Poster Presentation Abstracts

Poster 1

Lessons Learned in Application of Framework to Quantitatively Integrate Key Characteristic of Carcinogen (KCC) Data

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Mechanistic information is often the diverse, challenging, and having-less-developed-approach-and-tool part of systematic review and cancer hazard identification. The CRAB project developed a public tool http://crab3.lionproject.net enabling users to enter a search term (e.g., a(n) substance, occupation, cancer) and immediately receive PubMed abstracts that are tagged according to scientific evidence, mode of action (MoA) of cancer, and toxicokinetics. In scientific evidence, study design is tagged for subject (human, animal, cell, subcellular, microorganism), study length, and outcome types (biomarker, tumors, morphological effects, biochemical/cell biological effects etc.) In MoA, studies are tagged as genotoxic (include event types) or nongenotoxic with events of co-initiation, promotion (e.g., specific receptor/pathway activation), promotion, progression (e.g., immunosuppression), and multiphase (e.g., transcriptional modification, inflammation). Except electrophilicity and altered nutrient supply, all 10 characteristics of carcinogens are covered. Additionally, each sentence of the abstract is color-coded as describing the background, objective, method, result, conclusion, related work, or future work of the study. For example, searching “benzo(a)pyrene” lead to nearly 12,000 abstracts, among which over 4000 are on genotoxicity (with adducts, strand breaks and mutations being most common, each with over 1300 abstracts), 475 on epigenetics, 0 on angiogenesis, and 50 on toxicokinetic modeling. Users can also search by PubMed IDs to tag specific abstracts. This tool provides a great coverage of mechanistic information landscape and detailed and thoughtful tagging structure is effective and rapid. In the future CRAB will interface with other databases and software, providing even greater support to existing working practices in systematic review and cancer hazard identification.

Poster 2

Biologically-based Bayesian Networks Applied to Chemical Carcinogenesis

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Bayesian Networks (BN) provide a probabilistic means to predict an outcome based on known data. This approach can be applied to predicting in vivo effects based on responses to high throughput screening (HTS) in vitro tests such as those from the Tox21/ToxCast programs, which screen thousands of chemicals across hundreds of assays. Here we provide an updated mapping of the Tox21/ToxCast assays to cancer hallmarks, i.e. ten biological attributes common to tumor development, using gene and pathways databases: the Gene Ontology (GO) and the Kyoto Encyclopedia of Genes and Genomes (KEGG). More than 1,000 genes were mapped to cancer hallmarks and were related to at least one in vitro assay. For every chemical tested in the Tox21/ToxCast programs a hallmarks score (HMscore) was computed related to their positive responses on the set of hallmark-mapped assays. From the U.S. EPA's ToxRefDB, a database of guideline animal studies, we developed a cancer score (Cancerscore) from a range of in vivo endpoints (pathology proliferative, neoplastic lesion and no response) in two animal models (rat and mouse). More than 400 chemicals were found with a Cancerscore and HMscores that were used to develop a BN predictive model for a chemical's carcinogenicity. The best model had more 82% predictive accuracy with a very high negative predictivity rate, predicting 94% of non-carcinogenic compounds. This work supports the idea that it is possible to correlate the in vitro bioactivity response patterns of certain chemicals and their carcinogenic potential in vivo using mechanistically-informed in silico approaches.

Poster 3

Semi-automated Systematic Review to Map Assays and Biomarkers to Hallmarks of Cancer and Key Characteristics of Carcinogens

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In support of the NTP's Strategic Health Effects Innovation on Carcinogenicity Testing for the 21st Century, a semi-automated systematic review of the literature is underway to identify novel assays and biomarkers that map to the hallmarks of cancer and the key characteristics of carcinogens. The overarching goals of this effort include informing new testing strategies, refining frameworks to incorporate mechanistic data in cancer hazard identification and risk assessment, and developing effective screening tools to detect the carcinogenic potential of environmental chemicals and mixtures. To identify the most relevant cutting-edge technologies (and those that are still in widespread use), only publications from the past ten years were included. Search strings for hallmarks, key characteristics, assays, and biomarkers were developed specifically for PubMed and Scopus. Our systematic literature search initially yielded ~57,000 unique publications published between Nov 2010 and Nov 2018. All references were uploaded onto sysrev website (https://sysrev.com/), a collaborative data extraction platform with machine learning to facilitate title and abstract screening as well as tagging (e.g., hallmarks, key characteristics, test system, etc.). Each reference is screened by at least two experts with cancer knowledge, with the additional option to annotate/tag each abstract. The sysrev platform also automatically tracks MeSH terms. Overall, these metadata tags allow for grouping references via species, technologies, pathways, and keywords. At this stage, several thousand publications have been screened, informing and improving inclusion models and providing an initial literature database that can be investigated.

Please join our reviewer team via the sysrev platform, project "*Hallmark and key characteristics mapping*": https://sysrev.com/p/3588.

Poster 4

Targeted Expression Profiling Identifies Mechanisms of Mammary Toxicants

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Over 200 chemicals have been associated with altered mammary gland development and cancer, yet the molecular mechanisms by which this diverse set of chemicals affects the breast remain poorly understood. We investigated gene expression profiles of eight suspected mammary toxicants using the TempO-Seq platform and a targeted gene expression panel, Breast Carcinogen Screen (BCScreen). The BCScreen panel has 500 genes and includes at least 30 genes strongly associated with each of 14 biological processes relevant to breast cancer and mammary gland development. We compared gene expression profiles in MCF-7 cells treated with four concentrations (1 nM to 10 uM) of PFOA, PFHXA, PFNA, genistein, 1,4 benzoquinone (BQ, a genotoxic metabolite of benzene), BPA, butyl benzyl phthalate (BBP), or tamoxifen (Tam) for 24hrs. We identified expression patterns activated by mammary toxicants with known ER agonist activity and suppressed by mammary toxicants with antagonist or no known direct ER activity. The known weak estrogens genistein, BPA, and BBP had similar gene expression profiles and were enriched for genes associated with cell cycle and DNA repair, particularly at high doses. Notably, PFOA, Tam, and BQ had greater gene expression changes at lowest (1nM) vs higher doses and were enriched for genes associated with cell cycle. PFOA profiles were enriched for several transcription factors including, E2F1 and E2F4, which regulate cell cycle genes and important processes in mammary development and tumor progression. Utilizing the BCScreen gene panel we have identified mechanistic targets relevant to breast cancer and perturbed by mammary toxicants.

Poster 5

Systematically Evaluating and Integrating Evidence on Cancer in National Ambient Air Quality Standards (NAAQS) Reviews

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As part of the review process for National Ambient Air Quality Standards (NAAQS), the United States Environmental Protection Agency (EPA) assesses causal relationships between air pollutant exposures and health effects, including cancer, using a framework it developed specifically for this purpose. Here, we discuss how this framework could be improved by adding detailed methods for integrating studies in a way that fully and systematically considers individual study quality and relevance, and the coherence of results across studies within and across scientific disciplines. For example, the framework should include not just a list of study quality aspects for evaluating human and animal studies, but also aspects for evaluating in vitro studies, and it should specify the criteria that must be met to demonstrate that an aspect has been fully addressed. In addition, these aspects should be considered in a transparent and systematic fashion for each individual study, with the quality evaluations forming the basis for weighing evidence as it is integrated within and across disciplines, and ultimately for conclusions regarding causality. We will also specifically address the human relevance of mechanistic evidence, with a particular focus on studies that evaluate upstream events vs. apical effects, and how informative they are for interpreting the results of epidemiology and toxicity studies. Incorporating the suggestions discussed here will make NAAQS causality assessments more transparent and reflective of the weight of scientific evidence, and will allow for scientifically defensible decision-making.

Poster 6

Adverse Outcome Pathways for Ionizing Radiation and for In Utero Estrogens Leading to Breast Cancer Highlight Characteristics of Breast Carcinogens

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Knowledge about established breast carcinogens can support improved 21st century toxicological testing by identifying key mechanistic events. To clarify mechanisms, we developed adverse outcome pathways for two well-established breast carcinogens: ionizing radiation and the hormone diethylstilbestrol (DES). The AOP for ionizing radiation includes these elements: ionizing radiation (stressor) increases production of reactive oxygen and nitrogen species (RONS, MIE1), and directly and indirectly causes DNA damage (MIE2). DNA damage leads to mutations (KE1) and proliferation (KE2), leading to increased breast cancer. RONS also increases inflammation (KE3), which contributes to direct and indirect effects (effects in cells not directly reached by IR) via positive feedback to RONS (MIE1) and separately increases breast cancer through increased proliferation of cells (KE2) and increased tumor growth and invasion (AO). Estrogen and progesterone also influence the risk of breast cancer from ionizing radiation. For DES, the AOP links gestational estrogen exposure (MIE) to transcriptional activity that promotes altered signaling between the epithelial and stromal tissue compartments leading to disrupted development, including altered tensional homeostasis and tissue architecture, inflammation, and altered cellular differentiation. These key events (KEs) lead to several adverse outcomes at the tissue- and organ-level, including altered density, structure and hormone sensitivity along with hyperplasia. Epigenetic alterations are a cellular-level AO that propagate gestational EDC exposure to later-life risk through cellular memory that directs ER-mediated gene expression and altered mammary development. Risk of breast cancer follows from these AOs. Dose-response, developmental timing of exposure, and generalizability to mechanistically similar stressors are discussed in both AOPs.

Poster 7

Better Ways than the Bioassay: Weight-of-evidence Approach to Assess Carcinogenicity Potential of Food Use Pesticides

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Abstract - Rodent cancer bioassays have been used for decades to identify chemicals that may be carcinogenic to humans. However, numerous retrospective analyses and reviews of data collected from the bioassay over the past 40 years have raised questions about the relevance and regulatory need for the bioassay to assess risk to human health. As a result, a working group comprised of different sectors and stakeholders have developed case-examples using a weight-of-evidence (WoE) mechanism-based approach to determine the appropriateness of waiving rodent cancer bioassays in the context of crop protection chemical registration. The WoE approach was used to evaluate exposure, mode-of-action, physiochemical properties, and toxicological data from defined endpoints. Selected pesticides that represented different classes of chemistry were reviewed using the WoE approach to evaluate available information on pesticide mode of action, indication for use, metabolic profile, toxicokinetics, genetic toxicology, histopathology from dose-response studies, tumour formation, hormonal perturbation, immune response, read-across, margins of exposure, uses, human exposure scenarios, and other relevant endpoints used in risk assessment. These data were collated to determine if there would have been sufficient information to perform a health protective chronic risk assessment without performing rodent cancer bioassays. Additional analyses are being conducted of a much larger set of pesticides to ensure adequate coverage of chemical space. The results of these analyses will be used to establish the criteria for when the mouse and/or rat cancer bioassay can be waived with sufficient confidence to protect public health.

Poster 8

High-throughput Pro-angiogenesis Assay Using Human Endothelial Colony Forming Cells

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Endothelial colony-forming cells (ECFCs) are circulating progenitors involved in angio- and vasculogenesis during embryonic development and adulthood and, possibly, in tumor neovascularization. Isolated ECFCs represent a unique model of endothelial cell function with excellent growth and differentiation capabilities. A single cell-derived ECFC cell line can produce billions of cells, which is critical for successful high-throughput assay development. We have developed a novel pro-angiogenesis assay using ECFCs stably expressing mCherry fluorescent protein (ECFC-Red). ECFC-Red form angiogenic structures in the presence of Vascular Endothelial Growth Factor A (VEGFA) and a tumor derived extracellular matrix (ECM). This VEGFA and ECM-stimulated process depends on the α2 integrin subunit, which plays a key role in tumor invasion. Using a high content imager, we analyzed the ability of various chemicals to stimulate ECFC angiogenesis. Multiparameter image analysis demonstrated a strong pro-angiogenic effect by copper sulfate and a weak effect by nicotine and bacterial endotoxin. Arsenic (III), stannous chloride, and cadmium chloride were pro-angiogenic at low but cytotoxic at high concentrations, while arsenic (V) and TGF-beta (ALK5) inhibitor were weakly anti-angiogenic at low concentrations but pro-angiogenic at high concentrations. Our data demonstrate the feasibility of using donor-specific ECFCs for screening substances potentially capable of stimulating tumor angiogenesis.

Poster 9

Cumulative Risk, Key Characteristics of Carcinogens, and Hallmarks of Cancer Analysis for Carcinogenic Drinking Water Contaminants

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Classic toxicological and carcinogenic evaluations involve exposure to a single agent, an approach that misses the health impacts of co-occurring contaminants. To understand the molecular processes that underpin cancer development in people and the carcinogenic impact of environmental pollutants, it is critical to assess the potential health impacts of co-occurring contaminants that are found in common media such as air, water, food products, and consumer products. If environmentally relevant mixtures of chemicals are causing or substantially contributing to cancer, the public health consequences would be profound. We posit that existing cumulative cancer risk methodologies can be informative for the development of rational hypotheses for texting mixtures of chemicals that trigger carcinogenesis. Here we present an analysis for drinking water in which we identify common combinations of co-occurring carcinogenic water contaminants that can be tested for their carcinogenic potency and other toxicological effects with in vitro methodologies and in vivo studies. We also utilize a risk-based cancer metric combined with mode of action data from the Hallmarks of Cancer and Key Characteristics of Carcinogens frameworks, as well as Global Burden of Disease disability weights for assessing the severity of cancer outcomes. Applying this method to drinking water contaminant occurrence dataset for the United States allows for a calculation of estimated lifetime cancer cases due to carcinogenic chemicals in tap water. In conclusion, real-life exposure information can be helpful for designing mixtures studies for probing the pathways leading to environmental carcinogenesis and also for integrating information from multiple risk assessment frameworks.

High-throughput Detection of Endocrine-Disrupting Chemicals (EDCs) in the Environment

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Endocrine-disrupting chemicals (EDCs) are substances in the environment (air, soil, water supply etc.), that interfere with normal function of the endocrine system and have been associated with metabolic disorders, immune dysfunction, developmental defects, and cancer. Thus, presence of EDCs in the environment is a major health concern.

Standard identification of EDCs in the environment relies on a laborious analysis of chemical structures using HPLC, MS/GS and related technologies. These methods are costly, time consuming and frequently fail to identify a specific chemical structure for EDC, because they are subjected to bio-modifications in the environment and may not be present in the currently existing chemical libraries. Consequently, the levels of EDCs are not efficiently monitored or regulated. In addition, it is unclear whether the EDCs detected by chemical methods elicit biological responses specifically in mammalian systems.

To overcome these obstacles, we developed a high-throughput assay for biological testing of EDCs using mammalian cell lines. This assay is based on translocation of fluorescently labeled nuclear receptor constructs. These constructs translocate from the cytoplasm to the nucleus in the presence of EDCs acting as ligands on a specific receptor. At the present, we can screen for EDCs interacting with seven individual nuclear receptors: aryl hydrocarbon [AhR], androgen [AR], thyroid [TR], estrogen [ER], glucocorticoid [GR], progesterone (PR), and retinoic acid receptor (RAR). Using these assays, we have demonstrated hormonal activities in water sources and conclude that this contamination is a health hazard for the aquatic ecosystems and could also negatively impact the human population.

In Silico Toxicity Protocols and Models for Genetic Toxicity and Cancer

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In silico models are increasingly used to predict toxicity. Although quickly providing a prediction, the process of selecting/acquiring models, performing an expert review, integrating data/model results, and documenting conclusions and uncertainties can be time-consuming and difficult to repeat. It is also challenging to defend the results, primarily due to a lack of published procedures for performing an *in silico* assessment. To support the development of such protocols, a consortium has been assembled that includes representatives from regulatory agencies and government research laboratories, companies in major industrial sectors, academic groups, and other stakeholders. The protocols will ensure that *in silico* assessments are performed in a consistent, repeatable, and well-documented manner to support their broader acceptance. The consortium is currently developing *in silico* protocols to cover different toxicological endpoints; the first protocol to be developed is for genetic toxicology, which incorporates data/models covering gene mutation, clastogenicity, aneugenicity, and DNA damage. This protocol is being integrated into a comprehensive protocol for cancer that also takes into consideration non-genotoxic mechanisms as well as *in vivo*, human, ADME, and 'omics information. This poster describes the consortium's activities as well as a framework for conducting such an assessment using the existing genetic toxicity protocol and the current efforts to develop a protocol for cancer.

Use of the 10 Key Characteristics of Carcinogens (KCs) in Report on Carcinogens (RoC) Cancer Hazard Assessments

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The RoC is a congressionally mandated public health report that identifies agents, substances, mixtures, or exposure circumstances (collectively as "substances") that are known or reasonably anticipated to be human carcinogens. Substances are listed in the report based on a formal review process, systematic assessment of the scientific literature, and application of established RoC listing criteria. These criteria allow for substances to be listed based on convincing relevant information that the substance acts through mechanisms indicating it would likely cause cancer in humans or belongs to a well-defined structurally related class of substances whose members are listed in the RoC.

Using KCs to help unbiasedly search, organize, and review mechanistic information, we developed literature search terms derived from the KCs to search in PubMed, Scopus, and Web of Science. Evidence mapping of mechanistic (e.g., by KC) and other relevant data was conducted by screening and tagging the literature using Health Assessment Workspace Collaborative (HAWC) software. This process helps the development of the methods used (i.e., protocol) in the review. Each mechanistic study was evaluated for strength of evidence to inform carcinogenesis, which not only provides levels of support to epidemiology or animal cancer study findings, but also informs potential modes of action, adverse outcome pathways, or read-across approaches to fill data gaps. Here we demonstrate use of the KCs in three NTP ORoC cancer hazard assessments: haloacetic acids (drinking water disinfection byproducts), antimony trioxide, and shift work.

Poster 13

CRAB: Automatic Text Mining of PubMed for Cancer Mechanism/Mode of Action (MoA)

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Mechanistic information is often the diverse, challenging, and having-less-developed-approach-and-tool part of systematic review and cancer hazard identification. The CRAB project developed a public tool http://crab3.lionproject.net enabling users to enter a search term (e.g., a(n) substance, occupation, cancer) and immediately receive PubMed abstracts that are tagged according to scientific evidence, mode of action (MoA) of cancer, and toxicokinetics. In scientific evidence, study design is tagged for subject (human, animal, cell, subcellular, microorganism), study length, and outcome types (biomarker, tumors, morphological effects, biochemical/cell biological effects etc.) In MoA, studies are tagged as genotoxic (include event types) or nongenotoxic with events of co-initiation, promotion (e.g., specific receptor/pathway activation), promotion, progression (e.g., immunosuppression), and multiphase (e.g., transcriptional modification, inflammation). Except electrophilicity and altered nutrient supply, all 10 characteristics of carcinogens are covered. Additionally, each sentence of the abstract is color-coded as describing the background, objective, method, result, conclusion, related work, or future work of the study. For example, searching “benzo(a)pyrene” lead to nearly 12,000 abstracts, among which over 4000 are on genotoxicity (with adducts, strand breaks and mutations being most common, each with over 1300 abstracts), 475 on epigenetics, 0 on angiogenesis, and 50 on toxicokinetic modeling. Users can also search by PubMed IDs to tag specific abstracts. This tool provides a great coverage of mechanistic information landscape and detailed and thoughtful tagging structure is effective and rapid. In the future CRAB will interface with other databases and software, providing even greater support to existing working practices in systematic review and cancer hazard identification.

Evaluating Evidence of Mechanisms: A Philosophy of Science Perspective

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The philosophy of science has recently undergone a *mechanistic* revolution (Machamer et al., 2000). Many philosophers now accept that to explain some scien- tific phenomenon, it is helpful to describe a mechanism, where a mechanism consists of entities and activities organized in such a way that they are responsible for the phe- nomenon (Illari and Williamson, 2012). For example, in order to explain an observed correlation between the consumption of aristolochic acid and urothelial cancer, it is helpful to describe the mechanism linking aristolochic acid and urothelial cancer. Given this, some philosophers have argued that evidence of mechanisms plays a crucial role in understanding causal inference in epidemiology, because evidence of mechanisms can rule out alternative explanations of an observed correlations, expla- nations such as confounding, bias, or chance (Clarke et al., 2014; Gillies, 2019). This has led to an influential philosophical theory about the underlying logic of causal inference, a logic that appeals to a combination of both evidence of correlation and evidence of mechanisms (Russo and Williamson, 2007; Williamson, 2018). This un- derlying logic gives a precise account of exactly how a variety of evidence is involved in establishing a causal hypothesis, from epidemiological evidence, to mechanistic evidence and animal studies (Figure 1). It has also led to the recommendation of a set of principles and procedures for systematically evaluating such a variety of evidence (Parkkinen et al., 2018). Recently, these principles and procedures have informed changes to the *Preamble* to the Monographs of the International Agency for Research on Cancer.

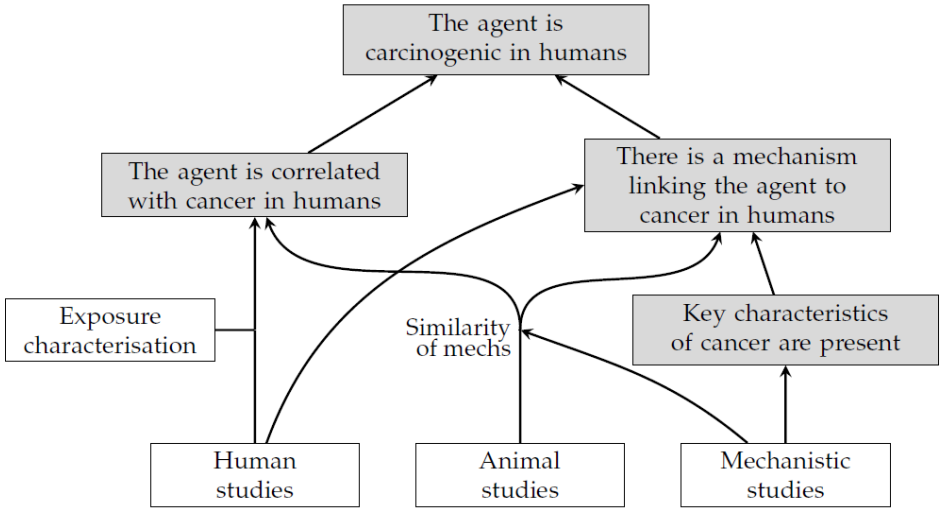

Figure 1: A graph informed by an influential theory in the philosophy science, which shows how a variety of evidence is involved in establishing a causal hypothesis, from epidemiological evidence, to mechanistic evidence and animal studies.

Application of an Integrated Approach for Chemical Evaluation of Human Cancer Risk

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An exposure-driven assessment for chemicals proposes a paradigm shift in support of risk assessment-based regulatory decision-making. The Health and Environmental Sciences Institute (HESI) Risk Assessment in the 21st Century (RISK21; www.RISK21.org) project is a scientific, transparent, and efficient approach to inform human health risk assessment. This systematic approach evaluates and integrates mechanism-based knowledge with exposure consideration and allows scientifically defensible and appropriate hazard characterization for regulatory decision-making. The RISK21 problem formulation based strategy enables public health protective decisions to be made without unnecessary use of animals in large scale and redundant studies. Using the knowledge accumulated from the use and class of chemistry will focus the questions that need to be answered to protect human populations from cancer risk. Cumulative risk assessment (CRA) poses additional problems and questions that can be addressed using the RISK21 approach. Commonly CRA has been focused on chemicals that have common mechanisms of action. Recently, concern has also been expressed about chemicals acting on multiple pathways that lead to a common health outcome, and non-chemical stressors that can lead to or modify a common outcome. As part of the problem formulation process, this evidence-based framework allows the identification of the circumstances in which it is appropriate to conduct a CRA for a group of compounds. A tiered approach is then proposed, where additional chemical stressors and/or non-chemical modulating factors are considered sequentially. This transparent, systematic approach enables an improved process to efficiently achieve innovative solutions with confidence in protecting public health.

Poster 15

Evaluating Mechanistic Evidence: Beyond the IARC 10 Key Characteristic Framework for Carcinogens

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The International Agency for Research on Cancer (IARC) developed a framework for evaluating mechanistic evidence on carcinogenicity that emphasizes 10 key characteristics of carcinogens. While this framework is useful for organizing mechanistic evidence, it does not provide sufficient guidance for implementation, and thus has limited utility for evaluating carcinogenic potential in humans. In addition, it does not include explicit criteria for evaluating the biological significance of mechanistic endpoints, inter- and intra-individual variability, or study quality and relevance. It also does not explicitly address how mechanistic evidence should be integrated with other realms of evidence. Because mechanistic evidence is critical to understanding human cancer hazards, systematic and detailed guidelines for the use of this framework are warranted so that mechanistic evidence can be evaluated in a robust manner and properly integrated with other realms of evidence, to reach an appropriate conclusion regarding cancer hazards in humans. We propose that the IARC 10 key characteristic framework be used as a system to categorize studies, and other established frameworks that address biological significance, study quality, and relevance be used to evaluate and integrate mechanistic evidence in systematic reviews of potentially carcinogenic substances.