American Board of Toxicology, Inc.
Recertification Literature Review 2018

Article 1: Key Characteristics of Carcinogens as a Basis for Organizing Data on Mechanisms of Carcinogenesis
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4892922/pdf/ehp.1509912.pdf

Article 1 Questions

1. What did the authors propose to facilitate a systematic and uniform approach to organizing mechanistic data relevant to carcinogens?
    A. Use the mechanistic data to introduce an entirely new way for classifying potential human carcinogens by the International Agency for Research on Cancer (IARC).
    B. Use of a key characteristic approach to reclassify the previously assigned IARC categorization of potential human carcinogens
    C. Use of 10 key characteristics of human carcinogens as a basis for identifying and categorizing scientific findings relevant to cancer mechanisms when assessing whether an agent is a potential human carcinogen
    D. Since human carcinogens most commonly show only 1 of the 10 key characteristic properties, the proposed concept does not provide consistent and systematic approaches for carcinogen identification.

2. What example of relevant evidence reflects the corresponding key characteristic of a carcinogen?
    A. DNA adduct formation – induces epigenetic alterations
    B. reduced proliferation and increased apoptosis – alters cell proliferation, cell death or nutrient supply
    C. elevated leukocytes – is immunosuppressive
    D. DNA intercalation – is genotoxic

3. What approach is used to systematically identify and organize carcinogenicity mechanistic information using key characteristics?
    A. performing comprehensive searches of the peer-reviewed literature relevant to mechanism of action
    B. limiting literature searches to existing human data
    C. assessing only mechanisms that are most published widely
    D. assessing only government published sources

4. What conclusion could be reached in using key characteristics to synthesize mechanistic information to develop adverse-outcome networks for potential carcinogens?
    A. All existing data suggest that often a single biological mechanism is involved in transformation of a cell that ultimately develops into a tumor.
    B. Once a specific mechanism is identified for a carcinogen, the resulting overview does not provide guidance for further assessments of the literature.
    C. Using the key characteristics as a basis, the collected information can be organized to form hypotheses and evaluate the evidentiary support for mechanistic events as a function of relevant aspects.
    D. In the absence of human data, carcinogen hazard identification cannot be made.

5. What was identified as a key characteristic of a specific carcinogenic chemical that may assist in organizing the mechanistic data?

    A. The mechanistic data for polychlorinated biphenyls (PCB) were associated with key characteristics that induces immunomodulation and inflammatory response.
    B. The mechanistic data for benzene associated with the development of leukemia is supported by multiple key characteristics of carcinogenicity.
    C. The mechanistic data for dichloro-diphenyl-trichloroethane (DDT) carcinogenicity is limited to evidence of oxidative stress, electrophilic binding and DNA intercalation.
    D. The key characteristic involved in malathion carcinogenicity is strictly oxidative stress.

Article 2: Thresholds of Toxicological Concern – Setting a Threshold for Testing Below Which There Is Little Concern
http://www.altex.ch/resources/altex_2017_3_331_351_FFT_Hartung3.pdf

Article 2 Questions

1. For what primary reason has the thresholds for toxicological concern (TTC) approach been considered controversial?
    A. because it carries out risk characterization without the usual toxicity data
    B. because it replaces the no observed adverse effect level (NOAEL)
    C. because it requires probabilities of risk that extend to zero
    D. because it does not depend on the validity of the databases used

2. For what two purposes does the US FDA currently use the TTC approach?
    A. GRAS food additives and colors
    B. generic drugs and medical devices
    C. food packaging migrants and drug impurities
    D. cosmetics and other consumer products

3. For what level and/or class of toxicants were the first TTC values proposed?
    A. high-levels of food flavoring agents intentionally added to processed meats
    B. low-levels of chemicals in food introduced unintentionally from packaging
    C. chemicals intended as chemotherapeutic agents and their excipients
    D. known carcinogenic food additives based on structural alerts and toxicity studies

4. What Cramer Class represents the lowest TTC and to which most complex chemicals are assigned?
    A. Cramer Class I
    B. Cramer Class II
    C. Cramer Class III
    D. Cramer Class IV

5. In what significant way does the TTC approach differ from (Q)SAR?
    A. TTC is based on existing data whereas (Q)SAR predicts properties of untested substances.
    B. TTC cannot define a NOAEL whereas (Q)SAR can predict toxicity endpoints.
    C. European REACH legislation is very open to the use of TTC but not to (Q)SAR.
    D. The European Food Safety Authority (EFSA) favors the use of (Q)SAR over TTC.

Article 3: Toxicity and management in CAR T-cell therapy
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5008265/pdf/mto201611.pdf

Article 3 Questions

1. What is the most prevalent adverse effect following infusion of CAR T cells?
    A. insertional oncogenesis
    B. on target/off-tumor toxicity
    C. cytokine release syndrome
    D. anaphylaxis/allergy

2. Why is on-target/off tumor toxicity a concern with CAR T therapy?
    A. CAR T cells often utilize antigen-recognition domains derived from murine monoclonal antibodies.
    B. Most CAR T antigen targets share expression on both malignant and normal cells.
    C. CAR T therapy results in an elevation of inflammatory cytokines.
    D. CAR T cells can cross-react with non-specific antigens.

3. Why is tocilizumab used to treat cytokine release syndrome?
    A. It is an interleukin 6 (IL-6) receptor inhibitor.
    B. It is an interleukin 10 (IL-10) receptor inhibitor.
    C. It is an interferon gamma (IFNγ) inhibitor.
    D. It is a tumor necrosis factor alpha (TNFα) inhibitor.

4. What dimerizable molecule can deplete CAR T cells by inducing apoptosis?
    A. herpes simplex thymidine kinase
    B. dexamethasone
    C. ganciclovir
    D. inducible Fas

5. What is required for targeted activation of CAR T cells?
    A. CD 28 or 4-1BB costimulatory signaling on CAR T cells to complete activation
    B. expression of a known cell-surface antigen such as endothelial growth factor receptor (EGFR) on the CAR T cells to complete activation
    C. dual-antigen binding of the CAR T cells to the malignant cells to complete activation
    D. expression of inducible caspase 9 on CAR T cells to complete activation

Article 4: Application of Adverse Outcome Pathways to U.S. EPA's Endocrine Disruptor Screening Program
https://ehp.niehs.nih.gov/doi/10.1289/EHP1304

Article 4 Questions

1. What is the purpose of the first tier assay screen in the Endocrine Disruptor Screening Program (EDSP)?
    A. to characterize the dose-response relationships of endocrine disruption
    B. to determine potential activity in the estrogen, androgen and thyroid pathways of both sexes of several vertebrate taxa
    C. to use the battery of in vitro assays to definitively conclude the cause of the endocrine disruption
    D. to determine the guideline studies that have been submitted to the U.S. EPA as part of the pesticide registration process

2. What is the relationship between adverse outcome pathways (AOPs) and toxicity pathways?
    A. AOPs represent an evolution of the toxicity pathway concept, describing a framework for linking mechanism of chemical interaction with the apical endpoint.
    B. Toxicity pathways were described initially in the National Research Council report to support existing AOPs.
    C. Toxicity pathways and AOPs both start with a molecular initiating event (MIE).
    D. Toxicity pathways and AOPs both have tiered testing programs.

3. What is the intent of the Tier I screening battery within the EDSP?
    A. to identify ecological receptors that may be exposed to potential pesticides
    B. to represent conclusive evidence of potential adverse outcomes
    C. to provide an organizing framework linking mechanisms and adverse effects
    D. to show the potential for endocrine activity rather than to represent conclusive evidence of potential adverse outcomes

4. What requirement is reported by the authors to define the "reference chemicals" for a biological effect within predictive model building for high-throughput endocrine screening methods?
    A. chemicals for which an AOP has been determined
    B. chemicals that have been tested in both the ToxCast^{TM} and Tox21 programs
    C. chemicals that are active in more than one type of endocrine assay
    D. chemicals that have been tested in both Tier I and Tier II EDSP assays

5. How is U.S. EPA's EDSP used in linking toxicity pathways and AOP frameworks?

   A. a way to organize the data when an understanding of all key events are available
   B. to model the interactions between multiple endocrine pathways, identify possible points of convergence, and identify potential biomarkers around which assays and testing strategies may be developed
   C. an alternative to simple and complex predictive models to completely replace in vivo animal testing
   D. a way to fill in all data gaps for selected modes of action