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SCIENTIFIC SESSION III
The key characteristics approach to hazard identification

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Introduction to the key characteristics approach

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Background: The key characteristics (KCs) of human carcinogens were recently introduced as the basis of a uniform approach for searching, organizing, and evaluating mechanistic evidence to support cancer hazard identification. The KCs comprise the properties of known human carcinogens, including their ability to, be genotoxic; be immunosuppressive; or modulate receptor-mediated effects. Established human carcinogens commonly exhibit one or more of these characteristics, and therefore, data on these characteristics can provide independent evidence of carcinogenicity when human data are lacking. Such data can also help in interpreting the relevance and importance of findings of cancer in animals and in humans.

Method/Approach/Results: In its 2017 report on "Using 21st Century Science to Improve Risk-Related Evaluations", the National Research Council (NRC) recently opined that the KCs approach "avoids a narrow focus on specific pathways and hypotheses and provides for a broad, holistic consideration of the mechanistic evidence." Th NRC further suggested that KCs be developed for other endpoints, such as endocrine disruption and reproductive toxicity. These KCs have recently been published and KCs for neurotoxicants are being developed.

Conclusions: The KC approach holds great potential to improve hazard identification and risk assessment, but still needs to be further developed, especially regarding its potential for helping analyze the toxic effects of untested chemicals and chemical mixtures in cell culture and experimental animals. Unfortunately, the current Tox21 and Toxcast repertoire of assays are mostly lacking in relevance to the KCs, as are most clinical biomarkers. Approaches to developing a new set of high-throughput tests and biomarkers will be described along with a discussion of the use of the key characteristics approach in hazard identification and risk assessment instead of, or in addition to, the current Mode of Action/Adverse Outcome Pathway (MOA/AOP) approach.

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Martyn Smith is a Professor of Toxicology and Cancer Epidemiology in the School of Public Health at the University of California Berkeley. He received his Ph.D. in Biochemistry from St. Bartholomew's Hospital in London and did post-doctoral training in toxicology at the Karolinska Institute in Stockholm. Dr. Smith is a laboratory scientist with expertise in molecular epidemiology, toxicology and genomics, and his research is aimed at finding the causes of chronic diseases, including cancer.

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The key characteristics approach to hazard identification

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Background: The key characteristics (KCs) of carcinogens reflect the chemical and biological properties of cancer-causing agents and were introduced in 2015 to provide a common basis for assembling and evaluating mechanistic evidence to support cancer hazard identification. They are becoming increasingly used by multiple authoritative bodies, including IARC, NTP and regulatory agencies. One important aspect of using the key characteristics to assemble data relevant to carcinogenic mechanisms is that an a priori hypothesis about the mechanism of action is not required. Instead, the key characteristics are based on the common properties of known carcinogens, and avoid "a narrow focus on specific pathways and hypotheses" and instead "provides for a broad, holistic consideration of the mechanistic evidence" (National Academy of Science, 2017). This same 2017 National Academy of Sciences report recommended that the KCs approach be expanded to other endpoints, including reproductive effects, endocrine disruption and cardiovascular disease. In 2018, 3 working groups have developed KCs for endocrine disrupting chemicals (EDCs), and male and female reproductive toxicants. A group recently met to develop KCs for neurotoxicants.

Methods: The speakers are: Martyn Smith (UC Berkeley), Introduction to the KC Approach; Michele LaMerrill (UC Davis), KCs of EDCs; Kathryn Guyton (IARC), Application of the KCs of Carcinogens in IARC Monographs; Linda Birnbaum (retired), KCs of Bioactive Chemicals; Lauren Zeise (OEHHA), KC Approach to Organizing and Assessing Upstream Toxicity Information.

Results/Conclusion: We describe the development and application of KCs for carcinogens, EDCs and reproductive toxicants and discuss their application at IARC and elsewhere.

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Martyn Smith is a Professor of Toxicology and Cancer Epidemiology in the School of Public Health at the University of California Berkeley. He received his Ph.D. in Biochemistry from St. Bartholomew's Hospital in London and did Post-Doctoral training in toxicology at the Karolinska Institute in Stockholm. Dr. Smith is a laboratory scientist with expertise in molecular epidemiology, toxicology and genomics, and his research is aimed at finding the causes of chronic diseases, including cancer.

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Key characteristics of endocrine-disrupting chemicals

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Background: Endocrine-disrupting chemicals (EDCs) are exogenous chemicals that interfere with hormone action, thereby increasing health risks, e.g., for cancer, reproductive impairment, cognitive deficits, and obesity. A complex literature of mechanistic studies provides evidence on EDC hazard, yet there is no widely accepted, systematic method to integrate these data to help identify EDC hazards.

Methods/Approach/Results: Inspired by work to improve hazard identification of carcinogens using key characteristics (KCs), we have developed 10 KCs of EDCs based on our knowledge of hormone actions and EDC effects as follows: 1) Interacts with or activates hormone receptors, 2) antagonizes hormone receptors; 3) alters hormone receptor expression; 4) alters signal transduction in hormone receiving cells; 5) induces epigenetic modifications in hormone producing or receiving cells; 6) alters hormone synthesis; 7) alters hormone transport across cell membranes; 8) alters hormone distribution or circulating hormone levels; 9) alters hormone metabolism or clearance; and 10) alters fate of hormone producing or receiving cells. We describe the logic by which these KCs are identified and the assays that could be used to assess several of these KCs.

Conclusions: We reflect on how these 10 KCs can be used to identify, organize and utilize mechanistic data when evaluating chemicals as EDCs, and use diethylstilbestrol, bisphenol A, and perchlorate as examples to illustrate this approach.

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Michele A. La Merrill learned her Ph.D. in Toxicology from the University of North Carolina, Chapel Hill and her M.P.H. in epidemiology at the Mount Sinai School of Medicine. Dr. La Merrill is an Associate Professor of Environmental Toxicology at the University of California, Davis. She served on an International Agency for Research on Cancer Monograph that evaluated pesticides as potential carcinogens and is a current appointee of the California Carcinogen Identification Committee.

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Application of the key characteristics of carcinogens in IARC Monographs

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Background: The key characteristics (KCs) of carcinogens have recently been introduced to facilitate systematic consideration of mechanistic evidence in IARC Monograph evaluations.

Methods/Approach/Results: KCs have been applied in evaluations of more than 50 mechanistically diverse chemicals and complex exposures classified into Groups 1, 2A, 2B, and 3 by IARC Monographs expert Working Groups since 2015. Further, in 2019 amendments, the IARC Monographs Preamble has adopted an approach based the KCs approach. Because they are based on empirical observations of properties associated with known carcinogens rather than on an a priori hypothesis about a mechanism of action, the KCs provide an agnostic and unbiased survey of the mechanistic literature. This improved uniformity across evaluations of mechanistically diverse agents reveals strengths as well as gaps in evidence and highlights mechanistic similarities and differences. However, some challenges, including in interpreting evidence on individual KCs were also identified and are addressed in the amended Preamble. For instance, as non-carcinogens can also induce oxidative stress, and thus evidence of this KC alone should be interpreted with caution. The Preamble also provides guidance on evaluating the quality of study design, exposure assessment methods, and biologic assay validity and reliability for human mechanistic studies. Similarly, quality considerations are emphasized in the review of studies in experimental systems.

Conclusions: In all, the KCs approach provides for a rigorous review of the relevant mechanistic evidence. In the Preamble revision, this approach was taken forward to harmonize approaches to evidence evaluation across scientific disciplines, leading to a single-step integration of mechanistic, animal bioassay, and human cancer evidence streams. As such, the amended Preamble includes important advancements to prepare for future advances in molecular research aimed at identifying the causes of human cancer, the first step in cancer prevention.

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Dr. Guyton is a Senior Toxicologist at the International Agency for Research on Cancer (IARC), where she contributes leadership and expertise in toxicology and carcinogen mechanisms to the Monographs, an authoritative reference on the causes of human cancer. Dr. Guyton earned her BA (cum laude) and her PhD degrees from Johns Hopkins University, and completed her postdoctoral training at the National Institutes of Health. Dr. Guyton has been certified as a Diplomate of the American Board of Toxicology since 1998.

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Key characteristics of bioactive chemicals

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Background: The great majority of synthetic chemicals have never been tested for their biological activity. For the relatively small number (

Approach: Their bioactivity may be driven by Key Characteristics of Bioactivity, which parallel many of the key characteristics of carcinogens (KCs), reproductive toxicants, and endocrine disruptors. Some of these include: receptor binding; interaction with DNA; induction of epigenetic alterations; electrophilic or metabolic activity; induction of oxidative stress. Other characteristics may include bioaccumulation, biopersistence, and resistance to biotransformation. A chemical need not possess all characteristics to be bioactive.

Results: How the bioactivity of a chemical will be manifested is determined by the dose and many other factors such as the inherent susceptibility of the organism (e.g., age, sex, genetics, past history), and the timing of the exposure, such as acute high level vs chronic low dose.

Conclusions: By understanding the KCs of bioactive environmental chemicals, we hope to better understand the mechanistic basis of chemical hazards and target limited research resources to answer questions that the public and regulators can use to make better health-protective decisions.

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Dr. Birnbaum has just retired from the US government after 40 years of service. For the past 10+ years, she has been Director of the NIEHS and NTP. She is former President of the Society of Toxicology, Vice-President of the International Union of Toxicology, and Chair of the Division of Toxicology in the American Society of Pharmacology and Therapeutics. She is a member of the US National Academy of Medicine and the Collegium Ramazzini.