American Board of Toxicology, Inc.
Recertification Literature Review 2020

Article 1: Dose-dependence of chemical carcinogenicity: Biological mechanisms for thresholds and implications for risk assessment.

R. A. Clewell, et. al. Chemico-Biological Interactions 301: 112-127
https://www.sciencedirect.com/science/article/pii/S0009279718314467

Article 1 Questions

1. What low-dose extrapolation approach, developed in the early years of cancer assessment, was based on statistical approaches and provides highly conservative estimates of cancer risks from low-dose exposures?

    a. No Observed Adverse Effect Level (NOAEL)/Uncertainty Factor (UF) approach
    b. Linearized Multistage Model
    c. Biologically Based Dose-response Model
    d. Multistage-Weibull Model

2. In the context of understanding the potential for carcinogenesis, how are DNA adducts considered?

    a. Biomarkers of exposure
    b. Mutations
    c. Biomarkers of effect
    d. Precursors of carcinogenicity

3. What model has been recommended by the National Academy of Sciences and can be used to determine the most scientifically plausible risk estimates?

    a. Computational Fluid Dynamic (CFD)
    b. DNA-protein crosslinks (DPX)
    c. Compensatory Cytolethal-regenerative cellular proliferation (CRCP)
    d. Biologically based dose-response (BBDR)

4. According to the authors, what can be used to quantify the first irreversible step of cancer development?

    a. Transcriptomics
    b. Apoptotic signaling
    c. Mutation Assays
    d. High Content Imaging

5. The first legal decision requiring quantitative low-dose extrapolation was for what chemical?

    a. Formaldehyde
    b. Benzene
    c. Chromium
    d. TCDD

Article 2: Next generation physiologically based kinetic (NG-PBK) models in support of regulatory decision making.

Paini A, Leonard JA, Joossens E, et al. (2019). Computational Toxicology 9:61-72.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6472623/pdf/main.pdf

Article 2 Questions

1. What scientific field saw the greatest percent increase in publications on physiologically based kinetic (PBK) models since 2007?

    a. Veterinary medicine
    b. Toxicology
    c. Forensics
    d. Pharmacology

2. What was the central feature of the URL ECVAM "Strategy on Toxicokinetics" document published in 2015?

    a. PBK modeling to integrate *in vitro* and *in silico* data to predict human target organ toxicity
    b. Using quantitative *in vitro* to *in vivo* extrapolation (QIVIVE) to estimate human external doses
    c. Developing PBK models based on QIVIVE data from humanized transgenic animals
    d. Deriving human PBK data using novel allometric scaling and *in vitro* biotransformation

3. The concept of "next-generation physiologically based kinetic (NG-PBK)" models is based on what advancement or set of advancements?

    a. Existing PBK models combined with advancements in *in vitro* and *in silico* methodologies
    b. Existing PBK models combined with more powerful computer algorithms and equations
    c. Existing PBK models combined with new animal data including from fish and bees
    d. Existing PBK models combined with advanced artificial intelligence and machine learning

4. A minimalist, one-compartment PBK model for ADME properties has been developed and used to support chemical screening and prioritization based only on what two types of data?

    a. *In silico* and *in vitro*
    b. Protein binding and clearance
    c. 3-D lung and skin tissue metabolism
    d. Transporter kinetics and mode of action

5. The "credibility matrix" allows for locating specific model types based on the information available. In the matrix, what alternate-approach model would correspond to the highest level of confidence in its predictability?

    a. Model based on *in silico* data and one well-designed human study
    b. *In silico* model based on untested hypotheses with no reference data
    c. Heuristic model based on *in silico* and *in vitro* tests
    d. Heuristic model based on *in silico, in vitro* and human data

Article 3: Understanding the Importance of Low-Molecular Weight (Ethylene Oxide- and Propylene Oxide-induced) DNA Adducts and Mutations in Risk Assessment: Insights from 15 years of Research and Collaborative Discussions.

Pottenger LH, Boysen G, Brown K, et al. (2019). Environmental and Molecular Mutagenesis 60:100-121.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6590209/pdf/EM-60-100.pdf

Article 3 Questions

1. Current US EPA regulatory guidance uses what dose-response model to determine risk below the identified point of departure when a mutagenic MOA is established?

    a. Non-linear
    b. Linear
    c. Probit
    d. Gamma Multi-hit

2. Ethylene Oxide (EO) is produced in humans from metabolism of ethylene generated during physiological processes. For risk assessment, it is essential to determine the relative contributions of endogenous versus exogenous EO-induced DNA damage. According to the authors, what approach made it possible to delineate the *in vivo* dose-response relationship in rats over a relevant concentration range to assess the risk from exogenous EO exposure?

    a. Tri-Isotope
    b. Flow cytometry irradiation
    c. Dual-Isotope
    d. Guanine residue

3. According to the authors, what synthetic method was not appropriate for the preparation of the N7-alkyG containing oligonucleotides due to instability of the N-glycosidic bond and the potential for opening of the imidazole ring of the 7-substituted guanine 2'-deoxyribonucleosides?

    a. Solid-phase phosphoramidite
    b. Liquid-phase phosphoramidite
    c. Gas-phase phosphoramidite
    d. Aqueous-phase phosphoramidite

4. To achieve maximal sensitivity in assessing the potential effect of N7- or O^6-alkylG adducts on DNA polymerase bypass activity, the authors measured the effects of these adducts on replication in bacteria with what type of plasmid probes?

    a. Double-stranded plasmid probes carrying multiple lesions
    b. Double-stranded plasmid probes carrying a single lesion
    c. Single-stranded plasmid probes carrying multiple lesions
    d. Single-stranded plasmid probes carrying a single lesion

5. Dose-responses for genotoxic effects from a series of DNA-reactive chemicals [vinblastine sulfate (VB), ethyl methane sulfonate (EMS), ethyl nitrosourea (ENU), methyl methane sulfonate (MMS), methyl nitrosourea (MNU), and bleomycin (BLEO)] were evaluated *in vitro* for induction of micronuclei using flow cytometry. Of this series of test chemicals, what subseries had a dose-response that demonstrated a better statistical fit with a nonlinear dose-response model?

    a. VB, MNU, BLEO, ENU, MMS
    b. VB, MMS, MNU, EMS, ENU
    c. MNU, BLEO, ENU, EMS, MMS
    d. VB, BLEO, ENU, EMS, MMS

Article 4: Critical review of the association between perineal use of talc powder and risk of ovarian cancer.

Taher et al., *Reproductive Toxicology* (2019) 90:88-101.
https://www.sciencedirect.com/science/article/pii/S0890623818306373

Article 4 Questions

1. Smith et. al. have identified ten key characteristics common to established human carcinogens. What three key characteristics have been associated with talc exposure *in vitro*?

    a. Oxidative stress, inflammation, and cell proliferation
    b. Epigenetic alterations, oxidative stress, and altered DNA repair
    c. Receptor mediated effects, inflammation, and direct acting genotoxicity
    d. Cell proliferation, electrophilic, and immunosuppressive activity

2. Subgroup analysis by ethnicity has indicated a significant increase in talc-associated ovarian cancer risk for what groups of women?

    a. Caucasian women and Asian women exposed to perineal talc
    b. Hispanic women and Caucasian women exposed to perineal talc
    c. African American women and Hispanic women exposed to perineal talc
    d. Asian women and African American women exposed to perineal talc

3. What data support the hypothesis that hormonal factors, especially estrogens, influence the risk of developing ovarian cancer with concomitant perineal talc exposure?

    a. Pre-menopausal women showed the greatest risk of ovarian cancer
    b. Post-menopausal women not receiving hormonal therapy showed the greatest risk
    c. Women with prior tubal ligation showed the greatest risk of ovarian cancer
    d. Women receiving hormonal therapy showed the greatest risk of ovarian cancer

4. Analysis of what study provided the strongest evidence for a dose-response relationship between perineal talc exposure and ovarian cancer?

    a. The Nurses' Health Study
    b. The Quebec Cancer Genetics Network
    c. The Women's Health Study Group
    d. The African American Cancer Epidemiology Study

5. Using the GRADE framework to assess the quality of data, what factor resulted in the certainty of findings in the Taher paper as being classified as very low?

    a. Lack of consistency
    b. Risk of bias
    c. Lack of precision
    d. Indirectness