APPLIED PHARMACOLOGY AND TOXICOLOGY, INC.

Consulting & Research Services

Censorship and issue-specific advocacy: Is "consensorship" the new paradigm?

SOT Webinar
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Virtual Meeting

Christopher J. Borgert, PhD
cjborgert@apt-pharmatox.com

What is Scientific "Consensus"

Scientific Consensus is a state in which the range of interpretations consistent with a sufficiently probative dataset is so narrow as to have no practical significance. [CJB]

Science is a process wherein facts are asked to speak for themselves to enhance objectivity, and by which consensus can be achieved only as an increasingly broad and probative dataset narrows the range of interpretations consistent with the data.

Compromise and vote are anathema, as competing theories vie for prominence on the merits of the evidence rather than on the agreement of affiliated practitioners.

Borgert CJ. 2007. Conflict of interest or contravention of science? *Regul Toxicol Pharmacol*. 48: 4-5.
Borgert CJ. 2007. Conflict of interest: kill the messenger or follow the data? *Environ Sci Technol*. 41: 665.

Summary

"*Consensorship*" is a term invented by the author to convey the intersection of two claims that are increasingly advanced in controversial areas of science:

1. There is "consensus" among the experts, therefore, the science is settled.
2. Since there is "consensus," those who disagree are simply "deniers"
    a. Deniers' motives and intelligence is suspect
    b. Deniers' views need not and should not be heard
3. "Endocrine Disruptors" is a prime example of the advancement of *Consensorship*
4. *New examples covered in this presentation:*
    a. LNT (Linearized No-Threshold Model)
    b. Key Characteristics
    c. SAB-Packing

Example: Blatant Consensorship

Brescia S. 2020. Thresholds of adversity and their applicability to endocrine disrupting chemicals. Crit Rev Toxicol. 1-6.

"It is often argued that in the developing organism, homeostatic mechanisms are not sufficiently developed such that a threshold of adversity cannot be assumed for EDs acting during the developmental stages of the life cycle of an organism (Zoeller et al. 2012). Again, this position is rather extreme and not supported by decades of observations and safety testing of developmental toxicants, with little evidence suggesting that the fundamental rules governing endocrine function cease to apply during this life stage (Borgert et al. 2013)."

The first author of Brescia's citation for this statement has been barred from "EDC Advocacy Strategy" sessions of The Endocrine Society, of which he is a full member . . . because . . .according to Mila Becker, Chief Policy Officer of the Endocrine Society:

" I'm sorry. This is a policy session that is bringing together people who have endorsed the Society's official policy on EDCs. You have said quite publicly that you disagree with that…"

Consensorship is not new: *the LNT scandal - 1*

Year	Event
1927	Herman J. Muller demonstrates that ionizing radiation caused mutations in germ cells of male fruit flies. Muller worked hard to convince others of the implication of his findings; in the era of the nuclear bomb, he focused on the broad implications to humans exposed to radiation. Evolutionary geneticists used this discovery to argue a mechanism for evolution. **Both arguments were undermined by the existence of a threshold for radiation effects**
1946	Herman J. Muller awarded Nobel Prize for 1927 discovery In his acceptance speech, Muller claimed there was no longer any doubt that the dose-response for radiation lacked a threshold [CONSENSUS claimed] • Muller knew of contractory data and ignored it; • Muller side-stepped the fact this experiments were conducted at radiation doses thousands of times higher than human exposures (1,000 chest X-rays in 3.5 minutes); • Muller and his long-time colleague, esteemed radiation geneticist Curtis Sterns collaborated to repress publications showing a dose-threshold, including data from Sterns' own laboratory, and limit the participation of 'deniers' in NAS BEARS Panel [CONSENSORSHIP ACHIEVED]

Consensorship is not new: *the LNT scandal - 2*

1950's	U.S. National Academy of Sciences Biological Effects of Atomic Radiation panel (BEAR) – Muller and Stern worked to solidify agreement with the LNT theory of radiation dose-response.
1977	U.S. EPA adopts LNT for carcinogens under Safe Drinking Water Act
2019	Golden R, Bus J, Calabrese E. 2019. An examination of the linear no-threshold hypothesis of cancer risk assessment: Introduction to a series of reviews documenting the lack of biological plausibility of LNT. *Chem Biol Interact*. 301: 2-5.

Calabrese EJ. 2013. How the US National Academy of Sciences misled the world community on cancer risk assessment: new findings challenge historical foundations of the linear dose response. *Arch Toxicol*.

Calabrese EJ. 2015. An abuse of risk assessment: how regulatory agencies improperly adopted LNT for cancer risk assessment. *Arch Toxicol*.

Calabrese EJ. 2009. The road to linearity: why linearity at low doses became the basis for carcinogen risk assessment. *Arch Toxicol*. 83: 203-225.

Calabrese EJ. 2011. Muller's Nobel lecture on dose-response for ionizing radiation: ideology or science. *Arch Toxicol*. 85: 1495-1498.

Calabrese EJ. 2015. Cancer risk assessment foundation unraveling: new historical evidence reveals that the US National Academy of Sciences (US NAS), Biological Effects of Atomic Radiation (BEAR) Committee Genetics Panel falsified the research record to promote acceptance of the LNT. *Arch Toxicol*. 89: 649-650.

Calabrese EJ. 2019. The linear No-Threshold (LNT) dose response model: A comprehensive assessment of its historical and scientific foundations. *Chem Biol Interact*. 301: 6-25.

Calabrese EJ, Golden RJ. 2019. Why toxicologists resisted and radiation geneticists supported EPA'S adoption of LNT for cancer risk assessment. *Chem Biol Interact*. 310: 108736.

Golden R, Bus J, Calabrese E. 2019. An examination of the linear no-threshold hypothesis of cancer risk assessment: Introduction to a series of reviews documenting the lack of biological plausibility of LNT. *Chem Biol Interact*. 301: 2-5.

Concensorship is alive and well: *Key Characteristics - 1*

- KC Concept: chemicals that produce certain types of adverse effects exhibit common "key characteristics" that serve as distinguishing features.
- Examples
  - Carcinogens (Smith et al., 2017)
  - Male reproductive toxicants (Luderer et al., 2019)
  - Female reproductive toxicants (Arzuaga et al., 2019)
  - Endocrine Disruptors (La Merrill et al., 2020)
- Concept formulated during so-called "expert workshops" (e.g., La Merrill et al., 2020)
- Concepts applied in recent publications
  - Agrochemicals
  - Glyphosate
  - Others – see bibliography

Concensorship is alive and well: *Key Characteristics - 2*

The KCs for EDCs were developed based on KCs for carcinogens.

Flaws in the KC approach for carcinogens have not been addressed or corrected and were repeated in the KCs for EDCs.

Becker RA, Dreier DA, Manibusan MK, Cox LAT, Simon TW, Bus JS. 2017. How well can carcinogenicity be predicted by high throughput "characteristics of carcinogens" mechanistic data. Regul Toxicol Pharmacol. 90: 185-196.

The KC approach requires less data and fewer resources than the WoE approach but lacks the basic elements of rigor and reproducibility that should be a standard requirement for regulatory science.

U.S. House of Representatives, Subcommittee on Energy and Environment, Committee on Energy and Commerce. 2010. Endocrine Disrupting Chemicals in Drinking Water: Risks to Human Health and the Environment. Available: http:// energycommerce.house.gov/hearings/hearingdetail.

Birth Defects Research and Prevention Society 2021 Annual Meeting, Session on Key Characteristics presented only viewpoints favoring the approach. A "response" session will follow in 2022.

Publications on the KC Approach Through December 2020

1. Al-Zoughool M, Bird M, Rice J, Baan RA, Billard M, Birkett N, Krewski D, Zielinski JM. 2019. Development of a database on key characteristics of human carcinogens. *J Toxicol Environ Health B Crit Rev*. 22: 264-287.
2. Arzuaga X, Smith MT, Gibbons CF, Skakkebæk NE, Yost EE, Beverly BEJ, Hotchkiss AK, Hauser R, Pagani RL, Schrader SM, Zeise L, Prins GS. 2019. Proposed Key Characteristics of Male Reproductive Toxicants as an Approach for Organizing and Evaluating Mechanistic Evidence in Human Health Hazard Assessments. *Environ Health Perspect*. 127: 65001.
3. Goodman JE, Lynch HN, Rhomberg LR. 2018. Letter to the editor re: Guyton et al. (2018), 'Application of the key characteristics of carcinogens in cancer hazard identification'. *Carcinogenesis*. 39: 1089-1090.
4. Guyton KZ, Rieswijk L, Wang A, Chiu WA, Smith MT. 2018. Key Characteristics Approach to Carcinogenic Hazard Identification. *Chem Res Toxicol*. 31: 1290-1292.
5. 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: 614-622.
6. Guyton KZ, Rusyn I, Chiu WA, Corpet DE, van den Berg M, Ross MK, Christiani DC, Beland FA, Smith MT. 2018. Re: 'Application of the key characteristics of carcinogens in cancer hazard evaluation': response to Goodman, Lynch and Rhomberg. *Carcinogenesis*. 39: 1091-1093.
7. Krewski D, Bird M, Al-Zoughool M, Birkett N, Billard M, Milton B, Rice JM, Grosse Y, Cogliano VJ, Hill MA, Baan RA, Little J, Zielinski JM. 2019. Key characteristics of 86 agents known to cause cancer in humans. *J Toxicol Environ Health B Crit Rev*. 22: 244-263.
8. La Merrill MA, Vandenberg LN, Smith MT, Goodson W, Browne P, Patisaul HB, Guyton KZ, Kortenkamp A, Cogliano VJ, Woodruff TJ, Rieswijk L, Sone H, Korach KS, Gore AC, Zeise L, Zoeller RT. 2020. Consensus on the key characteristics of endocrine-disrupting chemicals as a basis for hazard identification. *Nat Rev Endocrinol*. 16: 45-57.
9. Luderer U, Eskenazi B, Hauser R, Korach KS, McHale CM, Moran F, Rieswijk L, Solomon G, Udagawa O, Zhang L, Zlatnik M, Zeise L, Smith MT. 2019. Proposed Key Characteristics of Female Reproductive Toxicants as an Approach for Organizing and Evaluating Mechanistic Data in Hazard Assessment. *Environ Health Perspect*. 127: 75001.
10. Muñoz JP, Bleak TC, Calaf GM. 2020. Glyphosate and the key characteristics of an endocrine disruptor: A review. *Chemosphere*. 128619.
11. Nicole W. 2020. Potential Male and Female Reproductive Toxicants: Applying the Key Characteristics Approach. *Environ Health Perspect*. 128: 34001.
12. Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, DeMarini DM, Caldwell JC, Kavlock RJ, Lambert PF, Hecht SS, Bucher JR, Stewart BW, Baan RA, Cogliano VJ, Straif K. 2016. Key Characteristics of Carcinogens as a Basis for Organizing Data on Mechanisms of Carcinogenesis. *Environ Health Perspect*. 124: 713-721.
13. Smith MT, Guyton KZ, Kleinstreuer N, Borrel A, Cardenas A, Chiu WA, Felsher DW, Gibbons CF, Goodson WH, Houck KA, Kane A, La Merrill MA, Lebrec H, Lowe L, McHale CM, Minocherhomji S, Rieswijk L, Sandy MS, Sone H, Wang A, Zhang L, Zeise L, Fielden M. 2020. The Key Characteristics of Carcinogens: Relationship to the Hallmarks of Cancer, Relevant Biomarkers, and Assays to Measure Them. *Cancer Epidemiol Biomarkers Prev*.
14. Temkin AM, Hocevar BA, Andrews DQ, Naidenko OV, Kamendulis LM. 2020. Application of the Key Characteristics of Carcinogens to Per and Polyfluoroalkyl Substances. *Int J Environ Res Public Health*. 17:
15. Vandenberg LN, Najmi A, Mogus JP. 2020. Agrochemicals with estrogenic endocrine disrupting properties: Lessons Learned. *Mol Cell Endocrinol*. 518: 110860.

Concensorship is ubiquitous: *we all play the game*

IN THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF COLUMBIA

DR. S. STANLEY YOUNG, 3401 Caldwell Drive Raleigh, NC 27607,
Plaintiff, *v.*

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY,
1200 Pennsylvania Avenue, NW Washington, DC 20460,
MICHAEL S. REGAN, in his official capacity as Administrator of the EPA,
1200 Pennsylvania Avenue, NW
Washington, DC 20460,
SCIENCE ADVISORY BOARD, 1200 Pennsylvania Avenue, NW Washington, DC 20460,
ALISON C. CULLEN, in her official capacity as Chair of the Science Advisory Board,
1200 Pennsylvania Avenue, NW
Washington, DC 20460,
CLEAN AIR SCIENTIFIC ADVISORY COMMITTEE,
1200 Pennsylvania Avenue, NW Washington, DC 20460, and
ELIZABETH A. SHEPPARD, in her official capacity as Chair of the Clean Air Scientific Advisory Committee,
1200 Pennsylvania Avenue, NW Washington, DC 20460,
Defendants.

Concensorship is ubiquitous: *we all play the game*

Plaintiff Dr. S. Stanley Young, by and through his undersigned attorneys, alleges as follows:

INTRODUCTION

1. The Environmental Protection Agency ("EPA") has a problem with dissent. In an unprecedented purge, EPA eliminated all industry representatives from two important advisory committees in order to stack those committees with academics who are financially beholden to EPA for multi-million dollar research grants. Through this mass dismissal, EPA guaranteed that the committees will rubber stamp the new administration's regulations without the inconvenience of an objecting voice from the very industries targeted by those regulations and bearing the cost of those regulations, to the tune of billions of dollars a year. These newly constituted, industry-free advisory committees are neither fairly balanced nor protected from inappropriate influence in violation of the Federal Advisory Committee Act ("FACA")…..

Defendants contend the last administration did the same.

Conclusions … what do YOU think ….?

- *Is Consensorship Real ?*
- *Is Consensorship Pervasive ?*
- *Is Consensorship increasing ?*
- *If real, pervasive, and increasing how will Consensorship affect new chemistry?*
- *Is Consensorship a problem that scientific societies should address ?*

- *If so, what are the solutions. . .*

. . . . Stay tuned.

Expert Witness Testimony and Ethics: Science Over Advocacy

ELFSI and SCCSOT Webinar Series: Webinar #1

September 23, 2022

Laura M. Plunkett, PhD, DABT

Toxicology and Legal Testimony

- Can be either criminal or civil actions
- Typical areas of testimony by toxicologists
  - Forensic toxicology (cases involving death, injury, intoxication) typically involves interpretation of chemical analyses of tissues and fluids (*e.g.,* blood, vitreous fluid, urine)
  - Causation assessment (linking an injury to exposure)
  - Exposure assessment (including pharmaco-/toxicokinetics)
  - Regulation of chemical substances (state and federal)
- Science not advocacy

Legal Work and Methodology

- Judges perform “gate-keeper” duties related to expert testimony
- State vs. Federal courts may differ in standards applied
- Federal court = Daubert Standard (1993)
  - Assess whether an expert witness’s scientific testimony is based on “scientifically valid reasoning” that which can properly be applied to the facts at issue
  - *The Reference Manual on Scientific Evidence* (3rd Edition)

    (https://nap.nationalacademies.org/catalog/13163/reference-manual-on-scientific-evidence-third-edition)
- Frye Standard (1923)
  - Scientific evidence must be interpreted by the court as "generally accepted" by a meaningful segment of the associated scientific community

Methodology (cont.)

- Methodology used may depend on the area of testimony
  - Weight-of-the-evidence (WOE)
  - “Bradford-Hill” criteria (general causation)
  - Differential diagnosis (specific causation by clinical toxicologist)
  - Human health risk assessment (individuals versus population)
  - “Experience and training”
  - Area-specific methods (*e.g.,* analytical data)
- Toxicologists should choose method(s) appropriate to the scientific questions being asked
- KEY = “sound science” based on “reliable” information

Ethics As a Core Principle

- Toxicologists should adhere to ethical principles in all work, including in the legal arena (science not advocacy)
- “Ethical” in this context is “performing work in accordance with the rules or standards for right conduct or practice, especially the standards of a profession”
- In toxicology, there are several organizations that set forth ethical “standards” such as the SOT, ACT, SOFT
  - Organization websites specify the ethical standards to be adhered to by members (e.g., https://www.soft-tox.org/ethics; https://www.toxicology.org/about/vp/code-of-ethics.asp; https://www.actox.org/about/code-of-ethics.asp)

Key Concerns for Toxicologists

- A toxicologist's role should be
  - Stay within bounds of your training and expertise!
  - To teach complex issues to non-scientists
    - It can be helpful to visually convey complex information
    - Jurors and judges should not be assumed to have a science background
    - In cases where "novel" substances/chemicals are at issue, the "unbiased" viewpoint of the jurors can be important (no pre-conceived opinions)
  - To apply the same methodology in legal work as would be applied outside of court
    - Carefully lay out the scientific methodology used
    - Address the limitations (if any) of the methodology
    - Ensure that you have access to all relevant information (important issue)
  - To acknowledge any biases in methods and/or opinions (credibility)
    - Actual as well as perceived