Absence of Morphologic Correlation between Chemical Toxicity and Chemical Carcinogenesis

by James Huff

The experimental data set used to evaluate site-specific histopathologic correspondence between the morphologic end points of toxicity and carcinogenicity comprises 130 chemical carcinogenesis studies. Nearly 1500 sex-species-exposure-group experiments were evaluated for a) evidence of toxicity or and carcinogenicity, b) dose-response relationships, c) site-specific correlations of toxicity and carcinogenicity, and d) correspondence with Salmonella mutagenicity. The major conclusions are that chemicals evaluated for long-term toxicity and carcinogenicity in experimental animals divide typically and consistently into three categories: a) chemicals causing organ toxicity without cancer, b) chemicals causing site-specific cancer with no associated toxicity, and c) chemicals causing both toxicity and cancer in the same organ. Few chemicals overall (and none in this data set) fit the remaining group that cause neither toxicity nor carcinogenicity under these protocol conditions. Mutagenicity exhibited no consistent pattern with any of these groupings. Only 7 of 53 "positive" chemicals had target organ toxicity at all sites of carcinogenicity. Just three chemicals showed carcinogenic effects at the highest exposure concentrations without supporting evidence of tumors at the lower levels. From these comparative morphological analyses, and for almost all cases, available data do not support a correlation between chemically induced toxicity or regenerative phenomena and carcinogenicity. Consequently, until scientific knowledge about molecular mechanisms of chemical carcinogenesis becomes better understood and generally accepted, attempts to use toxicity findings to modify risk assessment processes will be fraught with uncertainty and thus could have a negative impact on public health.

Introduction

Most naturally occurring and synthetically made chemicals are considered neither potentially carcinogenic to humans (1-3) nor to animals (2,4-6), and the proportion of chemicals eventually identified to cause cancer in experimental animals or in humans is predicted to be relatively low (7-9). For those chemicals identified as being causally associated with cancers in humans, all have been shown to cause cancer in laboratory animals (10,11) with at least one site of cancer being common to both mammalian subspecies (12-18). This knowledge, together with patent similarities in mechanisms of carcinogenesis across species, led to the scientific and public health logic that chemicals shown clearly to be carcinogenic in animals (2,10-12, 15,16, 19-26) should be considered as likely to present cancer risks to humans (1,3). So far, fewer than 200 agents or exposure circumstances have been identified as being causally or strongly implicated in human cancers. One key public health factor too long ignored shows that of the discrete chemicals associated with these human diseases, nearly 30 were found to cause cancer in experimental animals before being identified as carcinogenic to humans (12,17-18). Chemical carcinogenesis experiments are conducted largely to identify those chemicals, mixtures of chemicals, or environmental and occupational exposures that may potentially induce cancer in humans (4,5,15,29-31). Results from these studies are the most reliable and practical means to identify carcinogenic hazards in the absence of adequate and dependable human data (9,15, 29,32), and their value and use for protection of public health are without peer (16,18,33). In the last decade and continuing into this one, as we accumulate more knowledge about the molecular biology of cancer, scientific debates resurface periodically over the value,
relevance, and use of various practical or mechanistic assumptions or data in risk assessments of chemical carcinogens (34–46).

One mechanistic issue centers on whether chemical-induced toxicity per se (typically including adaptive responses and cellular degeneration, death, and regeneration, thus signalling cellular proliferation) exerts any significant influence on the chemical carcinogenesis processes. An empirical assessment of an extensive series of long-term chemical carcinogenesis experiments was made to ascertain whether there were any direct and uniform causal associations between chemically induced cellular toxicity and carcinogenicity. This issue is the central topic of this paper.

**Experimental Data Sources**

The core carcinogenicity database used for these morphologic comparisons was originated in the late 1960s by the National Cancer Institute, and since 1978 has been continued by the National Toxicology Program. The extensive files contain, among other sets of information, a) gross and histopathology data from long-term (typically 24-month) carcinogenesis studies on more than 450 natural or synthetic chemicals, b) nearly 1800 individual sex–species experiments, c) 6000 separate control and exposure groups, d) data and tissues on 325,000 laboratory rodents, and e) 13 million tissue sections that have been evaluated for toxicity and carcinogenicity.

The experimental histopathology data used to evaluate site-specific correspondence between toxicity and carcinogenicity comes from a subset of 130 chemical carcinogenesis studies. Nearly 1800 sex–species control and exposure group experiments were evaluated for evidence of toxicity or/and carcinogenicity, dose–response relationships, site-specific correlations of toxicity and carcinogenicity, and correspondence with Salmonella mutagenicity.

**Composite Results**

Experimental details for the data summarized in this paper are given in the NTP Technical Reports on individual chemicals, from other compilations made from this data set (4–6,17,32,47–49), and from previous analyses of this mechanistic issue (43,50,51). These references should be consulted for more details about the experiments, names of chemicals evaluated, and results.

Table 1 shows the numbers of experiments and the summary findings on the percentages of experiments with positive (35%), equivocal (11%), and no evidence (54%) of carcinogenicity. By viewing the data in this manner (as opposed to simply a “positive” or “negative” per chemical classification), one gets a better appreciation for the actual rate or magnitude of positive responses. An even more valid approach involves a qualitative grouping according to the number of sex–species positive responses and carcinogenic target organs one finds in these chemical studies (43); for example, allyl isothiocyanate induced a few benign tumors of the urinary bladder in male rats and no carcinogenic response in female rats or in male and female mice, whereas glycidol caused tumors at 16 sites among the four sex–species experiments. Thus, one should not group all carcinogens together for the purposes of setting priorities for public health protection or for attempting to belittle the value of experimental data.

Table 2 divides the data on 99 chemicals from Hoel et al. (50) into various groups for deciphering the issue surrounding the “high dose only” paradigm of carcinogenicity in rodents (38). For illustration, of the 127 “positive” responses, only 12 (or 6% of 198) of the experiments showed chemically induced cancers at the highest exposure level without similar related tumors in the same organ at lower levels. Obviously, the “high-dose-only carcinogens” theory does not reflect the experimental findings. In most typical 2-year studies, those chemicals inducing positive carcinogenesis responses do so at each of the exposure concentrations (>90%); one does not know nor can one predict with utmost confidence what the exact responses will be at lower exposures, and the assumption must be that carcinogenic activity will be evidenced at lower doses as well. In those cases in which additional experiments were undertaken to obtain better knowledge about the

| Parameter | Number (%) |
|-----------|------------|
| Chemicals evaluated | 99 |
| Individual sex and species experiments | 370 |

| Parameter | Number (%) |
|-----------|------------|
| 53 chemicals (198 experiments): | |
| Positive at more than one dose | 73 (37) |
| Positive at top exposure, supported by lower dose increases | 39 (20) |
| Positive at top exposure, not supported by lower dose effects | 12 (6) |
| Positive at only dose studied | 3 (2) |
| Equivocal and no evidence | 71 (36) |
| Total with positive evidence | 127 (34) |
| Equivocal findings [overall] | 38 (9) |
| No evidence of response [overall] | 208 (55) |
dose–response relationship, we invariably found continuation of carcinogenicity and/or preneoplasia at the lower exposure concentrations. These findings are similar to those reported by Tennant et al. (51), who evaluated an additional 51 chemicals.

As a classical illustration of these natural phenomena and to introduce the important issue of competing risks, 1,3-butadiene was shown to be particularly carcinogenic at 625 and 1250 ppm when administered for 1 year (52). To extend the response curves, Melnick et al. (53) designed a matrix of experiments including groups exposed to only 6.25 ppm (as well as a series of “start–stop” exposure groups). 1,3-Butadiene was carcinogenic even at 6.25 ppm, induced tumors at a site (lung) different from higher exposures when animals survived longer due to fewer lymphomas (“competing risks”), and caused cancers with only 13 weeks of exposure to 625 ppm. Benzene is another example of a particularly potent carcinogen (20), first shown by Maltoni and Scarnato (54,55) and Maltoni et al. (56) to cause cancers in laboratory animals at exposures of 50 mg/kg and above by the oral route and at concentrations of 200 ppm by the inhalation route. We substantiated the responses at 50 mg/kg and extended this to 25 mg/kg [or by conversion factors to 19 ppm by inhalation (57)]. Clearly, benzene (and 1,3-butadiene) would be carcinogenic at exposures below those so far evaluated and reported.

Other examples of repeated experiments are few, but several can be mentioned, each of which is carcinogenic at all exposures studied—dibromochloropropane (0.6 ppm lowest exposure level), dibromoethane (10 ppm) and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD; 0.001 µg/kg). Other chemicals have been evaluated and shown to be carcinogenic at very low exposures, and there is no need to conduct repeat studies—for examples, C.I. Acid Red 114 (70 ppm in water), dimethyldizane (30 ppm in water), ethylene oxide (50 ppm inhalation), furan (2 mg/kg oral), ochra-toxin A (70 µg/kg oral), tetratromethane (0.5 ppm inhalation), and trichloroethylene (3 mg/kg oral). Of course, the important issue should not center on the exposure concentration alone (4), but should also consider the amounts, diversity, and multiplicity of exposures humans receive typically and constantly. Clearly, human exposures are predicted on the acute toxicity of a chemical; that is, humans are exposed to considerably more dichloroethylene (methylene chloride), often up to 4000 ppm in paint stripping, than to more toxic chemicals such as formaldehyde (5–10 ppm). Thus, potency of carcinogenic activity must be gauged using other information as well. For example, for two chemicals considered to be carcinogenic to humans, TCDD, the most potent carcinogen yet discovered in animals (58–60), would appear to be less hazardous to humans (i.e., few people exposed at relatively low levels) than analgesic mixtures containing phenacetin (i.e., many people exposed occupationally and therapeutically at relatively high levels).

### Table 3. Summary results on toxicity and carcinogenicity from 53 chemicals causing tumors in at least one sex of one species.

| Result                        | Number (%) |
|-------------------------------|------------|
| **Target organ effects**      |            |
| Site-specific carcinogenic effects | 207        |
| No toxic lesions or hyperplasia | 91 (44)    |
| Hyperplasia without toxicity  | 52 (25)    |
| Toxic lesion with hyperplasia | 34 (16)    |
| Toxic lesion without hyperplasia | 30 (14)   |
| **Liver lesions**             |            |
| Carcinoma                     |            |
| Without toxicity              | 13 (56)    |
| With toxicity                 | 8 (44)     |
| Rat                            | 21         |
| Mouse                         | 42         |

Table 3 separates the 207 carcinogenic responses induced by these 53 chemicals into those with and without toxicity and hyperplasia. Again, one must evaluate the spectrum of responses observed before deciding whether an empirical association between various endpoints (e.g., toxicity and carcinogenicity) reflects a cause-and-effect relationship—especially for a single chemical regarding mechanism. For the actual data, the majority of site-specific responses (44%) showed no toxicity or hyperplasia, and for only 14% (30 sites) of the carcinogenic effects were there toxic lesions in the organ sites exhibiting carcinogenic effects.

### Liver Carcinogenesis

For chemically induced carcinogenic responses in the liver, there seems to be an increasing tendency to posit that toxicity is indeed associated with carcinogenesis (and in particular for “nongenotoxic chemical carcinogens”). Because of this and because chemically induced liver tumors in rodents represent the most frequent target site (61,62), these were tabulated separately (Table 3). The above contention has little support, as there appears to be no consistent pattern of toxicity with or without neoplasia. The recorded observations divide almost evenly regarding chemicals causing cancer with or without toxicity, orienting toward those chemicals inducing cancer without toxicity (56% versus 44%). This nearly equal distribution was consistent for both species. As with other organs, whether more subtle lesions were occurring than could be observed using light microscopy remains to be determined. Conversely, for those livers exhibiting overt patterns of toxicity, there was little or no chance of overlooking a neoplasm (63).

1,4-Dichlorobenzene, unleaded gasoline, and furan are interesting examples for which cell proliferation studies were conducted after the knowledge that these “nongenotoxic” chemical were carcinogenic to laboratory animals. Using 1,4-dichlorobenzene for illustration, increases in hepatocyte proliferation (and in liver
weights) were observed in both sexes of mice and in female (males not studied) rats (64); yet hepatocarcinogenic responses were restricted to mice. The major increases in S-phase labeling were seen only at week 1 of the 13-week studies and diminished substantially thereafter. The labeling index increase at week 1 was greatest in female rats (35% of hepatocytes in S-phase at 600 mg/kg dose versus 1.2% in controls) and lowest in female mice (7.5% versus 2.9% in controls; males, 7.3% versus 0.1% in controls), yet tumors of the liver were induced only in mice (females from 15/50 in controls to 36/50 exposed; males from 17/50 to 40/50) compared to none in rats (only one carcinoma in a control male rat; none in exposed male or female rats). Clearly, one must question the \textit{a priori} notion that toxicity and cellular proliferation (for 1 week) were intimately and ultimately involved in the mechanism of liver carcinogenesis (65) for 1,4-dichlorobenzene. Similarly, unleaded gasoline induced liver tumors in female mice, whereas increased cellular proliferation was observed in both sexes of mice (66). Both of these studies suggest additional factors are involved in the hepatocarcinogenicity of chemicals.

Furan-induced carcinogenicity of the liver in rats and mice illustrates another potentially premature mechanistic interpretation. In a 6-week study using only the highest exposures from the 2-year NTP carcinogenesis studies, the labeling index in hepatocytes was elevated at week 1 in rats (3.2% in males versus 0.08% in controls, 11.7% in females versus 0.8% in controls) and in male mice (25.1% versus 0.4% in controls; female mice not studied). For mice, the rate of labeling at 6 weeks was only about 3%, down from roughly 13% at week 3, and 25% at week 1 (67); thus, one could assume physiologic adaption to this chemical effect. The major carcinogenic response from furan was cholangiocarcinomas of the liver, but bile duct cell proliferation was not measured. The proliferative response was greater in female than in male rats, while the carcinogenic response was much greater in males.

Table 4 divides the chemicals by various toxic and preneoplastic end points (as compared to Table 3 for individual target sites). For 29 of 53 chemicals (55%) showing a positive carcinogenic response in at least one organ of one sex of one species, 11 of these induced toxic lesions in all cancer sites. Four of these 11 induced toxicity not considered likely to influence the particular tumor type observed; thus for 7 of the 53 chemicals (13%), toxic lesions occurred in all target sites and at each of the exposure levels. Table 5 lists the 11 chemicals with the target organs and the mutagenicity results from the Salmonella assay. Three of these chemicals caused tumors in all four sex–species experiments, and in each case the carcinogenic responses were single target sites: ethyl acrylate caused benign and malignant neoplasia of the forestomach; polybrominated biphenyls induced cholangiocarcinomas of the liver; propylene oxide produced hemangiosarcomas of the nasal cavity. Two chemicals caused tumors in one site of one sex of one species: isophorone (kidney) and melamine (tumors of the urinary bladder). Only one chemical (1,4-dichlorobenzene) induced tumors in two organs, kidney and liver.

Table 6 summarizes results from the 90-day toxicity experiments, used mainly to determine target organs and toxicity dose–response relationships, as well as to aid in the selection of exposure levels for the longer-term carcinogenesis studies. In most if not all cases, the concentrations used in the 13-week studies were higher than those eventually selected for the 2-year studies (31,32), the thesis being that if exposures are
chosen below those that showed overt (histologically detectable) toxicity in short-term experiments, it will prevent or reduce confounding interpretative factors such as the development of life-threatening lesions or excessive adverse influences on normal health and well-being (e.g., lowered body weight gain and reduced survival compared to controls) from factors other than carcinogenesis. Nine chemicals showed toxic lesions in each of the eventual cancer target sites. Five of these nine chemicals induced cancer in organs not showing any concomitant toxicity, probably because the lesions were seen at higher ("toxic") doses in the 90-day experiments or because adaptation occurred during the long-term exposure regimen.

As an illustration, 13-week exposures to trichloroethylene were associated (only retrospectively) with minimal or mild cytomegaly and karyomegaly of the renal tubular epithelial cells of the inner cortex in 8/9 male rats receiving 2000 mg/kg and with equivocal or minimal lesions in 5/10 female rats given 1000 mg/kg. The renal effects were so minimal that they were diagnosed only during a reevaluation after definite renal toxicity was seen in the 2-year studies. In the latter experiments, "toxic nephrosis" (called "cytomegaly") was present in 98% of males and in 100% of females (severity grades ranging from 1.9 to 3.1), but was not found in controls. Despite this consistent toxicity, only three high-dose males had adenocarcinoma of the tubular cells, two low-dose males had tubular cell adenomas, and one high-dose female rat had a tubular cell adenocarcinoma.

Nonetheless, these tumors are quite rare in control animals, and the detection of even one such tumor in female rats may be cause for further investigation (including step-sectioning remaining portions of kidney). Control male rats typically show moderate-to-marked nephropathy (grades 2.5-3.5) at 2 years, and kidney tumors in controls (80% benign in males and 100% benign in females) occur in only 10/1000 (0.5 tumors/group of 50) male Fischer rats and in 1 or 2/1000 (0.15 tumors/group of 50) female rats. Thus, even a low incidence in this strain must be evaluated closely for possible chemical causation. To ascertain the possible effect of aging on tumor incidences, a histopathologic comparison was made (68) of 2320 young (110-116 weeks of age for 2-year studies) and 529 old (140-146 weeks) F344 control male rats; no differences were reported for tubular cell tumors of the kidney: 0.3% (3/1000) versus 0.6% (6/1000). Given that all animals with tumors of the kidney invariably exhibit toxicity ("spontaneous" nephropathy) as well, and typically there are larger numbers of animals (control and exposed) with toxic lesions (trichloroethylene, for example, mentioned above) and/or no cancer of the kidney (69,70), empirical correlations are virtually impossible. If a chemical induces a unique and easily discernable toxic lesion (e.g., tris(2,3-dibromopropyl)phosphate [71]) or a lesion of a greater severity than that seen in aged animals and only those animals get cancer, then a more logical correlation can be made. Nonetheless, more mechanism-oriented studies are then needed to ascertain correlation causality.

On examining the non-neoplastic and neoplastic data reported in the NTP Technical Report Series for those approximately 40 chemicals causing tumors of the kidney (62,69), some might conclude that an empirical correlation exists between toxicity (e.g., nephropathy) and carcinogenicity (tumors) because all animals with tumors exhibit toxicity. The interpretative difficulty for the kidney has been mentioned above in that if all animals have nephropathy, there can be no or little chance for statistical correlation. In some but not all cases, one can differentiate between age-related nephropathy and chemical nephropathy (e.g., TRIS); however, even in these situations the differences in severity rarely exceed a half grade point, and some believe that at least a full grade point difference is needed in this subjective diagnostic criteria before one could conclude that a significant biological difference exists.

Regarding the effects of trichloroethylene in B6C3F1 mice, 13 weeks of exposure resulted in centriflobular necrosis of the liver in 6/10 males and in 1/10 females given 6000 mg/kg; ≤3000 mg/kg did not induce this lesion. As in rats, reevaluation of kidney sections revealed cytomegaly and karyomegaly in both sexes of most animals in the 3000 and 6000 mg/kg groups and none in the 1500 mg/kg or lower exposure groups. In the single exposure level of 1000 mg/kg selected and used in the 2-year studies, toxic nephrosis ("cytomegaly") was diagnosed in 90% of males (1.5 severity) and in 98% of females (1.8 severity; none in controls). One control male (adenoma) and one exposed male (adenocarcinoma) had tubular cell tumors. In the liver,

### Table 6. Summary results on toxicity observed from 51 prechronic (13-week, 90-day) studies compared to positive carcinogenicity from 2-year studies.

| Lesion                                      | Number |
|---------------------------------------------|--------|
| No lesions of toxicity or preneoplasia      | 13     |
| Toxic lesions only in organs not resulting in cancer (nontargets) | 16     |
| Toxic lesions in some 2-yr target sites      | 13     |
| Toxic lesions in all eventual cancer target sites | 9      |
| Salmonella                                   |        |
| 1. C.I. Disperse Blue 1 (anthraquinone)      | +      |
| 2. C.I. Solvent Yellow 14 (monooazo)         | +      |
| 3. D & C Red No. 9 (azo pigment)            | ±      |
| 4. 1,4-Dichlorobenzene                      | -      |
| 5. Digicidol resorcinol ether               | +      |
| 6. Ethyl acrylate                            | -      |
| 7. Melamine                                  | -      |
| 8. Trichloroethylene                          | -      |
| 9. 4-Vinylcyclohexene                       | -      |

*aChemicals causing cancer but not showing toxic lesions in those same organs in 2-year experiments.*

*bHyperplasia only.*

*cHyperplasia with/without toxicity.*

*dNo toxicity or hyperplasia.*
adenomas, carcinomas, and metastases were increased in exposed animals; interestingly there was no evidence whatsoever of non-neoplastic (toxic) lesions of the liver. These responses (i.e., tumors with no toxicity) have been mimicked in methylene chloride inhalation experiments in which lung and liver cancers were induced with no observed toxicity or increase in cell proliferation. Thus, toxicity findings from higher exposures in short-term experiments or observed toxicity in long-term experiments (e.g., kidney) cannot be used mechanistically to either predict eventual carcinogenicity or to advocate toxicity and resultant sequelae as a mechanism of tumor development.

**Discussion**

The renewed attention given to the role of chemically induced and sustained cell proliferation in carcinogenesis (36-39,72) represents a renewed attempt to define this role, in spite of the fact that few studies have been accomplished in regard to this potential relationship. Statements are being made and debated about mechanisms of chemical carcinogenesis as if these statements were based on factual data, duly deliberated, and consensus reached in the historical scientific paradigm (73). Obviously, cell division and replication are essential to the carcinogenesis process (74); if these proliferative processes were not occurring, regardless of any carcinogenic exposures, then no cancers would develop. The question is, does cell proliferation, enhanced by whatever means, cause or influence the carcinogenesis process? I believe that, in addition to being necessary for tumor development, "induced" cell proliferation may indeed influence the carcinogenic activity of chemicals either by a) reducing the latency time for tumor development or/and by b) increasing the numbers and perhaps multiplicity of tumors harvested. I do not believe, and there are no data to support, the notion that simply increasing cell turnover leads to or causes cancer. A plethora of experimental data do exist to support the conclusion that toxicity and resultant compensatory cellular replacement do not often associate with cancer. The extensive facts to the contrary in this paper testify, as do other papers in these proceedings [e.g., Ward et al. (75)], to this conclusion.

As two examples, one regarding renal carcinogenesis and mechanism, Short (76) states that "correlative studies with a number of other renal carcinogens and noncarcinogens are warranted before general conclusions can be made", and that "underlying mechanisms of chemically induced cell proliferation must be understood before cause-and-effect relationships between renal cell proliferation and enhancement of the stages of renal cancer are made." Similarly, in the other example, relating to nasal cancer, Monticello et al. (77) stress "that cell proliferation in response to cell death is not the sole determinant in nasal carcinogenesis, since other inhaled irritant gases, such as dimethy-
chemicals not causing any toxicity or carcinogenicity; given that these are, in fact, toxicology experiments, few chemicals fit this group (e.g., resorcinol).

For chemicals in the first group (5a in Table 7), there can be no or little doubt that cell degeneration, cell death, and cell regeneration (and hence cell replication, although DNA synthesis was not measured) were actively taking place in affected organs, yet no carcinogenesis was observed. One can assume with reasonable but not complete certainty that the obverse existed for chemicals in group 5b in Table 7: no or only little or subtle cellular replication was taking place in the eventually affected tissues before the carcinogenesis process. Whether these chemicals may have preferentially exerted influence on the cancerous foci remains to be deciphered, but the evidence seems to indicate this would be unlikely. Even for chemicals in group 5c of Table 7, one would be mistaken to assume that the observed toxicity was indeed the origin of the carcinogenesis process, a mistake made often when one unwittingly correlates short-term cellular proliferation findings with eventual tumor development. Most would agree, however, that induced cellular proliferation may influence the interval to tumor occurrence as well as the yield of tumors (78). No data exist to indicate that a noncarcinogenic chemical can be made to be carcinogenic simply by enhancing cellular proliferation of normal tissue. Likewise, predicting whether a chemical will be carcinogenic using short-term data on induced cell proliferation will not likely be possible.

Too many variables and too many exceptions exist to formulate some universal algorithm or biological continuum. In fact, to better define the role of cell proliferation on the carcinogenesis process, more and better designed cell turnover studies are needed that mimic the experimental protocols used to determine the presence or absence of carcinogenesis in the first place. Few studies of this type have actually been designed or accomplished (79,80). Further, de novo long-term chemical carcinogenesis studies should incorporate (perhaps selectively) cell proliferation data collection in the experimental design. A misguided criticism of this generic experimental enhancement is the admonition that one does not know in advance which tissues (if any) will develop cancer; this actually does not matter because one will gain immeasurable information regardless of whether a particular chemical turns out to be carcinogenic or not or if it causes cancer in another organ. One needs only to direct efforts toward those tissues and organs where responses are most likely to be expected, using historical findings (62).

Until a considerably larger data set is established, the role of chemically enhanced cell proliferation in the carcinogenic performance of a chemical can only be speculated. And for now and into the immediate future, one would be premature and probably incorrect to make public health decisions on the basis of skimpy scientific data regarding the influence of cell proliferation per se on the carcinogenesis process.

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