

# For and against Which drugs cause cancer?

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## *Animal tests yield misleading results*

**FOR** Despite President Nixon's War on Cancer, launched in 1971, and billions of dollars spent since then, cancer remains the second-leading killer of Americans. Around 40% of us will get cancer, and half of us will die from it.<sup>1</sup> This ceaseless tide of human suffering starkly questions the effectiveness of our strategies, including the accuracy of our methods for identifying human carcinogens.

Millions of laboratory animals have been sacrificed for this purpose. Thousands of chemicals, including ever-increasing numbers of therapeutic drugs, are consequently described as potentially carcinogenic. Yet, are animal experiments really predictive of human carcinogenicity?

The agency most responsible for protecting Americans from environmental contaminants is the Environmental Protection Agency (EPA), and the chemicals of greatest public health concern are described within its Integrated Risk Information System (IRIS) toxic chemicals database. We recently surveyed this database to assess the human utility of animal carcinogenicity data. Most chemicals lack human exposure data and possess only animal carcinogenicity data. In the majority of cases, however—58.1% (93/160)—we found that the EPA considered the animal data inadequate to support the useful human carcinogenicity classifications of probable carcinogen or non-carcinogen.<sup>2</sup>

But at least the animal data were predictive for 42% of chemicals. Or were they? A comparison of EPA carcinogenicity classifications with those assigned by the World Health Organization's International Agency for Research on Cancer (IARC) yielded disturbing results. For the 128 chemicals with human or animal data assessed by both agencies, human carcinogenicity classifications were similar only for those 17 possessing significant human data. For the 111 primarily reliant on animal data, the EPA was far likelier than the IARC to assign carcinogenicity classifications indicative of greater human risk.<sup>2</sup>

The IARC is widely recognized as the world's leading authority on carcinogenicity assessments. Such profound differences in carcinogenicity classifications of identical chemicals between the IARC and the EPA appear to indicate that in the absence of human data the EPA is over-reliant on animal carcinogenicity data. Consequently, the EPA tends to over-predict carcinogenic risk.

The questionable reliability of EPA carcinogenicity assessments was also the topic of a 2000 Congressional investigation.<sup>3</sup> It concluded that despite being advertised as quantitative, science-based classifications, some were, in fact, more grounded

in EPA policy favoring classifications indicative of greater human risk.

No agency responsible for protecting public health is ever likely to be sued for excessive caution. As every medical professional is acutely aware, however, the converse in the case of medical mishap is not true. One cannot help but sympathize with the concerns of EPA policy-makers in the world's most litigious nation. Nevertheless, the resultant EPA carcinogenicity classifications cannot be regarded as generally correct.

On the face of it, the EPA's heavy reliance on animal carcinogenicity tests seems understandable. There is a longstanding tradition of animal testing, and virtually all human carcinogens, when tested in sufficient animal species, have generated positive results.<sup>4</sup> However, if enough animal testing is conducted, it appears that carcinogenesis will eventually occur in some species regardless of human risk. Of 20 human non-carcinogens studied in animals, 19 produced carcinogenic effects.<sup>5</sup>

The problem with animal carcinogenicity tests is not their lack of sensitivity for human carcinogens, but rather their lack of human specificity. A positive result has poor predictive value for humans. Reasons for this include the predisposition of chronic high-dose bioassays for false-positive results due to the overwhelming of natural tissue repair mechanisms, and the unnatural elevation of cell division rates during ad libitum feeding studies.<sup>6</sup> Such factors render accurate extrapolation from animals to humans virtually impossible.

The protracted time frames of animal carcinogenicity studies, and their substantial drain on human, financial, and animal resources, present other important disadvantages. Standard rodent bioassays take at least three years to plan, execute, and interpret.<sup>7</sup> They have cost hundreds of millions of dollars<sup>8</sup> and have consumed millions of skilled personnel hours.<sup>9</sup> They also account for many of the animals reported to be experiencing the highest levels of pain and distress in laboratories.<sup>10</sup>

Modern alternatives exist, such as quantitative structure-activity relationship (computerized) expert systems, which predict biological activity based on chemical structure; enhanced in vitro assays; and cDNA microarrays, which allow detection of genetic expression changes long before the development of macroscopic lesions. These methods have the potential to yield superior human specificity results, in greatly reduced time frames, with greatly reduced demands on financial, personnel, and animal resources.<sup>11</sup>

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Inexplicably, however, regulatory agencies have been frustratingly slow to accept modernized testing protocols. With some 400 new drugs now introduced annually,<sup>12</sup> a radical rethinking of our reliance on prolonged animal testing is required. The development and implementation of rapid and predictive non-animal assays will minimize cancer losses to society, and might even restore our faith in the accuracy of the neoplastic warnings metastasizing throughout our medical formularies. ♦

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## Cancer bioassays

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### *Informing public health decisions on environmental risks*

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**AGAINST** Cancer is a consequence of natural biological processes as well as potentially being caused or exacerbated by drugs and environmental chemicals. To perform its public health role regarding potential environmental carcinogens, the US Environmental Protection Agency (EPA) must make timely decisions based on available epidemiological, animal, and mechanistic information. Cancer bioassays with rats and mice remain a valuable source of data, particularly studies conducted by the National Toxicology Program under the National Cancer Institute (NCI-NTP) of the US Department of Health and Human Services (DHHS). Although we recognize the concerns and sentiments expressed by Knight and colleagues, these opinions misrepresent EPA's Integrated Risk Information System (IRIS) program, the value to public health of the cancer bioassay, and the current inability of alternative laboratory techniques to substitute for cancer bioassays in human risk evaluations.

EPA is among a number of federal, state, and international organizations that generate or use cancer bioassay information, including the DHHS with their *Report on Carcinogens*, the Food and Drug Administration, the Occupational Safety and Health Administration, and the World Health Organization's (IARC) cancer monographs. Bioassay information is included in EPA's cancer weight of the evidence evaluation of the full array of human,

animal, and mechanistic data, as detailed in the recently published EPA *Guidelines for Carcinogen Risk Assessment*.<sup>1</sup> Supported by extensive scientific peer review, these guidelines advance cancer risk assessment methods by moving beyond EPA's previous alphanumeric cancer classifications to a narrative paragraph with standard descriptors. The narrative format permits consideration of routes and nature of exposure, accompanied by a mode of action evaluation of the relevance to humans of tumors seen in bioassays.

EPA's primary consideration in cancer risk assessment remains the evaluation of available epidemiological studies, although adequate epidemiological information is often limited. In addition, epidemiology is inherently a retrospective science. Rather than wait for cancer to be demonstrated among exposed humans, federal agencies proactively use in vivo animal, in vitro, and computer modeling methods to inform decisions on the prodigious numbers of chemicals in modern commerce.

EPA's IRIS program serves as a principal source for qualitative and quantitative hazard characterization and dose-response assessments of these environmental pollutants. Contrary to the assertion by Knight et al of negative conclusions from a Congressional investigation, the referenced independent contractor and Science Advisory Board review spoke to the usefulness of IRIS for public health and risk as-

assessment, contemporary quality advances, and ways in which IRIS documentation can be improved.<sup>2</sup>

The report by Knight et al of "profound" differences when comparing EPA's IRIS Web site with IARC cancer classifications is also puzzling. The scientific community, through direct participation and/or independent peer review, is involved in all cancer hazard characterizations made by EPA, DHHS, and IARC. The conclusions of these organizations have generally been in reasonable concurrence, subject to procedural and timing differences. Unfortunately, the three central references upon which the Knight et al commentary is based are all unpublished self-citations, which were not available on request beyond abstracts.

Every known human carcinogen has tested positive in laboratory animals, and for almost one third of these the bioassay was the first indication of carcinogenic hazard, including aflatoxins, asbestos, diethylstilbestrol, and many others.<sup>3,4</sup> Rall<sup>5</sup> concludes that reports of high positive rates ( $\approx 50\%$ ) in early NCI-NTP bioassays were due to targeting of suspected carcinogens, accompanied by the use of any positive finding as the standard, irrespective of the strength of association. Rall's analysis actually concludes that only  $\approx 7\text{--}12\%$  of later NTP bioassays of chemicals selected on the basis of human exposure potential are positive under more generally accepted standards. The Knight et al assertion regarding the poor predictive value of the bioassay fails to fully convey the analyses in the listed citations. Referencing these calculations as sensitivity or specificity is also troubling, absent a gold standard for separating genuine human carcinogens from non-carcinogens. Given these facts, the assertion that EPA and other public health agencies are overpredicting human risk should be viewed cautiously.

Cancer bioassays at US federal facilities must be conducted consistent with the Animal Welfare Act (7 US C et seq) and rigorous institutional animal care policies.<sup>6,7</sup> The reference by Knight et al to these animals "experiencing the highest levels of pain and distress in laboratories" is not reflective of typical test conditions, nor, indeed, is there any mention of chronic cancer bioassay testing in the cited reference, which excluded rats and mice from the analysis.<sup>8</sup>

In providing the above response to Knight et al, our intent is to clarify the relative merits of the cancer bioassay to inform public health protection in a weight of evidence framework. We agree that more efficient test methods are needed. In addition to US federal efforts toward development of alternative toxicological methods,<sup>9</sup> EPA has also created a National Center for Computational Toxicology to develop methods to incorporate expanding toxicogenomic and proteomic information into the risk assessment process.<sup>10</sup>

Cancer is a multisite, multifactorial process of still unknown mechanistic etiology. The cancer bioassay addresses this in a whole system model. The additional data obtained from alternative test methods can and do contribute to the weight-of-evidence cancer evaluations in EPA's IRIS program, but none of them obviates the continuing need to include bioassay results in evaluating environmental pollutants for the purpose of protecting public health. ♦

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Disclaimer: The views expressed in this commentary are those of the authors and do not reflect US Environmental Protection Agency policy.

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### *A patient who changed my practice* **A gnashing of teeth**

During my six months as a senior house officer in the emergency department, I was called to see an elderly woman in the resuscitation room. I think her triage card was marked "Collapse, query cause." She did not require immediate resuscitation. I took a history and examined her, including a rather slapdash cranial nerve examination. Testing the integrity of her seventh nerve, I asked her to "Show me your teeth." She obliged by spitting her dentures into her hand and nervously offering them to me for inspection. After a brief look, I told

her they looked satisfactory, and she replaced them.

Now when attempting to examine the cranial nerves, I ask the patient to "Clench your teeth at me" and mime the clenched jaw action. While I am sure I look silly doing this, I have been spared a palm full of teeth since.

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