Carcinogen Identification Committee Meeting

June 13, 2023

Background Materials

The June 13, 2023 meeting of the Carcinogen Identification Committee (CIC) will include two informational sessions: 1) Key Characteristics (KCs) of Carcinogens and their use in cancer hazard identification; and 2) Assessment of tumor data from animal carcinogenicity studies.

The session on KCs of Carcinogens will include presentations by three scientists, two of whom are invited speakers: Dr Vincent Cogliano, Deputy Director for Scientific Programs at OEHHA; Dr Kathryn Guyton, National Academies of Sciences, Engineering and Medicine; Dr Ivan Rusyn, Texas A&M University.

The session on assessment of tumor data from animal carcinogenicity studies will include a presentation from OEHHA staff scientists Ms Rose Schmitz (biostatistician) and Dr Jennifer Hsieh (staff toxicologist).

Below are lists of selected references that provide useful background information for each session.

Part I. Key Characteristics of Carcinogens and their Use in Cancer Hazard Identification

Background Information:

Barupal DK, Schubauer-Berigan MK, Korenjak M, Zavadil J, Guyton KZ. 2021. Prioritizing cancer hazard assessments for IARC Monographs using an integrated approach of database fusion and text mining. Environ Int 156:106624.

Guyton KZ, Rusyn I, Chiu WA, Corpet DE, van den Berg M, Ross MK, et al. 2018. Application of the key characteristics of carcinogens in cancer hazard identification. Carcinogenesis 39:614-622.

Guyton KZ, Schubauer-Berigan MK. 2021. Invited Perspective: Prioritizing Chemical Testing and Evaluation Using Validated in Vitro Assays Relevant to Key Characteristics. Environ Health Perspect 129:71303.

IARC. 2019. Preamble to the IARC monographs (amended January 2019). International Agency for Research on Cancer/World Health Organization Lyon. Available: https://monographs.iarc.who.int/wp-content/uploads/2019/07/Preamble-2019.pdf.

IARC Monographs Vol 125 group. 2020. Carcinogenicity of some industrial chemical intermediates and solvents. Lancet Oncol 21:25-26.

Krewski D, Bird M, Al-Zoughool M, Birkett N, Billard M, Milton B, et al. 2019. Key characteristics of 86 agents known to cause cancer in humans. J Toxicol Environ Health, Part B 22:244-263.

Rusyn I, Chiu WA, Lash LH, Kromhout H, Hansen J, Guyton KZ. 2014. Trichloroethylene: Mechanistic, epidemiologic and other supporting evidence of carcinogenic hazard. Pharmacol Ther 141:55-68.

Scholten B, Simón LG, Krishnan S, Vermeulen R, Pronk A, Gyori BM, et al. 2022. Automated Network Assembly of Mechanistic Literature for Informed Evidence Identification to Support Cancer Risk Assessment. Environ Health Perspect 130:37002.

Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, et al. 2016. Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. Environ Health Perspect 124:713-721.

Smith MT. 2019. Key characteristics of carcinogens. In: Tumour Site Concordance and Mechanisms of Carcinogenesis, IARC Scientific Publication 165: 85-91. Available: https://publications.iarc.fr/578

Smith MT, Guyton KZ, Kleinstreuer N, Borrel A, Cardenas A, Chiu WA, et al. 2020. The key characteristics of carcinogens: relationship to the hallmarks of cancer, relevant biomarkers, and assays to measure them. Cancer Epidemiol Biomarkers Prev 29:1887-1903.

Additional OEHHA References:

OEHHA. 2021. Evidence on the Carcinogenicity of PFOS and Its Salts and Transformation and Degradation Precursors. Available: https://oehha.ca.gov/media/downloads/crnr/pfoshid092421.pdf. (see pages 61 to 128 for discussion of data related to KCs; see pages xx to xxiii for summaries of data related to KCs)

OEHHA. 2022. Evidence on the Carcinogenicity of Bisphenol A (BPA). Available: https://oehha.ca.gov/media/downloads/crnr/bpahid093022.pdf. (see pages 127 to 229 for discussion of data related to KCs; see pages xxxi to xxxvii for summaries of data related to KCs)

Part II. Background Information Relevant to Assessment of Tumor Data from Animal Carcinogenicity Studies

References related to effective number:

Gold LS, Sawyer CB, Magaw R, Backman GM, De Veciana M, Levinson R, et al. 1984. A carcinogenic potency database of the standardized results of animal bioassays. Environ Health Perspect 58:9-319.

IARC. 2019. Preamble to the IARC monographs (amended January 2019). International Agency for Research on Cancer/World Health Organization Lyon. Available: https://monographs.iarc.who.int/wp-content/uploads/2019/07/Preamble-2019.pdf.

Specifically, on pages 24–25:

> "Key factors for statistical analysis include: (i) number of animals studied and number examined histologically, (ii) number of animals with a given tumour type or lesion, and (iii) duration of survival."
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> "The statistical methods used should be clearly stated and should be the generally accepted techniques refined for this purpose (Peto et al., 1980; Gart et al., 1986; Portier & Bailer, 1989; Bieler & Williams, 1993). The choice of the most appropriate statistical method requires consideration of whether there are differences in survival among the treatment groups; for example, reduced survival because of non-tumour-related mortality can preclude the occurrence of tumours later in life and a survival-adjusted analysis would be warranted. When detailed information on survival is not available, comparisons of the proportions of tumour-bearing animals among the effective number of animals (alive at the time that the first tumour was discovered) can be useful when significant differences in survival occur before tumours appear. The lethality of the tumour also requires consideration: for rapidly fatal tumours, the time of death provides an indication of the time of tumour onset and can be assessed using life-table methods; non-fatal or incidental tumours that do not affect survival can be assessed using methods such as the Mantel–Haenszel test for changes in tumour prevalence. Because tumour lethality is often difficult to determine, methods such as the poly-k test that do not require such information can also be used. When results are available on the number and size of tumours seen in experimental animals (e.g. papillomas on mouse skin, liver tumours observed through nuclear magnetic resonance tomography), other, more complicated statistical procedures may be needed (Sherman et al., 1994; Dunson et al., 2003)."

References related to trend tests:

Armitage P. 1955. Tests for linear trends in proportions and frequencies. Biometrics 11:375-386.

Cochran WG. 1954. Some methods for strengthening the common χ 2 tests. Biometrics 10:417-451.

Mehta CR, Patel N, Senchaudhuri P. 1992. Exact stratified linear rank tests for ordered categorical and binary data. J Comput Graph Stat 1:21-40.

Williams D. 1988. Tests for differences between several small proportions. J R Stat Soc Ser C Appl Stat 37:421-434.

References related to multiple comparisons:

Haseman JK. 1983. A reexamination of false-positive rates for carcinogenesis studies. Fundam Appl Toxicol 3:334-339.

Rusyn I, Chiu WA, Wright FA. 2020. Questioning existing cancer hazard evaluation standards in the name of statistics. Toxicol Sci 177:521-522.

References related to rare tumors and historical controls:

IARC. 2019. Preamble to the IARC monographs (amended January 2019). International Agency for Research on Cancer/World Health Organization Lyon. Available: https://monographs.iarc.who.int/wp-content/uploads/2019/07/Preamble-2019.pdf.

See page 25:

> "The concurrent control group is generally the most appropriate comparison group for statistical analysis; however, for uncommon tumours, the analysis may be improved by considering historical control data, particularly when between-study variability is low. Historical controls should be selected to resemble the concurrent controls as closely as possible with respect to species, sex, and strain, as well as other factors, such as basal diet and general laboratory environment, which may affect tumour response rates in control animals (Haseman et al., 1984; Fung et al., 1996; Greim et al., 2003). It is generally not appropriate to discount a tumour response that is significantly increased compared with concurrent controls by arguing that it falls within the range of historical controls."

US EPA. 2005. Guidelines for carcinogen risk assessment. US EPA, Washington, DC. Document number EPA/630/P-03/001F. Available:

https://www.epa.gov/sites/default/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf.

See page 2-21:

> "When historical control data are used, the discussion should address several issues that affect comparability of historical and concurrent control data, such as genetic drift in the laboratory strains, differences in pathology examination at different times and in different laboratories (e.g., in criteria for evaluating lesions; variations in the techniques for the preparation or reading of tissue samples among laboratories), and comparability of animals from different suppliers. The most relevant historical data come from the same laboratory and the same supplier and are gathered within 2 or 3 years one way or the other of the study under review; other data should be used only with extreme caution."

Additional OEHHA References:

OEHHA. 2002. Evidence on the carcinogenicity of N-carboxymethyl N-nitrosourea. FINAL. Available: https://oehha.ca.gov/media/downloads/proposition-65/chemicals/cmnufinal.pdf (see pages 5–7 for description and use of effective numbers in a Table)

OEHHA. 2012. Evidence on the carcinogenicity of C.I. Disperse Yellow 3. Available: https://oehha.ca.gov/media/downloads/proposition-65/chemicals/081012ciyhid.pdf. (see page 10 for a table with effective numbers)

OEHHA. 2013. Evidence on the carcinogenicity of butyl benzyl phthalate. Available: https://oehha.ca.gov/media/downloads/proposition-65/chemicals/bbphid10042013.pdf. (see page 16 for discussion of rare tumors; see page 14 for a table showing effective numbers)

OEHHA. 2021. Evidence on the Carcinogenicity of PFOS and Its Salts and Transformation and Degradation Precursors. Available: https://oehha.ca.gov/media/downloads/crnr/pfoshid092421.pdf. (see pages 46 and 49 for description of rare tumors reported; see page 47 for a table showing effective number)

OEHHA. 2022. Evidence on the Carcinogenicity of Bisphenol A (BPA). Available: https://oehha.ca.gov/media/downloads/crnr/bpahid093022.pdf. (see pages 63–74 for description of rare tumors reported; page 54 for a table showing effective number)