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### Which Drugs Cause Cancer?

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# For and against Which drugs cause cancer?

Andrew Knight, Jarrod Bailey, Jonathan Balcombe

## *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-