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April 2024

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Plaintiffs' Flawed Reliance on the So-Called "10 Key Characteristics" of Cancer

Counting Is Not Causation

By Heather Pigman and Marchello Gray

In this article, we will examine the origins of the theory, how it is used by plaintiffs, and how to successfully defend against it.

Plaintiffs in product liability litigation are increasingly using the so-called "10 key characteristics of cancer" to connect plaintiffs' alleged exposure to an alleged carcinogen with the development of cancer. The concept – at least as plaintiffs describe it to juries – is simple:

- Each of the "key characteristics" is a mechanism by which the chemical at issue can cause cancer;
- Plaintiffs' experts will explain to the jury that one or more "key characteristics" are met; and
- Jurors should "check the box(es)" for the "key characteristics" that are met and conclude there is causation.

Plaintiffs' counsel and their experts urge jurors to conclude that if a chemical satisfies even one of these "key characteristics," the mechanism by which the chemical can and does cause cancer is proven and so is causation. This "check the box" approach allows plaintiffs to claim they have established general causation (and perhaps specific causation depending on the expert's qualifications and materials reviewed) without meeting the generally accepted requirements for doing so. It also allows plaintiffs to claim their burden of proof is met by a lower level of evidence (i.e., screening-level mechanistic studies of varying - and often low - quality) than traditionally required (i.e., human data or high-quality rodent data).

In this article, we will examine the origins of the theory, how it is used by plaintiffs, and how to successfully defend against it.

Origins of the 10 KC Theory

In 2000, Hanahan and Weinberg published a paper entitled "The Hallmarks of Cancer." Douglas Hanahan & Robert A. Weinberg, *The Hallmarks of Cancer*, 100 Cell 57 (2000). Noting that cancer is "a disease involving dynamic changes in the genome," they identified four essential changes in cancer cells that control whether or how much cancer grows. "Each of these physiologic changes - novel capabilities acquired during tumor development - represents the successful breaching of an anticancer defense mechanism hardwired into cells and tissues." *Id.* at 57. In 2011, the same authors added two additional hallmarks. These factors are shared by many different cancers and are not unique to one type of cancer or tumor location. The authors noted that the hallmarks were merely features that healthy cells acquire in their transition to cancer cells regardless of the cancer's cause.

In 2016, and in part building off of the Hallmarks of Cancer, a different group of scientists led by Dr. Martyn Smith created a list of "10 key characteristics of carcinogens" as a way to organize mechanistic data when assessing "whether an agent is a potential human carcinogen." Smith et al., 124 Env't Health Persp. at 713. According to the authors, a chemical displays a "key characteristic" if it:

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1. Is electrophilic or can be metabolically activated,
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, or
10. Alters cell proliferation, call death or nutrient supply.

Id. at 714.

Like the Hallmarks, these characteristics were derived from features seen in cancer cells, not from the properties of substances that may cause cancer. This fact was made clear in the paper:

> Herein we describe these 10 key characteristics and discuss their importance in carcinogenesis. These characteristics are properties that human carcinogens commonly show and can encompass many different types of mechanistic endpoints. They are not mechanisms in and of themselves nor are they adverse outcome pathways. Further, we describe how the 10 key characteristics can provide a basis for systematically identifying, organizing, and summarizing mechanistic information as part of the carcinogen evaluation process.

Id. at 714; *see also* at 719 ("These characteristics, although not necessarily representing mechanisms themselves, provide the rationale for an objective approach to identifying and organizing relevant mechanistic data.").

In essence, the authors propose the use of characteristics seen in cancer cells to organize/prioritize the assessment of mechanistic data and to assess possible cancer hazards prior to conducting a full cancer risk assessment. *Id*. at 719 ("This approach also lays the groundwork for a structured evaluation of the strength of the mechanistic evidence base, and therefore its utility in supporting hazard classifications."). The authors contend that the presence of more than one of the "key characteristics" provides stronger evidence of a potential mechanism than satisfying only one "key characteristic." *Id*. at 714.

However, while the authors compare their list to two chemicals deemed by IARC to be known carcinogens, *id*. at 714, they do not apply their approach to known non-carcinogenic compounds. In fact, the "key characteristics" have not been validated against non-carcinogens, as would be necessary to support a causation analysis.

The authors acknowledge the weaknesses inherent in the approach they suggest. They concede that the proposed organizational system is difficult to translate to some chemicals and that it "would not permit comparisons across agents, including attempts to understand similarities or differences with human carcinogens." They also note that use of the "10 key characteristics" method to organize data "may be biased against the most recent mechanistic and molecular epidemiology studies that have not been the subject of a prior expert review." *Id*. at 714.

Comparing the "key characteristics" to substances deemed carcinogenic by IARC also ignores the suspect nature of IARC's own cancer classifications, including but not limited to the facts that IARC 1) conducts a hazard rather than human health risk assessment, 2) frequently prioritizes lower weight animal and mechanistic data over human data, and 3) adopted a protocol that prohibits it from reviewing all the relevant data. *See, e.g.*, Angela Logomasini, *U.S. Should Stop Funding the International Agency for Research on Cancer*, Competitive Enter. Inst. (Sept. 18, 2018), ***https://cei.org/studies/u-s-should-stop-funding-the-international-agency-for-research-on-cancer.***

At most, according to its creators, the "key characteristics" "provide guidance for further assessments of the science behind the chemical, including dose relevance, species relevance, and temporality of events." Smith et al., 124 Env't Health Persp. at 718. Simply possessing one or more characteristics does not establish that the substance causes cancer or that a specific plaintiff's injuries were caused by the substance at issue.

In the wake of Smith et al. 2016, several of the same authors applied the "key characteristics" approach to other chemicals IARC had already found to be carcinogenic or probably carcinogenic. Kathryn Z. Guyton et al., *Application of the Key Characteristics of Carcinogens in Cancer Hazard Identification*, 39 Carcinogenesis 614 (2018). Not surprisingly, they concluded that of 35 chemicals reviewed, only five did not meet one or more of the "key characteristics."

The lack of scientific rigor and potential biases by those who created the "key characteristics" concept as applied to unproven carcinogens have been noted in the scientific literature. For example, one set of authors noted the following critiques:

- "In addition, simply counting how many KCs known or probable carcinogenic agents possess is not informative regarding whether the approach is useful and accurate, on the whole. Rather, external validation of the methodology is needed, and in particular, it must be shown that these KCs can differentiate carcinogens from non-carcinogens. Guyton et al. (3) did not evaluate whether agents deemed non-carcinogens may also show evidence for KCs."
- "Perhaps even more importantly, in Table 3, Guyton et al. (3) stated the number of studies that addressed KCs for each agent, and simply checked off which KC is 'supported' by that evidence. However, as discussed in detail by Goodman and Lynch, IARC does not determine the level of support for KCs for each agent via a systematic evaluation of the literature; it does not consider the quality, external validity or relevance of each study, or whether evidence is consistent within and among KCs (6). A study merely has to have a positive finding, regardless of its quality, validity or consistency with other studies, for IARC to conclude it supports some evidence for a KC. Thus, determinations regarding the strength of a particular characteristic appear ad hoc, are not transparent, and cannot be objectively replicated by independent experts."
- "Guyton et al. briefly discussed a few examples of other weaknesses of the KC approach, including critical technical limitations of mechanistic evidence in general, such as difficulties in validation and extrapolation of in vitro to in vivo exposure levels, as well as the need for uniformity of evaluations through 'documentation and clarification of procedures by the IARC Secretariat'

(3). However, there was no thoughtful discussion of the implications of these various limitations on the utility of the KC approach. In fact, these issues may lead to false-positive results; i.e., a conclusion that an agent possesses a given KC, when the evidence as a whole does not indicate that it does."

- "As discussed by Goodman and Lynch, the KC approach may prove to be very helpful in identifying and classifying carcinogens (6). However, it needs to include a consideration of the biological significance of mechanistic endpoints, inter- and intra-individual variability, study quality and study relevance. It should explicitly address how mechanistic evidence should be integrated, and how it should be considered in light of other realms of evidence. Until this is done, the KC approach will have limited utility in evaluations of cancer hazards."

Although the "key characteristics" do not determine carcinogenicity, plaintiffs present them to juries as a useful checklist to assess complex mechanistic data

Julie E. Goodman, et al., *Letter to the Editor Re: Guyton et al. (2018), 'Application of the Key Characteristics of Carcinogens in Cancer Hazard Identification,'* 39 Carcinogenesis 1089 (2018). Not surprisingly, the authors of Guyton 2018 disagreed and defended their approach. Kathryn Z. Guyton et al., *Re: 'Application of the Key Characteristics of Carcinogens in Cancer Hazard Identification': Response to Goodman, Lynch and Rhomberg*, 39 Carcinogenesis 1091 (2018).

Although some regulatory agencies consider "key characteristics" as one of many parts of their scientific analysis, use of the "key characteristics" as a causation assessment tool is not supported in science or by courts that have addressed it. For example, in the pending *In re Zantac (Ranitidine) Products Liability Litigation*, the court declined to consider the plaintiffs' experts testimony regarding the "10 key characteristics" in excluding their testimony under *Daubert* and FRE 703. As the court noted:

> The Court does not consider the mechanistic in vitro studies and the IARC 10 Key Characteristics of Carcinogens upon which the Plaintiffs' experts relied. In their Response, the Plaintiffs assert generally that their experts rely upon "various mechanistic evidence," including the in vitro studies and the IARC 10 Key Characteristics of Carcinogens. The Plaintiffs' only argument on why relying upon this secondary mechanistic evidence constitutes a reliable methodology is that their experts considered this evidence as part of their weight-of-the-evidence methodologies. Id. The Plaintiffs' mere assertion that their experts followed weight-of-the-evidence methodologies is insufficient to carry their burden that their experts' opinion is reliable.

In re Zantac (Ranitidine) Prod. Liab. Litig., 644 F. Supp. 3d 1075, 1278 n. 164 (S.D. Fla. 2022).

How It Is Used Today in Litigation and Strategies for Defense

Although the "key characteristics" do not determine carcinogenicity, plaintiffs present them to juries as a useful checklist to assess complex mechanistic data, a process with which most jurors will have no scientific training or experience. Their impact on juries can be powerful, and the best defense will depend in large part on the nature of the chemical at issue, the accompanying science, and the operative defense strategy.

For example, for chemicals that the defense acknowledges are potentially carcinogenic at some level, focusing on certain "key characteristic" concepts may be part of a successful specific causation defense strategy. These include:

- The concepts of low exposure and/or internal dose;
- Species-specific mechanistic differences, particularly if animal models are the basis for the plaintiff's identification of a "key characteristic;"
- The presence of the same key characteristics in other, non-carcinogenic compounds;
- The method of exposure and its relationship to potential methods of human exposure;
- The many steps beyond cellular damage that must occur for cancer to develop.

Importantly, these lines of attack are supported by the authors of the "key characteristics" and elsewhere in the scientific literature. For example, Smith et al. 2016 noted:

> In general, the strongest indications that a particular mechanism operates in humans derive from data obtained in exposed humans or in human cells in vitro. Data from experimental animals can support a mechanism by findings of consistent results and from studies that challenge the hypothesized mechanism experimentally. Other considerations include whether multiple mechanisms might contribute to tumor development, whether different mechanisms might operate in different dose ranges, whether separate mechanisms might operate in humans and experimental animals, and whether a unique mechanism might operate in a susceptible group.

Id. at 719; see also U.S. EPA, Guidelines for Carcinogen Risk Assessment at § 1.3, *available at* ***https://www.epa.gov/sites/default/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf*** (last accessed Jan. 12, 2024) (discussing EPA's weight of the scientific evidence evaluation and the components thereof, including dose assessments and the types of evidence considered); *id.* at § 2.2.1 (noting "[e]pidemiologic data are extremely valuable in risk assessment because they provide direct evidence on whether a substance is likely to produce cancer in humans, thereby avoiding issues such as: species-to-species inference, extrapolation to exposures relevant to people, effects of concomitant exposures due to lifestyles. Thus, epidemiologic studies typically evaluate agents under more relevant conditions. When human data of high quality and adequate statistical power

are available, they are generally preferable over animal data and should be given greater weight in hazard characterization and dose-response assessment, although both can be used.").

For chemicals that do not cause cancer and/or are not labeled as a carcinogen, additional potential defenses may be available. For example:

- If high-quality human epidemiology studies in real people using the actual product at real-world exposure levels do not show an increased risk of cancer in a relevant population, the general causation question is answered regardless of how the mechanistic data is organized and interpreted and regardless of whether one or more of the "key characteristics" is present. These scenarios reveal the types of mechanistic data contemplated in the 10 KC theory for what they are – studies focused on whether there is a potential mechanism by which a substance *may* cause cancer. Many of these tests are *in vitro* test tube studies that do not do not mimic what happens in a living system. *If* there is a mechanism by which the substance being studies causes cancer in humans, it will be evident in high quality epidemiology data; and
- One common defense applicable to most chemicals without a signature disease or mutation is that none of the genetic damage purportedly seen in the presence of any of the "key characteristics" is unique to exposure to a chemical. In actuality, these are the standard cellular responses to environmental stress on the cells, which can result from both chemical and non-chemical, natural exposures. For example, the natural replication of cells in our body leads to many DNA copying errors per day, all of which have the potential to become genotoxic mutations possibly leading to cancer. *See* Cristian Tomasetti & Bert Vogelstein, *Variation in Cancer Risk Among Tissues Can Be Explained by the Number of Stem Cell Divisions,* 347 Science 78 (2015); and Christian Tomasetti

et al., *Stem Cell Divisions, Somatic Mutations, Cancer Etiology, and Cancer Prevention*, 355 Science 1330 (2017).

In short, the KC theory focuses on tests that look for any changes or alternations in the cell. To check the box, the change need not be detrimental, permanent, or problematic. Any change is assumed to be a causal change. However, science shows that this assumption is false. The human body has a variety of built-in defenses to repair or eliminate cells that are damaged by the natural occurrences or exposure to an environmental factors cells encounter. This includes the dozens of household and other chemicals humans are exposed to on a daily basis. Any defense should include explaining to the jury that our cells are prepared for that and can adapt or otherwise respond to influences. Not everything that could impact a cell will permanently impact a cell in a way that could cause cancer.

And, as always, the quality of the science offered to support checking a box next to one of the "key characteristics" matters a lot. Anyone can do a study, but that does not mean the study is of high quality or produces reliable results. For some "key characteristics," there are no methodologies or study types that reliably link an exposure to cancer. Even when high-quality guidelines studies exist, those often are not considered in the analyses present to juries. Because of the unproven nature of some of the "key characteristics," many of them are not considered by worldwide regulatory agencies as predictive of causality of cancer.

Ultimately, there is no "one-size-fits-all" defense to cases in which plaintiffs and their experts rely upon the "key characteristics" method of organizing data as a tool to demonstrate causation. However, keeping in mind what the characteristics are – and more importantly focusing the court (during pre-trial evidentiary challenges) and the jury (at trial) on what they are not – is a key step in the right direction.