January 22, 2014

Ms. Cynthia Oshita
Office of Environmental Health Hazard Assessment
P.O. Box 4010, MS-19B
Sacramento, CA 95814
Sent via email to: P65Public.comments@oehha.ca.gov

Subject: DART Data Tabulations: Request for Comment on Tabulating Epidemiological and Animal Data in Hazard Identification Documents for the Developmental and Reproductive Toxicant Identification Committee.

Dear Ms. Oshita:

The American Chemistry Council (ACC)[1] welcomes the opportunity to provide comments on the draft templates under consideration for use by the Office of Environmental Health Hazard Assessment (OEHHA) staff for tabulating epidemiological and animal data in the evaluations that will be submitted to the Developmental and Reproductive Toxicant Identification Committee (DART IC). Once studies are systematically collected for informing the review of the hazard of a chemical, it is critically important that the most relevant information from the studies is abstracted and considered. The comments provided below and the examples in Attachment 1 are intended to help improve upon the draft templates that have been released by OEHHA for public review and comment. [2]

The tables OEHHA circulated for review and comment appear to only be high-level summary tables. In lieu of presenting only high-level summary information in tables, we suggest that much more detailed information be abstracted and systematically presented in data tables. While there may still be a role for high-level summary tables,[3] detailed tables will likely be much more helpful as the DART IC conducts a thorough review of the information available.

We recommend that much more information be added to the OEHHA-proposed tables for both epidemiological and animal studies. In Attachment 1, we provide a series of tables, developed in collaboration with Dr. Julie Goodman (Gradient),[4] for tabulation of data for epidemiology and

[1] The American Chemistry Council (ACC) represents the leading companies engaged in the business of chemistry. ACC members apply the science of chemistry to make innovative products and services that make people's lives better, healthier and safer. ACC is committed to improved environmental, health and safety performance through Responsible Care®, common sense advocacy designed to address major public policy issues, and health and environmental research and product testing.
[2] OEHHA Request for Comment: http://oehha.ca.gov/prop65/CRNR_notices/120413requestEpidata.html and http://oehha.ca.gov/prop65/CRNR_notices/121213requestEpidata.html
[3] High-level summary tables may be useful for providing an overview of information in critical studies; however, detailed data tables will be more useful for conducting a robust weight of evidence review. In addition to the comprehensive robust data tables we suggest, if the DART IC continues to use a summary table, we suggest that at a minimum information on study quality be added to the tables (for instance, Klimisch scores should be added for experimental animal data).
[4] Dr. Goodman also provided some similar comments directly to the DART-IC in a letter dated November 19, 2013.

experimental animal studies of reproductive and developmental effects that can be used in hazard identification. These suggestions and proposed tables are based on best practices in weight of evidence (WoE) methodology (Rhomberg *et al*., 2013)[5] and include information that should be considered when evaluating study quality from epidemiology (von Elm *et al*., 2007; Guyatt *et al*., 2008)[6] and experimental animal studies (Macleod *et al*., 2009; Hooijmans *et al*., 2010; Kilkenny *et al*., 2010; van der Worp *et al*., 2010; Bevan and Strother, 2012).[7] In addition, for experimental animal studies, we have included information which is consistent with the ARRIVE guidelines[8] that have been endorsed by many journals including most recently by the editors of Environmental Health Perspectives.[9] (We have included, for ease of comparison, the tables proposed in December 2013 by OEHHA as Attachment 2.)

Decisions regarding the information that should be included in the tables are an important part of the analysis method. It should be emphasized that the purpose of these tables should be to present all the relevant evidence as part of a systematic review, not simply to provide a summary of the study and the data. Laying out the relevant data, including determinations of study quality and data reliability, in tables (as opposed to only discussing it in the text of a hazard evaluation document) can facilitate a WoE evaluation. Furthermore, such an approach will streamline some of the lengthy written discussion, as the reader can be referred to the tables for study details and results. Due to limitations in space, while we have not captured every aspect recommended in ARRIVE, for animal studies incorporating the information we have suggested in OEHHA's analysis, and including this in the data tables should significantly improve the ability of the DART IC to evaluate the studies.

In this vein, a series of tables that each focus on a specific element of the pertinent information is more useful than a single table with information from all studies, as different toxicants and outcomes may require different types of information. A template that provides a set of tables, such as those in Attachment 1, which can then be adapted based on the causal question, is likely to be the most helpful

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

[6] von Elm, E; Altman, DG; Egger, M; Pocock, SJ; Gotzsche, PC; Vandenbroucke, JP. 2007. "Strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies." BMJ 335(7624):806-808; and Guyatt, GH; Oxman, AD; Kunz, R; Vist, GE; Falck-Ytter, Y; Schunemann, H. 2008. "What is 'quality of evidence' and why is it important to clinicians?" BMJ 336(7651):995-998.

[7] Macleod, MR; Fisher, M; O'Collins, V; Sena, ES; Dirnagl, U; Bath, PM; Buchan, A; van der Worp, HB; Traystman, RJ; Minematsu, K; Donnan, GA; Howells, DW. 2009. "Reprint: Good laboratory practice: Preventing introduction of bias at the bench." J. Cereb. Blood Flow Metab. 29(2):221-223; Hooijmans, CR; Leenaars, M; Ritskes-Hoitinga, M. 2010. "A gold standard publication checklist to improve the quality of animal studies, to fully integrate the Three Rs, and to make systematic reviews more feasible." Altern. Lab. Anim. 38(2):167-182; Kilkenny, C; Browne, WJ; Cuthill, IC; Emerson, M; Altman DG. 2010. "Improving bioscience research reporting: The ARRIVE guidelines for reporting animal research." PLoS Biol. 8(6):e1000412; van der Worp, HB; Howells, DW; Sena, ES; Porritt, MJ; Rewell, S; O'Collins, V; Macleod, MR. 2010. "Can animal models of disease reliably inform human studies?" PLoS Med. 7(3):e1000245; Bevan, C; Strother, D. 2012. "Best Practices for Evaluating Method Validity, Data Quality and Study Reliability of Toxicity Studies for Chemical Hazard and Risk Assessments." American Chemistry Council (ACC), Center for Advancing Risk Assessment Science and Policy (ARASP). Accessed on December 30, 2013 at http://arasp.americanchemistry.com/Data-Quality-Evaluation, 26p.

[8] See ARRIVE guidelines available at: http://www.nc3rs.org.uk/page.asp?id=1357

[9] Tilson HA, Schroeder JC. 2013. Reporting of results from animal studies [Editorial]. Environ Health Perspect 121:A320–A321; doi: 10.1289/ehp.1307676.

for hazard identification. It is critical that tables be constructed in such a way that the data are abstracted the same way from each study of the same genre (e.g., there should be a template for epidemiological studies and a template for animal toxicity studies and approaches should be implemented to assure consistent use of these tables). Having columns with a lot of information in each is likely to result in inconsistent reporting across studies. As illustrated in our suggested tables, study results should be laid out separately by outcome to ensure that all data on each endpoint is reported and avoid the tendency to omit null data from the tables, which can make results appear more consistent than they actually are. Although we have not specifically included mode of action (MoA) to the tables in Appendix 1, where MoA information is available, this should be included in the tables. Alternatively a separate set of MoA tables could be provided.[10]

Although there is no perfect way to tabulate data from a set of studies that may have many differences among them, it is imperative that all of the relevant data (including null) be presented in a manner that will allow the DART IC and other readers to determine the consistency and coherence of results, considering study strengths and limitations. This is best accomplished by moving away from including diverse and lengthy information in a few columns and instead, by providing focused tables with more columns and very specific information in each column. While compiling tables in this manner may be a higher level of effort initially, it will significantly lower the risk of missing null data and the potential for biased analyses as the WoE analysis is conducted.

In the hypothetical examples we present in Attachment 1, we present separate tables for (1) basic information about the individual studies, with different epidemiology study designs (*e.g.*, cohort *vs*. case-control) or experimental animal studies with different exposure routes (inhalation, oral, *etc.*) and different types of toxicity (reproductive *vs*. developmental) in their own tables; (2) the outcomes examined across studies; (3) study quality; and (4) study results by outcome, with each outcome in its own table (or, alternatively, each outcome could be in a separate section of a larger table of related outcomes).

We appreciate the consideration OEHHA staff will give to our suggestions and request that public comments and OEHHA's response to comments be shared with the DART IC. We would welcome the opportunity to answer any questions you may have. Please feel free to contact me at nancy_beck@americanchemistry.com or 202-249-7000.

Sincerely,

Nancy B. Beck, PhD, DABT
Senior Director
Regulatory and Technical Affairs

[10] See for examples the tables presenting mechanism of action in Kushman ME, Kraft AD, Guyton KZ, Chiu WA, Makris SL, Rusyn I; A systematic approach for identifying and presenting mechanistic evidence in human health assessments. Regul Toxicol Pharmacol. 2013 Nov; 67(2):266-77. doi: 10.1016/j.yrtph.2013.08.005.

Attachment 1: ACC Recommended Data Tabulation Methods for Epidemiology and Experimental Animal Studies of Reproductive and Developmental Effects

A. Epidemiology Studies

Table 1. Basic Study Information – Cohort Studies

Study Reference	Location	Cohort Size	Exposure Metric (Examples Below)							
			Exposure Duration	Job Category	Cumulative Exposure	Air Concentration from Central Monitor	Air Concentration from Personal Monitoring	Maternal Blood Concentration of Chemical	Cord Blood Concentration of Chemical	Urinary Level of Biomarker
Author, Year	Sweden	5,000	Number of years prior to pregnancy							
Author, Year	Los Angeles, CA	500				Measured during second trimester		Measured during second trimester		

Table 2 Basic Study Information – Case-Control Studies

Study Reference	Location	Cases (*N*)	Controls (*N*)	Exposure Metric (Examples Below)					
				Cumulative Exposure	Air Concentration from Central Monitor	Air Concentration from Personal Monitoring	Maternal Blood Concentration of Chemical	Cord Blood Concentration of Chemical	Urinary Level of Biomarker
Author, Year	Seattle, WA	250	250				Measured at first visit to infertility clinic		
Author, Year	Spain	100	100			Measured during third trimester		Measured at birth	Measured during third trimester

Table 3 Study Outcomes

Study Reference	Outcomes Assessed (Examples Below)								
	Infertility	Miscarriage	Pre-term Birth	Stillbirth	Birth Defects	Low Birth Weight	Perinatal Mortality	Semen Quality	Others…
Author, Year	X	X							
Author, Year		X	X	X	X	X	X		
Author, Year	X							X	

Table 4 Study Quality

Study Reference	Study Design	Study Size	Presence of Selection Bias	Exposure Measurement Error	Outcome Measurement Error	Confounders/Effect Modifiers Considered	Statistical Methods	Sensitivity Analysis
Author, Year	Ecologic	Large (based on chosen cut-off)	Likely	Likely	Likely	List of confounders/ effect modifiers	Not appropriate	Not performed
Author, Year	Individual	Large	Likely	Not likely	Not likely	None	Appropriate	List of alternative analyses

Table 5 Study Results by Outcome (Example: Birth Defects)

Study Reference	Exposure Metric	Exposure Concentration/ Category	*N*	Unit of Measure	Covariates	Risk Estimate	95% CI
Author, Year	Duration of exposure	< 5 years	1,000	N/A	None	RR = 1.2	0.89-1.31
		5-10 years	3,000			RR = 1.4	0.92-1.55
		> 10 years	1,000			**RR = 2.1**	**1.8-2.4**
Author, Year	Air conc. from central monitor	Median: 11 ppb (range: 3-29 ppb)	500	RR for 5 ppb increase	None	**RR = 1.9**	**1.5-2.2**
					Ozone	RR = 1.0	0.9-1.1
					$PM_{2.5}$	RR = 0.9	0.7-1.1
Author, Year	Blood levels	< 10 nmol/L	25	N/A	None	OR = 1.1	0.8-1.2
		10-20 nmol/L	50			OR = 1.5	0.9-1.8
		> 20 nmol/L	25			**OR = 3.2**	**1.8-4.4**

B. Experimental Animal Studies

Table 1. Basic Study Information for Reproductive Toxicity (Inhalation Exposure)

Study Reference	Species/Strain	Age	Sex	Animals per Exposure Group	Exposure Concentration (ppb)	Exposure Length/Frequency
Author, Year	Rat, Wistar	6 weeks	Female	6	0, 0.1, 1, 10	4 h/d; 30 d
Author, Year	Rat, Sprague Dawley	4 weeks	Male	8	0, 5, 10, 20	4 h/d; 5 d/wk; 8 wk
Author, Year	Mouse, CD-1	8 weeks	Male	10	0, 0.025, 0.25, 2.5, 25	8 h/d; 5d/wk; 8 wk

Table 2 Basic Study Information for Reproductive Toxicity (Oral Exposure)

Study Reference	Species/Strain	Age	Sex	Animals Per Exposure Group	Dose Route	Dose (mg/kg-d)	Dose Period
Author, Year	Rat, F344	4 weeks	Male	8	Oral gavage	0, 5, 25, 50	10 days
Author, Year	Mouse, C57BL/6	3 weeks	Female	6	Oral gavage	0, 1, 10	30 days
Author, Year	Mouse, CD-1	8 weeks	Male	8	Drinking water	0, 0.5, 5, 50	6 weeks

Table 3 Basic Study Information for Developmental Toxicity (Inhalation Exposure)

Study Reference	Species/Strain	Study Design	Treatment Group (n, sex)	Exposure Concentration (ppb)	Exposure Length/Frequency
Author, Year	Rat, Wistar	One-generation	16 dams/group; 12 litters/group	0, 1, 5, 10	Dams dosed GD6-GD21
Author, Year	Rat, Sprague Dawley	One-generation	8 female offspring/group	0, 0.5, 5, 50	Dams dosed GD10-GD21

Table 4 Basic Study Information for Developmental Toxicity (Oral Exposure)

Study Reference	Species/Strain	Study Design	Treatment Group (n, sex)	Dose Route	Dose (mg/kg-d)	Dose Period
Author, Year	Rat, Wistar	One-generation	20 dams/group; 16 litters/group	Oral gavage	0, 1, 5, 10	Dams dosed GD6-GD21
Author, Year	Mouse, CD-1	Two-generation	15 dams/group; 12 F1 and 12 F2 offspring/sex/group	Drinking water	0, 0.2, 2	F0 and F1 dams dosed GD6-PND21; F1 and F2 offspring dosed PND21 to end of study

Table 5 Study Outcomes for Reproductive Toxicity

Study Reference	Outcomes Assessed (Examples Below)										
	Sperm Count	Sperm Morphology	Sperm Motility	Testis Weight	Testis Histology	Estrous Cyclicity	Ovary Weight	Uterus Weight	Ovary Histology	Uterus Histology	Others…
Author, Year	X	X	X	X	X						
Author, Year						X					
Author, Year							X	X	X		

Table 6 Study Outcomes for Developmental Toxicity

Study Reference	Outcomes Assessed (Examples Below)									
	Pregnancy Rate	Gestation Length	Litter Size	Sex Ratio	Gross Malformations	Anogenital Distance	Age at Vaginal Opening	Ovary Histology	OECD Guideline 416 Two-Generation Reproductive Study	Others…
Author, Year	P	P	F1	F1	F1					
Author, Year					F1, F2	F1, F2	F1, F2	F2		
Author, Year									X	

Table 7 Study Quality

Study Reference	Sample Size Calculation	Study Reliability (Klimisch Code)	Randomized Allocation to Experimental Groups	Blinded Outcome Assessment	Presence of Attrition Bias	Statistical Methods
Author, Year	Not performed	2 – Reliable with restriction (non-guideline study)	Not stated	Yes	Unknown	Appropriate
Author, Year	Sufficient study power	1 – Reliable without restriction (OECD guideline study)	Yes	Yes	Not likely	Appropriate

Table 8 Study Results by Outcome for Reproductive Toxicity (Sperm Count Example)

Study Reference	Species/Strain	Dose (mg/kg-d)	Sperm Count ($\times 10^7$ per g epididymal weight)	*P* Value
Author, Year	Rat, F344	0	2.2	-
		5	2.3	0.8
Author, Year	Mouse, CD-1	0	1.9	-
		0.1	1.8	0.1
		1	1.8	0.1
		10	**1.5**	**0.03**

Table 9 Study Results by Outcome for Developmental Toxicity (Anogenital Distance Example)

Study Reference	Species/Strain	Generation	Sex	Dose (mg/kg-d)	Anogenital Distance (mm)	*P* value
Author, Year	Mouse, CD-1	F1	Male	0	1.20	-
				0.5	**1.10**	**< 0.01**
			Female	0	1.15	-
				0.5	1.12	0.1
Author, Year	Rat, Wistar	F1	Male	0	1.52	-
				1	1.45	0.09
				5	1.50	0.4
			Female	0	1.40	-
				1	1.42	0.1
				5	1.39	0.09
		F2	Male	0	1.55	-
				1	1.50	0.08
				5	1.49	0.09
			Female	0	1.43	-
				1	1.44	0.2
				5	1.42	0.3

Attachment 2. Data Tabulation Tables Proposed by OEHHA (December 2013)

(http://oehha.ca.gov/prop65/CRNR_notices/120413requestEpidata.html)

http://oehha.ca.gov/prop65/public_meetings/pdf/1013SummMockupTabEpiStudies.pdf
Agenda Item III: Committee Discussion on How to Tabulate Data from Epidemiological Studies in Hazard Identification Documents

Study Reference/year/ Location	***Study Design (prospective cohort, historical cohort, case-control, randomized controlled trial) and Sample sizes***	***Outcomes of Interest***	***Exposure Measurement Methods and Likely routes of exposure***	***Exposure dosages measured***	***Covariates/ Confounders considered***	***Results (Odds ratios or relative risks or hazard ratios and 95% confidence intervals for outcomes adjusted for confounders)***	***Comments (potential biases, errors, omissions, etc.)***
1 – Smith 2003, Utah							
2 – Jones 2007, Paraguay							
3 – Wu 2010, Beijing							

Template for tabulating data from developmental toxicity studies

Reference	Experimental Parameters					Endpoints Assessed [Parents/ Offspring]	Results (Effects/NOEL/LOEL)		Comments
	Chemical [Source/ Purity/ Preparation]	Animal Model [Species/ Strain/Sex/ Age] Number per dose group	Study Design	Exposure [Route/ Period/ Frequency/ Vehicle]	Doses or Concentrations		Parents	Offspring	
[Study 1: authors, date]									
[Study 2: authors, date]									

Template for tabulating data from male and female reproductive toxicity studies

Reference	Experimental Parameters						Results (Effects/NOEL/LOEL)		Comments
	Chemical [Source/ Purity/ Preparation]	Animal Model [Species/ Strain/Sex/ Age] Number per dose group	Study Design	Exposure [Route/ Period/ Frequency/ Vehicle]	Doses or Concentrations	Endpoints Assessed	Systemic Toxicity	Reproductive Toxicity	
[Study 1: authors, date]									
[Study 2: authors, date]									