The Carcinogenesis Bioassay in Perspective: Application in Identifying Human Cancer Hazards

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Two-year chemical carcinogenesis studies using rodents are the major bioassay for identifying environmental carcinogens (1–3). Due largely to the limited number of animals per test (generally 50–60 animals of each sex of two species, rats and mice, in each experimental group), bioassays are conducted at relatively high exposure concentrations to optimize the probability of detecting a carcinogenic response. These long-term bioassays were originally designed primarily for qualitative identification of potential human carcinogens, so that further studies could be done as necessary to elucidate dose–response relationships for quantitative risk assessment. Unfortunately, subsequent experiments are often not possible due to limited resources and the need to test other chemicals; thus, carcinogenesis bioassay data are frequently used for quantitative risk assessments, despite potential limitations and confounding factors (4).

Carcinogenesis bioassays have been criticized for identifying "too many rodent carcinogens" and are criticized as not predicting carcinogenic hazards to humans, largely because of purported differences in exposures and lack of discrimination due to high-dose effects (5). Long-term bioassays are designed to expose rodents to chemicals or environmental mixtures that cause only minimal toxic effects. The highest dose selected for these studies has been termed the "maximum tolerated dose" (MTD), when, in fact, it actually represents a minimally toxic exposure dose (6–8). Since nearly half the chemicals tested by the National Cancer Institute (NCI) (9) and the National Toxicology Program (NTP) (10) elicited a positive response in the rodent bioassays, some researchers have postulated that carcinogenesis in these studies results from cell killing and increased cell division (mitogenesis) (5). However, no obvious correlation between toxicity and carcinogenicity exists (11–14). Mitogenesis is certainly crucial to the carcinogenic process (5,15–18), but the conclusion that the majority of positive carcinogenesis responses result from cell killing and mitogenesis requires a more critical evaluation (11,12,17–19).

Most of the chemicals selected for the NCI/NTP rodent bioassay program were suspect carcinogens. Thus, not surprisingly, many of these chemicals (two-thirds) did induce carcinogenic responses in well-controlled, 2-year rodent carcinogen bioassays. More criteria are used to predict the carcinogenic potential of chemicals since the inception of the bioassy program, as more information on mechanisms of carcinogenesis have become available. These criteria include 1) positive or suggestive evidence from epidemiological studies or previous experimental studies in animals, 2) potential to act as an electrophilic agent or to be metabolized to an electrophilic species, 3) potential to be metabolized to active free radical species, and 4) known biological activity, such as genotoxicity (20–23). Other information useful for assessing potential carcinogenicity includes data on levels and duration of exposure to the chemical, potential for bioaccumulation, mechanism of carcinogenic activity, species differences, and genetic susceptibility.

Some chemicals were selected for carcinogenicity testing based primarily on estimates of human exposures, without prior suspicion of carcinogenicity. Estimates of exposure were based on 1) production volume; 2) use pattern (e.g., is the chemical an intermediate or end product, is it used in an open or closed system, is it used in occupational settings or by certain subgroups of the general population); 3) environmental occurrence (e.g., naturally occurring products in certain foods and environmental pollutants such as pesticides); 4) potential to enter the food chain; 5) physical properties (e.g., vapor pressure and partition coefficients) that are relevant to the route of human exposure; 6) potential for bioaccumulation; and 7) worker and consumer exposure databases. This subset of chemicals represents a more randomly selected group of substances to ascertain more accurately the percentage of chemicals that are carcinogenic to rodents, assess whether testing chemicals at minimally toxic exposure levels generally results in carcinogenic responses, and predict the proportion of chemicals that may pose a carcinogenic risk to humans.

In this paper we have divided chemicals tested for carcinogenicity into two categories: those selected on the basis of being suspect carcinogens and those selected on the basis of exposure/production volume. Two-thirds of the suspect carcinogens exhibited carcinogenic activity, whereas the majority (nearly 80%) of the high-volume chemicals were not carcinogenic, even when tested at relatively high exposures. The scientific and public health significance of these observations is discussed.
Bioassay Results of 400 Chemicals

As of June 1994, NCI/NTP has completed carcinogenicity bioassays on 400 chemicals, and these have been peer reviewed in public forums. Of the 400 chemicals tested, 210 (52%) showed a statistically significant increase in the number of animals with tumors in at least one site or one organ of one sex of one species in the four typical sex–species groups of one or more exposure levels (Table 1). Fifty-five of the 210 "positive" chemicals were positive in only one sex-species group, 79 chemicals in 2 groups, 31 chemicals in 3 groups, and 45 chemicals in 4 groups (Table 2).

Our review of the selection criteria for the 400 chemicals indicated that 267 (67%) were selected with a suspicion of carcinogenicity, and 133 (33%) were selected mainly on the basis of production volumes and occupation/population exposures. Of the 210 positive chemicals, 181 (86%) were suspect carcinogens, and 29 (14%) were selected mainly on exposure considerations (Table 2). These results clearly demonstrate a bias in the chemical selection process toward chemicals that are suspect carcinogens.

Further analysis of the 181 positive chemicals that were suspect carcinogens showed that 42 were positive in only 1 of 4 sex–species groups, 70 in 2 groups (14 of these chemicals were positive in 2 species), 27 in 3 groups, and 42 in all 4 groups (Table 2). Thus, 83 (14 + 27 + 42) of the 267 suspect carcinogens were tested in 2 species and thus meet the international criteria to evaluate further for potential human cancer risk.

Only 29 of the 133 chemicals (22%) selected mainly on the basis of exposure considerations were positive in at least 1 of the 4 sex–species groups, 13 of these 29 chemicals were positive in only 1 sex–species group; 9 chemicals in 2 groups (2 of these chemicals were positive in 2 species), 4 chemicals in 3 groups, and 3 chemicals in all 4 experimental groups. Thus, 9 (2 + 4 + 3) of the 133 chemicals tested (6.8%) were positive in two species and would be considered for further evaluation as possibly carcinogenic to humans.

Chemicals Likely to Pose Carcinogenic Hazards to Humans

According to the strength-of-evidence criteria pioneered by the International Agency for Research and Cancer (IARC), which are used by the Department of Health and Human Services (DHHS) in its Annual Report on Carcinogens (ARC) and by others, chemicals that induce cancer in two species should be considered most likely to pose carcinogenic hazards to humans (24–27) and need more detailed and extensive evaluation of the available data and information.

These empirical and qualitative scientific criteria have been adopted by research and regulatory agencies worldwide for evaluating the available information to determine whether a chemical is carcinogenic to humans. Thus, 92 (44%) of the 210 positive chemicals (or 23% of the 400 chemicals tested) should be further evaluated as potential human carcinogens. Eighty-three of these 92 chemicals (90%) were suspect carcinogens; only 9 (10%) were selected mainly on the basis of production and exposure considerations. It is noteworthy that less than half of the 210 positive chemicals and only 23% (92/400) of all chemicals tested by NCI/NTP would be considered for further evaluation as likely to present carcinogenic hazards to humans using international criteria (e.g., IARC). Of course, we do not mean to imply that chemicals with positive results in only one species or in one sex of one strain are necessarily hazardous, for each chemical must be evaluated individually using all available toxicologic information to better determine potential carcinogenic risks to humans.

Classification of Chemicals by IARC and DHHS

To date, 75 (36%) of the 210 positive chemicals (or 19% of the 400 total chemicals) have been classified by IARC and/or DHHS. Sixty-three chemicals are considered by IARC as posing cancer risks to humans: 5 of these chemicals are in IARC group 1 ("agent is carcinogenic to humans"), 10 chemicals are in group 2A ("agent is probably carcinogenic to humans"); and 48 chemicals are in group 2B ("agent is possibly carcinogenic to humans"). Sixty chemical names are listed in the Annual Report on Carcinogens (ARC) as presenting carcinogenic hazards to humans: 4 chemicals are listed as "known to be carcinogenic to humans" (4 of the 5 in IARC) and 56 chemicals are listed as "reasonably anticipated to be a carcinogen to humans." For the majority of the chemicals there is excellent correspondence for listing by both IARC and in the ARC. The categories of evidence and names of the chemicals are provided in Tables 3 and 4.

Sixty-eight of the 75 chemicals (91%) listed by IARC or in the ARC were selected as suspect carcinogens, and 7 (9%) were selected on the basis of human exposure considerations. Fifty-seven of the 181 positive chemicals (32%) selected as suspect carcinogens are listed in one of the IARC categories: group 1 (5 chemicals), group 2A (10 chemicals), and group 2B (42 chemicals). Fifty-five of the 181 positive chemicals (30%) are listed in the ARC: 4 chemicals in the "known to be carcinogenic to humans" and 51 in the "reasonably anticipated to be a carcinogen" classification. Table 3 contains the names of the chemicals in the various IARC and ARC categories of evidence.

Six of the 29 chemicals (21%) selected on the basis of exposure considerations are listed in IARC group 2B; none is listed in group 1 or group 2A. Five of the 29 chemicals (17%) are listed in ARC classification, "reasonably anticipated to be a carcinogen"; none is listed in the "known" classification. Table 4 contains the names of these chemicals in the various IARC and ARC classifications.

Magnitude of Public Health Problem

These results may be used to better predict the percentage of the 75,000 chemicals in commercial use that would eventually prove to be carcinogenic to humans; of

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**Table 1. Statistics on selection rationale for 400 chemicals/chemical mixtures with published or peer-reviewed technical reports as of January 1994**

| Selection basis                              | Total no. of chemicals (%) | No. of chemicals with Positive results (%) | Negative results (%) |
|----------------------------------------------|---------------------------|------------------------------------------|----------------------|
| Completed bioassays                          | 400                       | 210 (52)                                 | 190 (48)             |
| Suspicion of carcinogenicity                 | 267 (67)                  | 181 (68)                                 | 86 (32)              |
| Production volumes and occupation/population exposures | 133 (33)                  | 29 (22)                                  | 104 (78)             |

**Table 2. Relationship between selection criteria and number of chemicals with evidence of carcinogenicity**

| Evidence of carcinogenicity in number sex/species experiments | Selection basis | Mainly human exposure considerations (%) |
|--------------------------------------------------------------|-----------------|------------------------------------------|
| Total                                                        | Suspection of carcinogenicity (%) | |
| None                                                        | 190             | 86 (45)                                  | 104 (55)             |
| One                                                         | 55              | 42 (76)                                  | 13 (24)              |
| Two                                                        | 79              | 70 (89)                                  | 9 (11)               |
| Three                                                       | 31              | 37 (87)                                  | 4 (13)               |
| Four                                                        | 45              | 42 (93)                                  | 3 (7)                |
| Total for chemicals with positive results                   | 210             | 181 (86)                                 | 29 (14)              |
Table 3. IARC and Annual Report on Carcinogens (ARC) classifications of chemicals selected for NCI/NTP bioassay based on a suspicion of carcinogenicity

| Category 1 (5 chemicals) | Known carcinogens (4 chemicals) | Reasonably anticipated to be carcinogens (51 chemicals) |
|--------------------------|---------------------------------|----------------------------------------------------------|
| Asbestos                 | Asbestos                        | 2-Aminoaanthraquinone                                    |
| Aspirin, phenacetin, caffeine mixture | Aspirin, phenacetin, caffeine mixture | 1-Amino-2-methylnaphthoquinone                           |
| Benzene                  | Benzene                         | o-Anisidine                                              |
| Ethylene oxide           | 8-Methoxysorales + PUVA         | Bromodichloromethane                                     |
| 5-Azacytidine            | 1,3-Butadiene                   | 1,3-Butadiene                                            |
| 1,3-Butadiene            | Chloroanilide                   | 1-Chloroanilide                                          |
| C.I. Direct Black 38     | Chloroform                      | 1,2-Dibromoethane                                        |
| C.I. Direct Blue 6       | Cupperron                       | 3-Chloro-4-methylpropane                                 |
| C.I. Direct Brown 95     | 2,4-Diaminoanisole              | 4-Chloro-o-phenyleneanilidamethane                       |
| 1,2-Dibromoethene (EDB) | 2,4-Diaminotoluene              | 1,2-Diphenylethanol                                      |
| Procarbazine-HCI         | 1,2-Dibromo-3-chloropropane     | 1,2-Dichloroanilide                                      |
| 1,2-Propanol oxime       | Dichlorodiphenyldichloroethane  | 1,2-Dichloroethane                                       |
| tris(Aziridinyl)phosphine sulfide (thio-TEPA) | Dichloroform | 1,2-Dichloropropane                                      |
| Category 2A (10 chemicals) | 2,4-Diaminoanisole sulfate       | Diglycidol resorcinol ether                              |
| Chloroform               | 2,4-Diaminotoluene              | 3,3'-Dimethoxybenzidine dihydrochloride                  |
| Chloroform               | 1,2-Dibromo-3-chloropropane     | 3,3'-Dimethylbenzidine dihydrochloride                   |
| 1,2-Dibromo-3-chloropropane | Chloroform | Dimethyl vinyl chloride                                  |
| Chloroform               | 1,2-Dichloroethane              | Ethyl acrylate                                           |
| Chloroform               | 1,3-Dichloropropene             | Ethylene oxide                                            |
| Dichlorovos (DVP)        | Ethylene thiourea               | Ethylene thiourea                                         |
| Chloroform               | 2,4-Diaminoanisole              | Hydrazobenzene                                           |
| Diglycidol resorcinol ether | Ethylene oxide                  | Lindane                                                  |
| 2,4-Diaminoanisole sulfate | Ethylene oxide                  | Methylene chloride                                        |
| 2,4-Diaminotoluene       | Ethylene oxide                  | 4,4'-Methylene diaminel dihydrochloride                  |
| 1,2-Dibromo-3-chloropropane | Ethylene oxide | 4,4'-Methylenebis/(N,N-dimethyl)benzenamine               |
| 1,2-Dichloroethane       | Ethylene oxide                  | Michler's ketone                                         |
| 1,3-Dichloropropene      | Ethylene oxide                  | Mirex                                                    |
| Dichloroform             | Ethylene oxide                  | Nitrofen                                                  |
| Ethylene oxide           | Ethylene oxide                  | Ochratoxin A                                             |
| Ethylene oxide           | Ethylene oxide                  | 4,4'-Oxydianiline                                        |
| Ethylene oxide           | Ethylene oxide                  | Phenazopyridine-HCl                                      |
| Ethylene oxide           | Ethylene oxide                  | Phenoxazopyridine-HCl                                    |
| Ethylene oxide           | Ethylene oxide                  | Polybrominated biphenyl mixture                          |
| Ethylene oxide           | Ethylene oxide                  | Firemaster FF-1                                           |
| Ethylene oxide           | Ethylene oxide                  | Procarbazine-HCI                                         |
| Ethylene oxide           | Ethylene oxide                  | 1,2-Propanol oxime                                       |
| Ethylene oxide           | Ethylene oxide                  | Reserpine                                                 |
| Ethylene oxide           | Ethylene oxide                  | Sulflinate                                                |
| Ethylene oxide           | Ethylene oxide                  | 2,3,7,8-Tetrachlorodibenzo-p-dioxin                     |
| Ethylene oxide           | Ethylene oxide                  | Tetrachloroethylenne                                     |
| Ethylene oxide           | Ethylene oxide                  | α-Toluidine-HCI                                           |
| Ethylene oxide           | Ethylene oxide                  | Toxaphene                                                 |
| Ethylene oxide           | Ethylene oxide                  | 2,4,6-Trichlorophenol                                    |
| Ethylene oxide           | Ethylene oxide                  | tris(Aziridinyl)phosphine sulfide (thio-TEPA)            |
| Ethylene oxide           | Ethylene oxide                  | tris(2,3-Dibromopropyl)phosphate                         |

In some cases, exposure patterns and other necessary conditions must also be considered (28–30). Our current review of the 400 chemicals tested in the bioassay program indicates that only 23% are positive in two species, and thus, using international criteria, these 92 chemicals may be considered for further evaluation as being most likely to pose carcinogenic risks to humans. However, because the majority of chemicals tested to date were selected as suspect carcinogens, this must be considered to be a high estimate. Only 6.8% of the chemicals selected on the basis of exposure/production volume may be considered as likely to pose carcinogenic risks to humans. Therefore, we predict that if all 75,000 chemicals in use were to be tested for carcinogenicity in the standard NTP bioassay, significantly less than 50% would be carcinogenic in animals, and even a smaller percentage (less than 5–10%) would need further evaluation (Huff et al., submitted).

Relevance of Animal Studies to Human Health

There are considerable molecular and cellular similarities in carcinogenic processes among mammals, including rodents and humans (31–35). For those agents identified as carcinogenic to humans, experiments in animals have shown remarkable target organ concordance (36–40). Nearly one-third of these agents confirmed as causing cancer in humans were identified first in experiments using laboratory animals (4,41–43). Nonetheless, Lijinsky (44) reminds us that there are indeed differences in carcinogenic responses of various species and strains to carcinogens, although these differences have not yet been explained (45).

Our evaluation and the knowledge that all chemicals known to induce cancer in humans that have been studied under adequate experimental protocols also cause cancer in laboratory animals (24,25,36,37,39,40) leads to the persuasive speculation that the obverse would often hold true: chemicals shown to unequivocally induce cancer in laboratory animals, especially in multiple species, must be considered capable of causing cancer in humans. Obviously further and detailed evaluations need to be made. The International Agency for Research on Cancer adopted this widely accepted scientific view: "In the absence of adequate data in humans, it is biologically plausible and prudent to regard agents and mixtures for which there is sufficient evidence of carcinogenicity in experimental animals as if they presented a carcinogenic risk to humans" (25). This public health statement has and should continue to be endorsed and used by those responsible for protecting human health.

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Table 4. IARC and Annual Report on Carcinogens (ARC) classifications of chemicals selected for NCI/NTCP bioassay mainly on basis of exposure

| IARC category | ARC classification |
|---------------|-------------------|
| None          | None              |
| Group 2B      | Reasonably anticipated to be carcinogens |
|   Toluenediisocyanate | (80% 2,4-isomer, 20% 2,6-isomer) |
| Di(2-ethylhexyl)phthalate |  |
| 1,4-Dioxane |  |
| Nitritetriacetic acid |  |
| Pentachlorophenol (Dowicide EC-7) |  |
| Pentachlorophenol (technical) |  |

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