statistical assessments, providing sufficient detail of the test being utilized, need to be provided. The basis of the tests' comparisons (e.g., litter-, dam-, fetus-basis) is central to the relevance of the statistical finding.

3. Adding reference to whether the test material and doses were analytically confirmed. This provides additional confidence in the relationship between a given finding and a particular level of exposure.

4. Including reference to study compliance with internationally-accepted guidelines such as the U.S. EPA's, the OECD, or GLP Guidelines to help ensure the study has met internationally-established standards for robust experimental design and data quality

Thank you for the opportunity to provide input into this productive process. Please contact me if you have any questions or need further information.

Sincerely,

Rachel Kubiak

Rachel Kubiak
Director of Environmental and Regulatory Affairs

Enclosure

Appendix I

Current proposed table

Study reference/year /location	Study design and sample size	Outcomes of interest	Exposure measurement and routes of exposure	Exposure dosages	Covariates/confounders considered	Results and 95% CI	Comments, other

Suggested Exposure Table

Study reference/year	**Population**	**Collection period**	**N**	**Frequency**	**Collection method**	**Exposure matrix**	**Chemicals metabolites**	**Levels1**	**Likely route of exposure**	**Contact (direct vs. bystander)**	**Comments, other**
Potter, 2013	UK Boarding school students	2000-2007	40	Episodic but daily	Spot urine samples 24 ambient air	Participant urine Air (dorm common room)	Flue Powder from a fireplace	LOD, Min, mean, Median, max	Inhalation	Indirect	

1Include results as available using percentiles, ranges, and central tendencies

Suggested Summary Table

Study reference/year	**Population /cohort**	**Characteristics (Ages, year of collection, etc.)**	**Design**	**N**	**Outcomes of interest**	**Results and 95% confidence interval (sample size for each analysis)**	**Covariate/confounders for each analysis**	**Comments**

Reference List

Klimisch HJ, Andreae M and Tillman U. (1997). A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regul Toxicol & Pharmacol,* 25(1): 1-5.

Adami, HO, Berry SC, Breckenridge CB, Smith LL, Swenberg JA, Trichopoulos D, Weiss NS, and Pastoor TP. (2011). Toxicology and epidemiology: Improving the science with a framework for combining toxicological and epidemiological evidence to establish causal inference. *Toxicol Sci,* 122(2): 223-234.

Rhomberg LR, Goodman JE, Bailey LA, Prueitt RL, Beck NB, Bevan C, Honeycutt M, Kaminski NE, Paoli G, Pottenger LH, Scherer RW, Wise KC, and Becker RA. (2013). A survey of frameworks for best practices in weight-of-evidence analyses. *Crit Rev Toxicol* 43(9):753-784.