CARCINOGENESIS

Specialty Section | Society of Toxicology | Founded 1986

In this issue:

Current CSS Officers

SOT | Society of Toxicology

Creating a Safer and Healthier World by Advancing the Science and Increasing the Impact of Toxicology

Letter from the President

Dear CSS members,

Greetings from the Board of Carcinogenesis Specialty Section! We hope that each of you and your loved ones are staying safe and healthy during the winter season and looking forward to enjoying the warm weather of the Spring!

The 2024 Annual Meeting in Salt Lake City is just around the corner, and we are expecting a great turnout. As a reminder, the CSS reception will be held Monday, March 11 from 6:00 PM - 7:30 PM in Aspen, Hyatt Regency. We cordially invite you to join us in congratulating our award winners. We will also introduce the newly elected officers. The incoming CSS President, Dr. John Wise, Sr. will provide his prospective on what the upcoming year will hold, and we will also hear from the winners of the James A. Swenberg Carcinogenesis Merit Award for Junior Faculty and the Environmental Carcinogenesis Young Investigator Award. There will be plenty of food and a cash bar, so please join us for a fun evening of catching up with old friends and networking with new colleagues.

This year, the board members of the CSS and our members have been continually active as always. I would like to thank our program committee who reviewed several great proposals seeking endorsement. It is again time to think about proposals for carcinogenesis related topics for continuing education, symposia, workshops, and roundtables for the 64th Annual Meeting held from March 16-20 at Orange County Convention Center in Orlando, FL. If you have a proposal that CSS could sponsor, please contact us. We would be happy to work with you to improve the chances of it being accepted.

Connect with CSS

I would like to thank our communications committee led by Kelly, Jon, Haiyan, and Idoia who produced two high quality newsletters over the last year. Please continue to send us your news/achievements for highlighting in our future newsletters. I would also like to thank CSS Councilor June Yan for representing CSS and organizing the recent webinar with Women in Toxicology SIG, which attracted many domestic and international attendees.

I look forward to seeing you all at our annual reception! I am excited to welcome you to Salt Lake City,

Sincerely,

Jia-Sheng Wang, PhD, ATS Fellow

SOT SALT LAKE CITY MARCH 10–14

Please join us!

The Carcinogenesis Specialty Section Meeting/Reception

is to be held at:

Hyatt Regency
Aspen Room

Monday, March 11th
6:00 PM - 7:30 PM (Mountain)

Join the Carcinogenesis Specialty Section for our Business Meeting and Reception. The event will include:

- a report of Section activities over the past year,
- award announcements,
- introductions of the 2024-2025 officers, and
- ample networking opportunities to connect with colleagues.

This event is open to all in-person Annual Meeting attendees interested in joining the Section, regardless of current membership status with the group.

SOT 2024 CSS Sponsored Events:

Tuesday, March 12, 4:45 PM to 6:15 PM, Grand Ballroom E, Salt Palace Convention Center

(S) Symposium Session: Long Non-coding RNA Dysregulations in Metal Toxicity and Carcinogenesis

Chair(s): Chengfeng Yang, Stony Brook University; and Yvonne Fondufe-Mittendorf, Van Andel Institute.
Primary Endorser: Metals Specialty Section
Other Endorser(s): Carcinogenesis Specialty Section; Mechanisms Specialty Section

Thursday, March 14, 8:30 AM to 11:15 AM, Room 251 A, Salt Palace Convention Center

(S) Symposium Session: Error-Corrected Next-Generation Sequencing Strategies for Direct Assessment of Mutagenesis and Early Identification of Cancer Risk IAT

Chair(s): Connie Chen, HESI; and Stephanie Smith-Roe, NIEHS/DTT.
Primary Endorser: Drug Discovery Toxicology Specialty Section
Other Endorser(s): Carcinogenesis Specialty Section; Regulatory and Safety Evaluation Specialty Section

Tuesday, March 12, 8:00 AM to 10:45 AM, Grand Ballroom F, Salt Palace Convention Center

(IS) Informational Session: Five Decades of Evaluating the Safety of Aspartame Consumption: Has Anything Changed?

Chair(s): Susan Borghoff, ToxStrategies LLC; and Sabine Francke, US FDA/CFSAN.
Primary Endorser: Food Safety Specialty Section
Other Endorser(s): Carcinogenesis Specialty Section; Regulatory and Safety Evaluation Specialty Section

CSS Leadership Welcomes Our New Members!:

Ghazwan Mohammed Raouf
Amber Goetz
Thomas Nolte
Michael Stevens
Josiane Weber Tessmann
Hollie Skaggs
Anthony Su
Iris Camacho
Fatai Salaudeen
Lissah Johnson
Michael DeLorme
Ruixin (Rachel) Hao
Luigi Manzo
Lu Cai
Amir Shadboorestan
Vipendra Singh
Bonnie Ransom Stern
Aleksandra Buha
Catia F. Marques
Kathleen Newhouse

Celebrating Member Accomplishments

Publications

Raouf GA, Mohammad FK, Merza MA. 2023. Polypharmacy and the In Silico Prediction of Potential Body Proteins Targeted by These Drugs Among Hospitalized COVID-19 Patients With Cytokine Storm. Cureus. 15(11):e48834. .

Raouf GA, Qader M, Abdullah I, Younis O, Mohammad F, Merza M. 2023. Detection of SARS-CoV-2 variants among travelers crossing the northern international border checkpoint in Duhok province, Iraq. J. Ideals Health [Internet]. 6(4):971-04.

Zeiger, E. 2023. Determination of a positive response in the Ames Salmonella mutagenicity assay. Environ Mol Mutagen 64: http://doi.org/10.1002/em.22538

Seo JE, **Li X**, Le Y, Mei N, Zhou T, Guo X. 2023. High-throughput micronucleus assay using three-dimensional HepaRG spheroids for in vitro genotoxicity testing. Arch Toxicol. 97(4):1163-1175.

Li X, Le Y, Seo JE, Guo X, Li Y, Chen S, Mittelstaedt RA, Moore N, Guerrero S, Sims A, King ST, Atrakchi AH, McGovern TJ, Davis-Bruno KL, Keire DA, Elespuru RK, Heflich RH, Mei N. 2023. Revisiting the mutagenicity and genotoxicity of N-nitroso propranolol in bacterial and human in vitro assays. Regul Toxicol Pharmacol. 141:105410.

Chen S, **Li X**, Li Y, He X, Bryant M, Qin X, Li F, Seo JE, Guo X, Mei N, Guo L. 2023. The involvement of hepatic cytochrome P450s in the cytotoxicity of lapatinib. Toxicol Sci. 197(1):69-78.

Li Y, **Li X**, Cournoyer P, Choudhuri S, Guo L, Chen S. 2023. Induction of apoptosis by cannabidiol and its main metabolites in human Leydig cells. Arch Toxicol. 97(12):3227-3241.

Publications (con't)

Thakkar S, Slikker W, Yiannas F, Silva P, Blais B, Rei Chng K, Liu Z, Adholeya A, Pappalardo F, da Luz Carvalho Soares M, Beeler P, **Roberts R,** et al. 2023. Artificial intelligence and real-world data for drug and food safety – A regulatory science perspective. Regulatory Toxicology and Pharmacology, 140, 105388 https://doi.org/10.1016/j.yrtph.2023.105388.

Gori GB, Aschner A, Borgert CJ, Cohen SM, Dietrich DR, Galli CL, Greim H**, Roberts R,** et al. 2023. US regulations to curb alleged cancer causes are ineffectual and compromised by scientific, constitutional and ethical violations. Archives of Toxicology, 97, 1813-1822. https://doi.org/10.1007/s00204-022-03429-5.

Connor S, Li T, **Roberts R**, Thakkar S, Liu Z, Tong W. 2023. Adaptability of AI for safety evaluation in regulatory science: A case study of drug-induced liver injury. Frontiers in Artificial Intelligence, 8, 1034631. https://Doi.10.3389/frai.2022.1034631

Roberts R, Jones D. 2023. Science-led regulatory strategies in nonclinical development of new medicines. Toxicology Research https://doi.org/10.1093/toxres/tfad017

Chung K, House JS, Akhtari FS, Makris KC, Langston MA, Islam KT, Holmes P, Chadeau-Hyam M, Smirnov AI, Du X, Thessen AE, Cui Y, Zhang K, Manrai AK, Motsinger-Reif A, Patel CJ, Members of the Exposomics Consortium. 2024. Decoding the exposome: data science methodologies and implications in exposome-wide association studies (ExWASs), Exposome, 4(1): osae001 https://doi.org/10.1093/exposome/osae001

Murray J, Bhatt P, Cox L, **Roberts RA.** 2024. Academic Drug Discovery: Challenges and Opportunities. Drug Discovery Today. 29, Online ahead of print https://doi.org/10.1016/j.drudis.2024.103918.

Coltman NJ, **Roberts RA**, Sidaway JE. 2023. Data science in drug discovery safety: Challenges and opportunities. Experimental Biology and Medicine, 248(21):1993-2000. https://doi:10.1177/15353702231215890I

Publications (con't)

Chen X, **Roberts R**, Liu Z, Tong W. 2023 A generative adversarial network model alternative to animal studies for clinical pathology assessment. Nature Communications 14, 7141-7148. https://doi.org/10.1021/acs.chemrestox.3c00037

Wu J, Ouyang J, Qin H, Zhou J, **Roberts R**, Siam R, Wang L, Tong W. 2023. PLM-ARG: antibiotic resistance gene identification using a pretrained protein language model. Bioinformatics 39, btad690. https://doi.org/10.1093/bioinformatics/btad690

Rockley, K, **Roberts, R**, Jennings, H, Jones, K, Davis, K, Levesque, P and Morton, M. 2023 An integrated approach for early in vitro seizure prediction utilising hiPSC neurons and human ion channel assays. Toxicol Sci, https://doi.org/10.1093/toxsci/kfad087.

Li, T, **Roberts, R**, Liu, Z, Thakker, S and Tong, W. 2023. DeepAmes: A deep learning-powered Ames test predictive model with potential for regulatory application, Regulatory Toxicology and Pharmacology, 144, 105486. https://doi.org/10.1016/j.yrtph.2023.105486

Li, T, **Roberts, R**, Liu, Z and Tong, W. 2023. TransOrGAN: An Artificial Intelligence Mapping of Rat Transcriptomic Profiles between Organs, Ages, and Sexes. Chemical Research in Toxicology. 36, 916-925. https://doi.org/10.1021/acs.chemrestox.3c00037

Chen, X, **Roberts, R**, Liu, Z and Tong, W. 2023. AnimalGAN: A Generative Adversarial Network Model Alternative to Animal Studies for Clinical Pathology Assessment. https://doi.org/10.1101/2023.03.25.534230

Zeiger E. 2023. "Inter-laboratory Studies of the Ames Test – What Are They and Why Do Them?" Invited presentation (via Zoom) at the XVI MutaGen Congress. Londrina, Brazil. October 2023.

We want to hear from you! Save your accomplishments and look out for a request to share late 2024!

Presentations

Raouf GA. 2023. Toxic impacts of SARS-CoV-2 variants and anti-viral potential effects in hospitalized patients in Duhok province (Presented in the 2nd Scientific Conference of the College of Health Sciences Hawler Medical University); https://hmu.edu.krd/announcements-of-health-sciences/1555-the-second-scientific-conference-of-the-college-of-health-sciences

Bisson, W. 2023. Environmental chemical mixtures and cancer hallmarks – new developments and open questions. Talk: The Halifax Project 10 years later: what we've learned and what we are still missing on the cumulative carcinogenic effect of environmental chemicals. EUROTOX CONGRESS 2023- September 2023- Ljubljana, Slovenia.

Book Chapters

Pecquet AM, Haber LT. 2023. Noncancer Risk Assessment: Principles and Practice in Environmental and Occupational Settings. In: Patty's Toxicology. (eds E. Bingham, B. Cohrssen and C.H. Powell). pp. 1-45. https://doi.org/10.1002/0471125474.tox005.pub3

Pecquet AM, Bates C, Maier A. 2023. Toxicology of Flavors in the Food Industry. In: Patty's Toxicology. (eds E. Bingham, B. Cohrssen and C.H. Powell). pp. 1-68. https://doi.org/10.1002/0471125474.tox114.pub3.

Awards

Cohen, S. 2023. International Achievement Award from the International Society of Regulatory Toxicology and Pharmacology

Cohen, S. 2024. Presented the IATP sponsored Robert Maronpot Lecture at the Japanese Society of Toxicologic Pathology

Cohen, S. 2024. Will receive the Founders Award at the upcoming Society of Toxicology meeting in Salt Lake City

Recent CSS Webinar

Carcinogenomics - Assessing the tumorigenic potential of chemicals through genomic biomarkers to reduce the reliance on the rodent cancer bioassay

February 23rd, 2024
10:00AM to 11:00AM EST

As part of the safety assessment for new agrochemicals and pharmaceuticals, the rodent cancer bioassay has been a long-required study for regulatory assessment of carcinogenic hazard and risk. There is growing recognition across broad sectors of the scientific community that the use of genomic biomarkers has the potential to reduce the need for conventional rodent carcinogenicity studies of industrial chemicals, agrochemicals, and pharmaceuticals through a weight-of-evidence approach. The goal of this research is to construct and qualify liver transcriptomic biomarkers of key molecular initiating events (MIE) in short-term rat studies that inform on liver tumorigenic risk in the rodent cancer bioassay. This webinar describes a collaborative approach launched to develop and qualify biomarker gene expression panels that measure widely accepted molecular pathways linked to tumorigenesis and their activation levels to predict tumorigenic doses of chemicals from short-term exposures. Success from these efforts will facilitate the transition from current heavy reliance on conventional rodent cancer bioassays to more rapid animal-and-resource-sparing approaches for mechanism-based carcinogenicity evaluation, supporting internal and regulatory decision making.

Speaker: Chris Corton, Ph.D., Research Biologist, US Environmental Protection Agency
Talk: Knock-out study overview and progress to date, including the plans for next steps following this research currently in progress.

Speaker: Connie Mitchell, Ph.D., Senior Scientific Program Manager, Health and Environmental Sciences Institute
Talk: Goals and objectives of the carcinogenomics project.

Speaker: Udayan Apte, PhD, Professor, University of Kansas Medical Center
Talk: Regulatory perspective and background to this project.

Did you miss it?
The recording of this webinar can be accessed on our website!

The Utility of the Key Characteristic (KC) Approach in the Identification of Carcinogenic Hazards to Humans

By Janice Britt, PhD, ERT, Managing Scientist
ToxStrategies, LLC

The Key Characteristics (KC) of carcinogens are an approach by which to evaluate mechanistic evidence as part of a cancer hazard identification (IARC, 2019; Smith et al., 2020). The KC are also sometimes referred to as the key characteristics of carcinogens or KCC (see Table 1). KC data can include evidence from exposed humans, *in vitro* studies using human cells, *in vivo* or *in vitro* animal studies, studies on alternate species such as fish or invertebrates, as well as high-content and/or high-throughput data. The KC were first identified as the result of IARC workshops held in 2012 which were later described in various publications (e.g., Smith et al., 2016, 2020; Guyton et al., 2018), and incorporated into the revised IARC Monograph's Preamble in 2019. It should be noted that the KC, which describe the properties of carcinogens that induce cancer, differ from Hanahan and Weinberg's "Hallmarks of Cancer," which describe the acquired properties of cancer cells (Smith et al., 2020; Hanahan, 2022). The KC have been used in the IARC Monograph process since 2015 (Rusyn and Wright, 2023) and have become an important part of IARC's decision-making process in the identification of an agent's carcinogenic hazard, especially when human data are inadequate (see Table 2) (Meek and Wikoff, 2023). In addition, the KC are used by the US National Toxicology Program, the California Office of Health Hazard Assessment, and others in their carcinogen evaluation processes.

KC are not necessarily "cancer mechanisms" but can be useful when included into the early organizational stages of a hazard assessment, e.g., when developing literature searches, screening approaches, and identification of mechanistic information and data (Wikoff et al., 2019). Some of the limitations of the use of KC include the lack of guidance to assess the biological meaning of various mechanistic endpoints, inter- and intra-individual variability, study quality, integration of the mechanistic data relative to toxicological and/or epidemiological data, and possible false positives (Wikoff et al., 2019; Smith et al., 2021). In addition, it should be kept in mind that these characteristics are not necessarily unique to chemicals that cause cancer. For example, oxidative stress (KC5), can be caused by stress, excessive exercise, or eating certain foods (Thorat and Kakade, 2021). Also, there are currently no formally accepted testing framework for the KCs or guidance by which to interpret the results of findings to determine whether an agent presents a carcinogenic hazard to humans. A recent analysis of IARC monographs by Rusyn and Wright (2023) underscores the degree to which subject matter expertise is utilized to make determinations on how informative an agent's KC profile might be to a carcinogenicity classification. It should be noted that KCs have also been used in association with various non-cancer endpoints including endocrine disruption, cardiovascular toxicity, reproductive toxicity, liver toxicity, neurotoxicity, developmental neurotoxicity, and immunotoxicity (https://keycharacteristics.org/). Overall, the KCs are a useful tool for organizing mechanistic data for subsequent evaluation of mode of action or biological plausibility (Meek and Wikoff, 2023).

Table 1: The key characteristics of carcinogens described by Smith et al. (2016).

Ten key characteristics of carcinogens
1. Is electrophilic or can be metabolically activated to an electrophile
2. Is genotoxic
3. Alters DNA repair or causes genomic instability
4. Induces epigenetic alterations
5. Induces oxidative stress
6. Induces chronic inflammation
7. Is immunosuppressive
8. Modulates receptor-mediated effects
9. Causes immortalization
10. Alters cell proliferation, cell death, or nutrient supply

Source: IARC Preamble (2019).

Table 2: Integration of streams of evidence in reaching overall classifications (the evidence in *bold italics* represents the basis of the overall evaluation).

Stream of evidence			Classification based on strength of evidence
Evidence of cancer in humans[a]	**Evidence of cancer in experimental animals**	**Mechanistic evidence**	
Sufficient	Not necessary	Not necessary	**Carcinogenic to humans (Group 1)**
Limited or Inadequate	***Sufficient***	***Strong (b)(1) (exposed humans)***	
Limited	***Sufficient***	Strong (b)(2–3), Limited, or Inadequate	**Probably carcinogenic to humans (Group 2A)**
Inadequate	***Sufficient***	***Strong (b)(2) (human cells or tissues)***	
Limited	Less than Sufficient	***Strong (b)(1–3)***	
Limited or Inadequate	Not necessary	***Strong (a) (mechanistic class)***	
Limited	Less than Sufficient	Limited or Inadequate	**Possibly carcinogenic to humans (Group 2B)**
Inadequate	***Sufficient***	Strong (b)(3), Limited, or Inadequate	
Inadequate	Less than Sufficient	***Strong b(1–3)***	
Limited	***Sufficient***	***Strong (c) (does not operate in humans)[b]***	
Inadequate	***Sufficient***	***Strong (c) (does not operate in humans)[b]***	**Not classifiable as to its carcinogenicity to humans (Group 3)**
All other situations not listed above			

[a] Human cancer(s) with highest evaluation

[b] The *strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans* must specifically be for the tumour sites supporting the classification of *sufficient evidence in experimental animals*.

Source: IARC Preamble (2019).

References:

Guyton KZ, Rusyn I, Chiu WA, Corpet DE, van den Berg M, Ross MK, Christiani DC, Beland FA, Smith MT. 2018. Application of the key characteristics of carcinogens in cancer hazard identification. Carcinogenesis. 39(4):614-22.

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

Meek ME, Wikoff D. 2023. The need for good practice in the application of mechanistic constructs in hazard and risk assessment. Toxicological Sciences. April 19:kfad039.

Rusyn I, Wright FA. 2023. Ten years of using key characteristics of human carcinogens to organize and evaluate mechanistic evidence in IARC Monographs on the identification of carcinogenic hazards to humans: Patterns and associations. Toxicological Sciences. Dec 23:kfad134.

Smith CJ, Perfetti TA, Hayes AW, Berry SC, Trosko JE, King JA, Goodman JI, Begley CG, Dayan A. 2021. Categorizing the characteristics of human carcinogens: a need for specificity. Archives of Toxicology. 95:2883-9.

Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, DeMarini DM, Caldwell JC, Kavlock RJ, Lambert PF, Hecht SS. 2016. Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. Environmental Health Perspectives. 124(6):713-21.

Smith MT, Guyton KZ, Kleinstreuer N, Borrel A, Cardenas A, Chiu WA, Felsher DW, Gibbons CF, Goodson III WH, Houck KA, Kane AB. 2020. The key characteristics of carcinogens: relationship to the hallmarks of cancer, relevant biomarkers, and assays to measure them. Cancer Epidemiology, Biomarkers & Prevention. 29(10):1887-903.

Thorat PR, Kakade VV. 2021. A Review On: “Oxidative Stress: Harms and Benefits for Human Health”. Int J Pharma Research Applications. 6:110-1016.

Wikoff DS, Rager JE, Chappell GA, Fitch S, Haws L, Borghoff SJ. 2019. A framework for systematic evaluation and quantitative integration of mechanistic data in assessments of potential human carcinogens. Toxicological Sciences. 167(2):322-35.