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INTERSPECIES COMPARISON OF CARCINOGENIC POTENCY

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For guidance in decisions on how to safeguard humans from carcinogens, it is necessary to use data on carcinogenesis in animals. This paper discusses how such data, combined with human experience, may be used quantitatively in such decisions. It is demonstrated empirically that good correlations exist between different species for suitably defined carcinogenic potencies for various chemicals. This allows sufficient accuracy in extrapolating from animal data to human risk to support a logical scheme for the evaluation of such risks. Some recommendations for future research are given.

INTRODUCTION

A prudent policy for cancer prevention requires that we use data on animal carcinogenesis as a quantitative predictor of human risk. No available theory allows such quantitative predictions, although they should be possible if the animals' metabolism is similar to that of humans. In this paper we outline and assess experimental data on which such comparisons could be based.

In the next section we give the definitions and assumptions used in this paper: the basic assumptions concerning the relation between cancer incidence and dose of carcinogen (a linear, no-threshold theory), and the definition of carcinogenic potency (for a given chemical and species of animal). The third section shows the results of computing the potency of various chemicals for various species. In particular, the potencies for ~ 70 chemicals are evaluated in 2 species from a set of experiments with nearly identical designs; there are good interspecies correlations between the potencies, allowing interspecies extrapolation within about an order of magnitude. Most important is a set of comparisons of carcinogenic potencies in animals and humans derived from the limited studies available. Despite the shortcomings of the "experimental design" of this data set, the results are consistent with the possibility of extrapolating between species, in particular between animals and humans, within a factor of 10.

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On this basis, a scheme is discussed in the fifth section for quantitatively estimating carcinogenic risk to humans. The accuracy of such estimates depends on the number of carcinogens included. Before this, a few of the possible confusing effects resulting from metabolism and synergisms are mentioned. Possible exceptions to the proposed scheme are discussed in the sixth section. Finally, possible improvements, modifications, and extensions are discussed, as well as ways to further verify the scheme.

ASSUMPTIONS AND DEFINITIONS

We make the following assumptions and test the results against experiment:

1. The lifetime probability P of an animal getting cancer depends on the integrated lifetime dose of the carcinogen. (We may restrict ourselves to cancer of a particular type or at a specific site.)

2. The relevant measure of dose is the ratio of the weight of carcinogen to the body weight of the animal.

3. Assumptions 1 and 2 hold for lifetime ingestion at constant dose rate, and to first approximation for nonconstant dose rates if the dose is spread over an appreciable fraction of a lifetime. In what follows, we always quote integrated lifetime dose as an equivalent lifetime average dose rate (mg/kg·d).

4. At low doses the dose-response curve is linear. We define the potency of a carcinogen as the gradient of the line

$$P = \alpha + \beta d \qquad \alpha \geq 0 \qquad \beta \geq 0 \tag{1}$$

where α is the probability of getting cancer in the absence of carcinogen, d is the measure of dose of carcinogen (mg/kg·d averaged over a lifetime), and β is the potency of the carcinogen (kg·d/mg).

5. At high doses, because the probability cannot exceed 1, we assume the dose-response curve saturates to 1 exponentially. This assumption is needed for some of the animal experiments, where large fractions of the experimental populations got cancer. The form of the dose-response curve we use is

$$P = 1 - (1 - \alpha) \exp\left(-\frac{\beta d}{1 - \alpha}\right) \tag{2}$$

which reduces to Eq. (1) for low doses, $d \ll (1 - \alpha)/\beta$.

6. In animal experiments, the number getting cancer is binomially distributed with probability P.

The question of linearity at low doses has been argued at length, but Eq. (2) has the merits of simplicity and of providing a plausible upper bound for a wide range of possible dose-response relationships (Guess et al., 1977), and hence is generally considered conservative. The absence of a threshold level for carcinogenic action is ensured by the restriction $\alpha > 0$, again to obtain conservative results for low doses. There is good evidence that assumption 5 above is incorrect in at least one case [vinyl chloride; see Maltoni et al., (1974)] and that it is possible for P to saturate to some value less than 1. This possibility makes little difference to the results reported here. The parameters α and β are estimated from experimental data, using maximum likelihood techniques (Appendix A). In most cases, experiments were performed at no more than two nonzero dose levels, and for many, especially studies of humans (Appendix B), only one dose level is available and the estimate of dose may have a large error.

INTERSPECIES COMPARISONS

Mouse and Rat

The National Cancer Institute (NCI) series of Carcinogenesis Bioassay Reports describe experiments performed with similar experimental designs on rats and mice, containing sufficient data to compute values of the carcinogenic potency. Maximum likelihood estimates for the parameters α and β in Eq. (1) were computed for those results in the carcinogenesis reports[1] that were considered statistically significant therein, together with some that were not statistically significant. Tables 1–3 list the potencies computed for the site of tumor incidence giving the greatest potency, even though in some cases the incidence at this site was not considered statistically significant, or other sites had a tumor incidence of greater significance. (Testicular tumors in male Fischer 344 rats were ignored.)

These results are plotted in Figs. 1–5. Figures 1–3 compare potencies in males and females of three species. In all cases there is good correlation (dashed lines are lines of equal potency), the potency in males being a good predictor of the potency in females and vice versa. Furthermore, the potencies are approximately equal over a wide range of values; best-fit straight lines of unit slope in Figs. 1–3 indicate slightly higher potencies in male mice and Fischer rats by factors of 1.1 and 1.7, respectively. Figures 4 and 5 show interspecies correlations in potency. The geometric mean potency in males and females of one species is plotted against the same mean for the other species. For the Osborne-Mendel rat versus the B6C3F1 mouse (Fig. 4) the correlation is excellent, and for the Fischer 344 rat versus the B6C3F1 mouse (Fig. 5) it is still good. In both cases, best-fit lines of unit slope (dashed lines) lie within an order of magnitude of most points and, with outlying points omitted, give ratios of potencies

[1] We had analyzed 90 such reports at the time this paper was revised.

TABLE 1. Potencies of Chemicals by Ingestion

Chemical	Potency (kg·d/mg)[a]			
	Osborne-Mendel rat		B6C3F1 mouse	
	Male	Female	Male	Female
Chloroform	2E-3[b]	2E-3	9E-3[b]	1E-2[b]
Chlordecone	8E-2[b]	1E-1	6E-1[b]	2E-1[b]
Trichloroethylene	[c,d]	[c,d]	7E-4[b]	2E-4[b]
Chlordane	6E-3	1E-2	2E-1[b]	9E-2[b]
Heptachlor	2E-2	1E-2	5E-1[b]	3E-1[b]
Dichlorvos	1E-2	1E-3[c]	[c]	[c]
Tetrachloroethylene	[c,d]	[c,d]	1E-3[b]	1E-3[b]
Aldrin	8E-2[b]	6E-2[b]	5E-1[b]	9E-2[c]
Dieldrin	3E-2[c]	6E-2	4E-1[b]	1E-1[c]
Picloram	7E-5[c]	3E-4[b]	[c]	[c]
Chloramben	2E-4	1E-4	1E-4[b]	9E-5[b]
Nitrofen	1E-3[e]	1E-3[b]	5E-3[b]	8E-3
Tetrachloroethane	1E-3[c]	4E-3	6E-3[b]	1E-2
Tetrachlorvinphos	2E-4[c]	3E-4[b]	1E-3[b]	2E-4
Trifluralin	4E-4	2E-4	2E-4[c]	1E-3[b]
Methoxyclor	4E-3	2E-3	[c]	[c]
Carbon tetrachloride	2E-3[b,c]	1E-3[b]	4E-3[b]	3E-3[b]
Endrin	9E-1	7E-1	3E-1	[c]
Chlorothalonil	2E-4[b]	2E-4[b]	[c]	[c]
1,2-Dichloroethane	3E-3[b]	6E-3[b]	2E-3[b]	2E-3[b]
1,4-Dioxane	1E-3[b]	6E-4[b]	7E-4[b]	2E-3[b]
1,2-Dibromoethane[d]	2E-1[b,e]	1E-1[b,e]	9E-2[b,e]	1E-1[b,e]
Dioxathion	3E-2	2E-2[c]	2E-3	1E-3
Parathion	1E-1	1E-1	1E-3[c]	4E-4[c]

[a] Value AE-B means A X 10^{B}.
[b] Significant effect noted in original study.
[c] Computed potency is less than twice the sensitivity.
[d] Study lasted only about half the lifetime because of high mortality.
[e] High-dose group omitted from analysis because of high mortality.

in Osborne-Mendel rats and Fischer rats to potency in B6C3F1 mice as 0.40 and ~ 4.5, respectively.

There is no a priori reason why any correlation should correspond to direct proportionality (unit slope on the figures). It is, however, the simplest hypothesis and it gives good agreement with the data. Further details of the derivation of the potencies from the experimental results are given in Appendix A.

With these data, the experimental evidence on carcinogenesis in one species can be used to estimate the carcinogenic potency of the same chemical in another species by simply multiplying by an interspecies relative sensitivity factor.

However, this argument applies only to potency summed over all tumor sites, or to potency at the most dominant site. The data show that

TABLE 2. Potencies of Chemicals by Ingestion

Chemical	Potency (kg·d/mg)			
	Fischer 344 rat		B6C3F1 mouse	
	Male	Female	Male	Female
Proflavine	1E-2	1E-3[a]	5E-3	1E-2[b]
Nitrilotriacetic acid (NTA)	2E-4	5E-4[b]	4E-4[b]	6E-5
Na_3NTA	[a]	[a]	4E-4[b]	1E-4[a]
Na_2NTA	7E-4[b]	6E-4[b]	–	–
Phenformin	9E-3	6E-3	6E-4	2E-4[a]
EDTA	4E-4	2E-4[a]	2E-4	1E-4
Dapsone	1E-2[b]	2E-3[a]	1E-4	[a]
2-Methyl-1-nitroanthraquinone	7E-3[b]	4E-3[b]	–	–
Aroclor	5E-2	1E-2[d]	–	–
Lasiocarpine	7E-1[b]	6E-1[b,c]	–	–
Tris (2,3-dibromopropyl) phosphate (TBP)	2E-1[b]	3E-2[b]	5E-3[b]	6E-3[b]
2,4-Diaminoanisole	2E-3[b]	6E-4[b]	8E-4[b]	6E-4[b]
Ethionamide	[a]	1E-3	1E-3	1E-3
Acetohexamide	3E-4	2E-5	[a]	[a]
3-Nitropropionic acid	8E-2	2E-2[a]	6E-3	5E-3
2-Amino-5-nitrothiazole	1E-2[b]	6E-3	2E-3[a]	1E-2
2,4-Dinitrotoluene[d]	3E-2[b]	3E-2[b]	[a]	[a]
4-Chloro-o-phenylenediamine	2E-3[b]	2E-3[b]	5E-4[b]	2E-4[b]
APC mixture	2E-4	2E-4	1E-4	3E-5[a]
Trimethylphosphate	4E-3	2E-3[a]	6E-5[a]	2E-3[a]
4-Chloro-*m*-phenylenediamine	9E-4[b]	7E-4	8E-5	2E-4[b]
dl-Menthol	[a]	[a]	2E-4	2E-4
Phenazopyridine hydrochloride	1E-3[b]	6E-4[b]	1E-3	7E-3[b]
Anilazine	3E-3	4E-3	[a]	[a]
5-Nitro-o-toluidine	2E-3[b]	2E-3[b]	[a]	[a]
3-Amino-4-ethoxyacetamide	[a]	[a]	3E-4[b]	9E-5[a]
5-Nitroacenaphthene	1E-2[b,c]	1E-2[b,c]	[a]	1E-2
Piperonyl sulfoxide	8E-5[a]	4E-4	1E-2[b]	8E-4
2,5-Toluenediamine sulfate	1E-3[a]	1E-3	2E-3	2E-3
5-Nitro-o-anisidine	6E-3[b]	9E-4[b]	3E-4[b]	1E-4[b]
Trimethylthiourea	4E-3[a]	2E-2[b]	1E-3	4E-4[a]
Aniline hydrochloride	2E-3[b]	3E-4[b]	4E-5[a]	7E-5
C.I. Vat Yellow 4	[a]	[a]	5E-5[b]	3E-5

[a] Computed potency less than twice the sensitivity (see Appendix A).
[b] Significant effect noted in original study.
[c] High-dose group omitted from analysis because of high mortality.
[d] Benign tumors in rats (skin in male, mammary in female).

TABLE 3. Potencies of Chemicals

Chemical	Potency (kg·d/mg)			
	Sprague-Dawley rat		B6C3F1 mouse	
	Male	Female	Male	Female
Isophosphamide	8E-2	8E-1	5E-2	7E-2
5-Azacytidine	4E-1[a]	7E-1[a]	3E-1	1E-0[a]
Emetine	9E-1[a]	4E-1	[b]	[b]
Acronycine	1E-1[c]	8E-2[c]	[b]	[b]
β-2'-Deoxy-6-thioguanosine monohydrate (β-TGdR)	9E-2[c]	2E-1[c]	[b]	[b]
Tris (1-aziridinyl) phosphine sulfide	2E-0[c]	2E-0[c]	3E-0[c]	3E-0[c]
Phenoxybenzamine hydrochloride	6E-1[c]	2E-1[c]	1E-1[c]	9E-2[c]
Estradiol mustard[d]	5E-1	4E-1	9E-2	9E-2[c]
Phenesterin[d]	8E-2	3E-1[c]	1E-1[c]	2E-1[c]

[a] High-dose group(s) omitted from analysis because of high mortality.
[b] High early mortality precluded useful analysis.
[c] Significant effect noted in original study.
[d] Gavage. All others by ip injection.

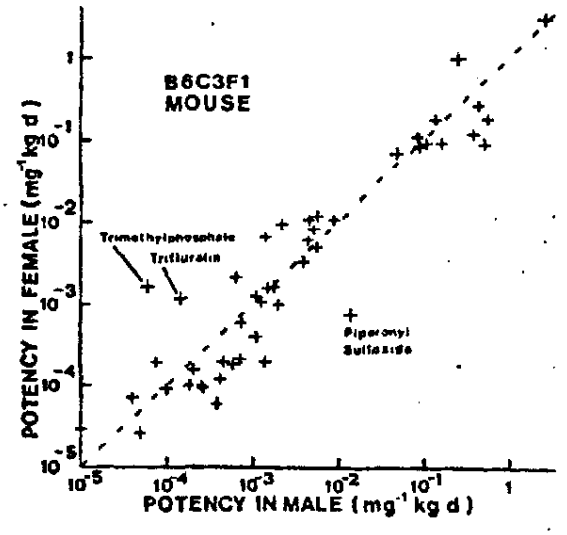

FIGURE 1. Carcinogenic potency in B6C3F1 mouse: male versus female.

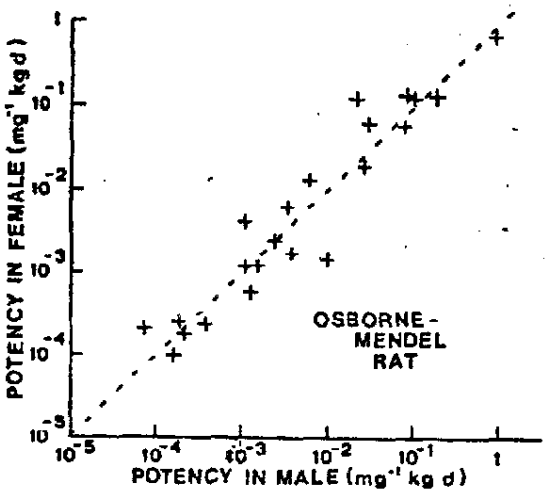

FIGURE 2. Carcinogenic potency in Osborne-Mendel rat: male versus female.

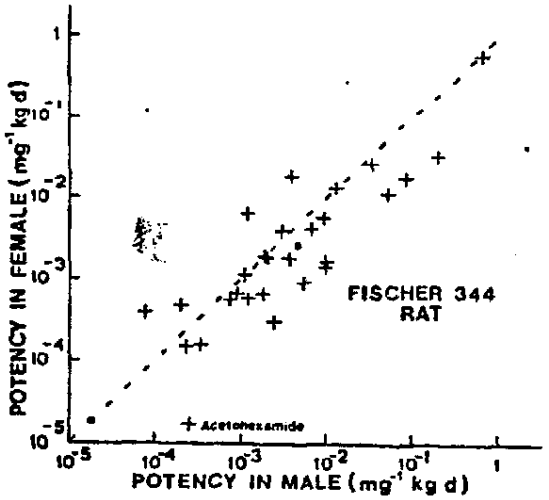

FIGURE 3. Carcinogenic potency in Fischer 344 rat: male versus female.

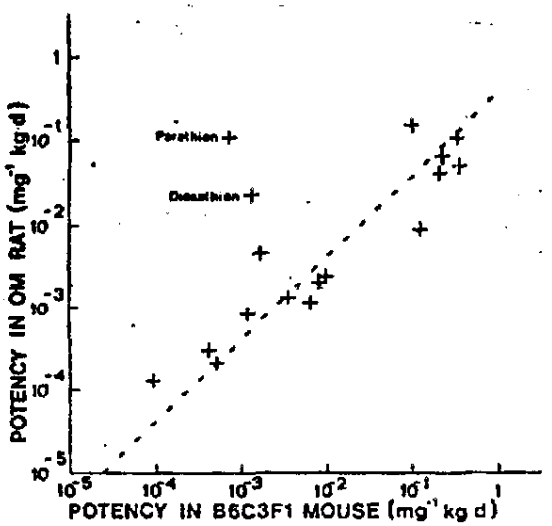

FIGURE 4. Geometric means of carcinogenic potencies in males and females: Osborne-Mendel rat versus B6C3F1 mouse.

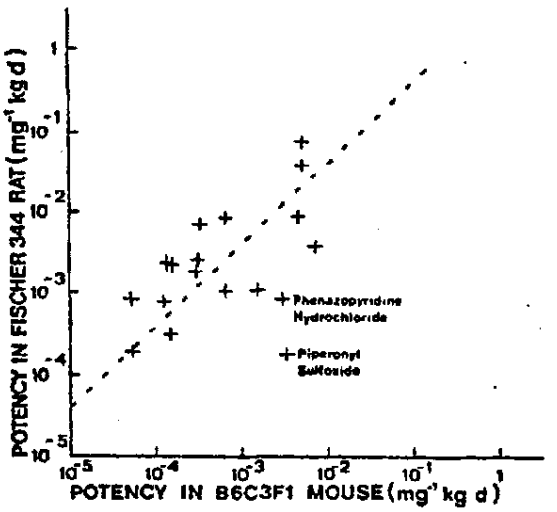

FIGURE 5. Geometric means of carcinogenic potencies in males and females: Fischer 344 rat versus B6C3F1 mouse.

the dominant site in these mice is often the liver, whereas the site could be thyroid, kidney, or mammary gland in the rat (and perhaps another site altogether in humans). Because our concern is for cancer, no matter what the site, this simplification is important.

Humans and Other Animals

There are few good data on human cancers from which the cause can be even probably assigned. The available data are primarily for a few workers industrially exposed to large concentrations of a substance and unexposed workers with whom their mortality or morbidity can be compared. The potencies derived from these data will be even less precise than those obtained from controlled experiments.

The animal data with which we compare the human cases comes from a diverse set of experiments with different protocols and different strains of the species considered. We cannot, therefore, expect correlations as good as those obtained in the last section (e.g., difference between 2 rat strains of a factor of ~10). It is necessary in some cases to estimate carcinogenic potencies from experiments in which observation was not continued for the lifetime of the experimental animals and/or the carcinogen was administered to the animals for only a fraction of their lifetime. In the latter case it was assumed that the lifetime average dose rate was the controlling variable (assumption 3), while in the former case the observed numbers of cancers were corrected for those missed because of the limited observation period. Because cancer incidence varies with age, this correction could have been made by using typical data on cancer incidence, but was in fact performed by using a simple theory that fits such cancer incidence. We used the theory of Armitage and Doll (1954) in its simplest form, in which the rate of appearance of cancers is given by

$$\frac{dN}{dt} = \lambda t^k \tag{3}$$

where dN/dt is the rate of appearance cancers, t is the elapsed time, and k is a function of the site of the cancer; empirically, $2 < k < 8$. Thus, for example, if the animals are observed only half their lifetime, the data can be corrected to a lifetime incidence by multiplying by 2^{k+1}. The correction will be uncertain to the extent that k is uncertain within the range $2 < k < 8$. Various authors have gone through the details of the procedure (Gehan, 1969; Peto, 1974), which can describe the cancer hazard for a wide range of variations from the linear theory (lengthening of time to tumors, thresholds, repair mechanisms).

An attempt has been made in a National Academy of Sciences (NAS) report (1975) to perform the comparison of this section, and Meselson and Russell (1977) compare carcinogenic and mutagenic potency. We review and suggest changes in these results (converting them to car-

cinogenic potencies) and add some new ones, mostly upper limits. The resulting comparisons are shown in Table 4 and their derivations are discussed in Appendix B. The same results are shown graphically in Figs. 6 and 7, where it is evident that they are consistent with correlations between human and animal carcinogenic potencies similar to those demonstrated above between mouse and rat (dashed lines on the figures are lines of equal potency). As expected, these data are not so well correlated, but the interspecies sensitivities appear to be ≤ 5:1 for both human:mouse and human:rat.

Various agencies, in attempting to derive carcinogenic potencies in humans from potencies in animals, have included multiplicative factors to account for differing sensitivities in different species. The NAS report assumes that animals and humans are equally sensitive when they have the same total intake (as a fraction of body weight) during a lifetime. The Food and Drug Administration (FDA) assumes that they are equally sensitive when they have the same fraction of pollutant in their food or water intake, whereas the Environmental Protection Agency (EPA) makes a correction for surface area by the factor $(M_{human}/M_{animal})^{1/3}$ where M is the mass. The procedure used here is to derive these interspecies relative

TABLE 4. Comparison of Potencies: Animal and Human

Chemical	Potency[a]			
	Mouse	Rat	Dog	Human[b]
AN	–	0.06	–	< 0.3
Aflatoxin B_1	130[c]	500–1300	–	200 (3)
As	1.5–30	< 0.01	–	15 (3)
Benzene	~ 0.0008	~ 0.0008	–	0.001 (3)
Benzidine	0.08	130–2500[d]	0.2	34 (10)
Chlornaphazine	20	–	–	2 (10)
Chloroform	0.01	0.002	–	< 0.001
DCB	0.006	0.025	0.14	≤ 5
Diethylstilbestrol	14	–	–	1[e] (10)
EDB	6	6	–	0.8 (10)
Lead acetate	0.001	0.007	–	< 2.5
Saccharin	–	0.0003[c]	–	< 0.04
Vinyl chloride	0.004	0.01	–	0.02 (3)
Radiation[f], $(rem/yr)^{-1}$	0.01	–	–	0.02 (3)
Smoking[f], $(no./d \cdot kg)^{-1}$	0.06	–	–	0.06 (3)

[a] Values are kg·d/mg except where noted.
[b] Number in parentheses next to human potency is our estimate of the accuracy of the number.
[c] Includes intrauterine exposure.
[d] Oral administration. Value for sc injection is 0.06 in rat and 0.08 in mouse (see text and Appendix B).
[e] Women ingesting pills in pregnancy, resulting in cancer in their daughters.
[f] Not included in Fig. 7.

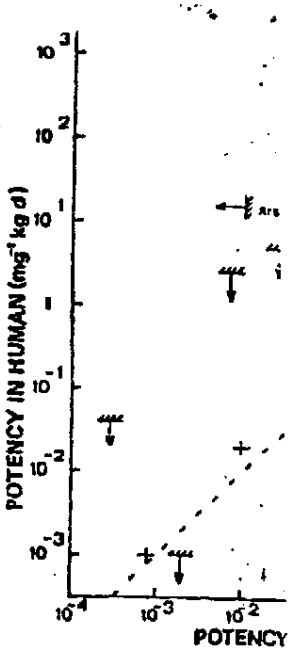

FIGURE 6. Carcin.

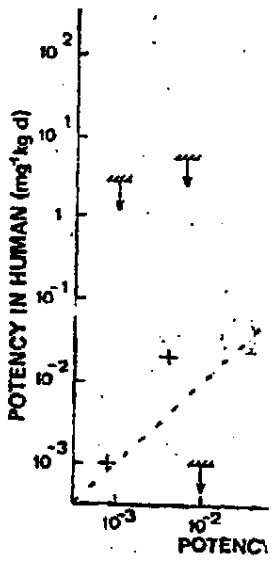

FIGURE 7. Carcinog

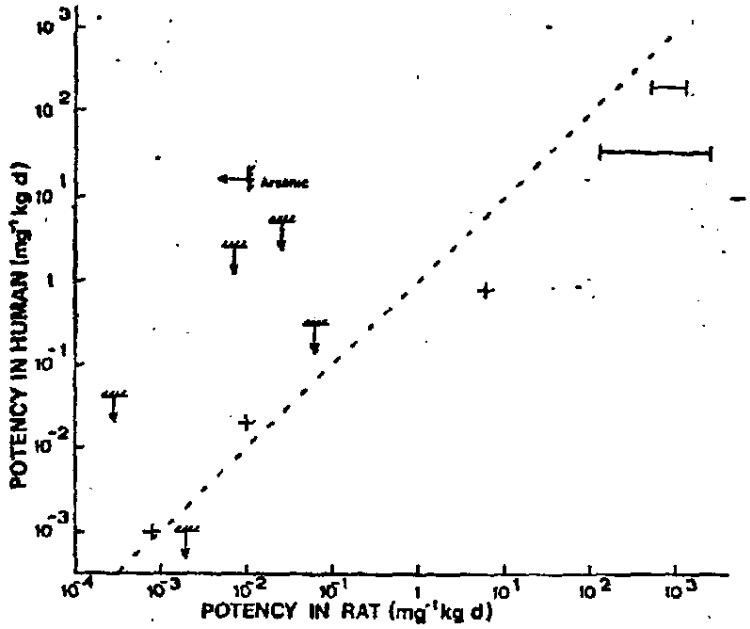

FIGURE 6. Carcinogenic potency in human versus rat.

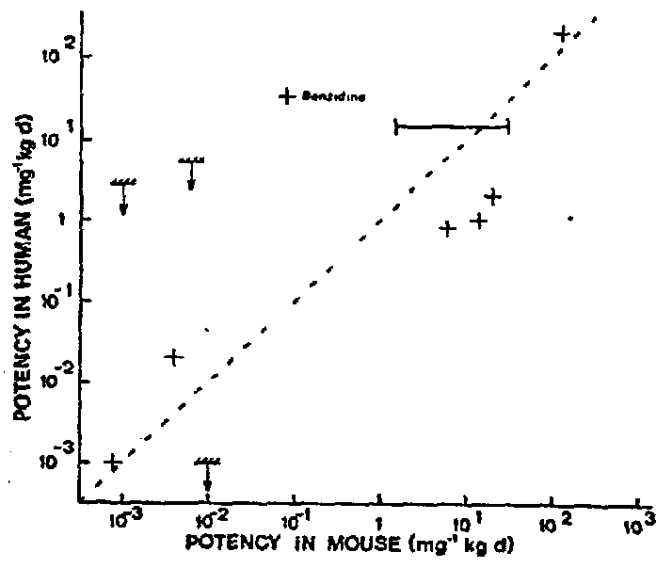

FIGURE 7. Carcinogenic potency in human versus mouse.

sensitivities from experiment. Table 5 lists the relative sensitivities (using our definition of potency).

METABOLIC EFFECTS

Insofar as possible, we compare data from experiments in which the same method of application of the chemical was used for both animal and human—and the exposure is for the same fraction of the lifetime in both animal and human. In some cases we have to compare animal exposure by ingestion with human exposure by inhalation or dermal contact, and the comparison is then less accurate.

Ideally, we would like to use data on animal and human metabolism to describe how the carcinogenic chemical reaches the organ of interest from the various sites of administration. The rat experiments with vinyl chloride show equal potencies for liver cancers by both ingestion and inhalation. For chemicals metabolized in the lung, such as benzo[*a*]-pyrene, we might expect a bigger difference. For benzo[*a*]pyrene applied on the skin, the sensitivity of mice apparently depends on the solvent system used (Bingham and Falk, 1969). In this experiment, the concentrations of benzo[*a*]pyrene in 2 different solvent systems required to elicit cancers differed by a factor of 1000, although the difference in numbers affected in each case reduces any apparent potency variation to 500. This difference may result from the relative efficacy of the two solvent systems in transporting the benzo[*a*]pyrene into or through the skin. By using the potency for ingestion given in Table 4 and the doses used by Bingham and Falk, the remarkable observation is the lack of sensitivity when the benzo[*a*]pyrene was applied in the "inert" solvent rather than the sensitivity when it was applied with the "cocarcinogen."

In some cases, giving a small number of large doses may result in fewer cancers than giving the same total amount in small daily doses, because metabolic activity may be saturated in the first case. For this reason, animal studies utilizing sc injection may be less sensitive than continuous ingestion or inhalation studies.

We note here that the correlations may be upset by synergistic effects.

TABLE 5. Relative Sensitivities between Species

Agency	Rat	Mouse	Human
National Academy of Sciences (1975)	~1.5	1	~35
Food and Drug Administration (% in diet)	1	0.35	4
Environmental Protection Agency (corrected for surface area)	1	0.43	4.7
This paper (experiment)	~$\frac{1}{3}$-3	1	≲5

In the animal experiments these effects should be small or absent, because the environment is controlled. However, our estimates of potency in humans necessarily include any synergistic effects resulting from other environmental carcinogens, so that the potency of the chemical acting alone on humans may differ from that given here. From a practical point of view this is irrelevant, provided the background of other carcinogens or cocarcinogens to which humans are exposed does not vary too much.

POLICY IMPLICATIONS

The results of the third section confirm that a logical policy can be followed, independent of the particular material involved.

1. Animal experiments at high doses determine the carcinogenic potency of the material.
2. Interspecies relative sensitivities allow comparisons of the animal experiments and extrapolation to humans, to obtain a good estimate of the (high-dose) carcinogenic potency in humans.
3. Use of the linear, no-threshold model gives a conservative estimate of the low-dose carcinogenic potency (i.e., that it is equal to the high-dose potency).
4. Evaluation of the expected human exposures (doses) allows computation of the expected human risk: for exposure to (lifetime average) dose d (mg/kg·d), the probability of cancer caused by the carcinogen is βd, where β is the potency in kg·d/mg (provided $\beta d \ll 1$).
5. Any available data on metabolic differences between animal and human may be used to modify this preliminary risk estimate.
6. A decision is then required as to whether the resultant individual risk or the total societal risk is acceptable.

EXCEPTIONS

Some materials do not fit into the scheme we have outlined, and such possible exceptions are identified by name on the figures. In Fig. 1, piperonyl sulfoxide, trimethylphosphate, and trifluralin lie substantially farther from the equal potency line than the other materials. Whereas the last two may simply represent the tails of a distribution, the position of the first in Fig. 5 confirms its exceptional nature. Similarly, acetohexamide (Fig. 3) and phenazopyridine hydrochloride (Fig. 5) may simply be cases of large random error, but parathion and dioxathion (Fig. 4) stand out as exceptions. The lack of controlled experiments and different experimental designs makes the identification of such exceptions more difficult in the human-animal comparisons, but there is a clear difference between Wistar and Sprague-Dawley rats in the case of benzidine (Appendix B), and As shows exceptional behavior in Fig. 6.

These exceptions may represent differences in the metabolism of these particular chemicals in these particular species (or even in one sex of a species) and are obvious candidates for metabolic studies and testing in other species. As (and possibly Pb) may have to be treated slightly differently, because in the case of such materials (as opposed to the organic chemicals otherwise included) we might expect the carcinogenic potency to be largely independent of the (inorganic) chemical form, except insofar as those forms are differently metabolized.

IMPROVEMENTS AND EXTENSIONS

The interspecies relative sensititivies, especially between animal and human, need further work. It would be useful to obtain them between the animal strains currently used for carcinogenicity testing and humans, by retesting on those strains the chemicals for which the potency in humans is known, using tests with exposure routes and times similar to those in the human exposure. There is evidently a wide variation in sensitivity between strains of a given species (e.g., the Fischer and Osborne-Mendel rats discussed in the third section have relative sensitivities differing by a factor of ~ 10).

Correlations between mutagenic potency (in *in vitro* tests) and carcinogenic potency should be searched for using quantitative measures of both. Meselson and Russell (1977), made a quantitative comparison of animal potency and mutagenesis for several chemicals. Direct correlation between mutagenic potency and human carcinogenic potency is even more desirable. We would welcome details of evaluations of mutagenic potency for the chemicals in Tables 1–4.

APPENDIX A

We give here details of the derivation of Tables 1–3. All are based on the NCI carcinogenesis bioassays, reported in their technical report series (NCI-CG-TR). Each report gave experimental design, together with results consisting of the number of animals with tumors of various types (sites) compared with the number of animals examined at those sites. Doses were computed from the experimental designs. Dose was given as (1) milligrams per kilogram or (2) fraction of diet. In case 1, it was straightforward to compute total lifetime dose (mg/kg) and average over the assumed lifetime (728 d in rats and 637 d in mice). In case 2 curves of food consumption (in body weights) as a function of age and sex were constructed from control animal feeding data in NCI-CG-TR-2 for B6C3F1 mice and Osborne-Mendel rats. These were assumed to be typical for all the mice and rats in all the experiments, except for a correction for body weight: food consumption (in body weights) was assumed to vary as (full-grown weight)$^{-1/3}$. The full-grown weight was estimated in each case by eye

from the growth curves in the technical reports. The weight-adjusted curves allowed consumption of lifetime doses (mg/kg), which were averaged as in case 1. (Better weight corrections could be made, but it was considered that errors resulting from the procedures adopted are small compared with statistical fluctuations.)

Thus the experiments gave, for each tumor type or tumor site, a dose level (d_l), the number of animals getting cancer (r_l), and the total number of animals examined (n_l) for various different doses (usually 3 or 5) labeled l ($l = 1, 2, \ldots, N$). For the particular tumor, the maximum likelihood estimates of the parameters α and β in Eq. (2) ($\alpha \geq 0$, $\beta \geq 0$) are the values that maximize

$$L\left(\alpha, \beta: \{d_l, r_l, n_l\}\right) = \prod_{l=1}^{N} \left\{ \binom{n_l}{r_l} \left[1 - (1-\alpha)e^{-\beta d_l/(1-\alpha)}\right]^{r_l} \cdot (1-\alpha)^{(n_l - r_l)} e^{-\beta d_l (n_l - r_l)/(1-\alpha)} \right\} \quad (4)$$

These values were computed, and the resulting values of β are shown in Tables 1–4 for the cases and tumor types or sites that were considered statistically significant in the original reports, together with some others. The rationale adopted for selection of the nonsignificant results was to include all those in which the potency at some site or for some tumor type was greater than twice the sensitivity of the experiment, defining the sensitivity as the 95% confidence upper bound on the potency if no cancers had been observed at all.

No account was taken of possible antitumor effects of the chemical under test, so any tumors or tumor sites showing such effects were ignored. The potency values shown are the largest that can be obtained from the data in the NCI reports.

APPENDIX B

The procedures used to calculate the potencies in Table 4 are simpler and less accurate than those described in Appendix A, the accuracy of comparison is low, and improved precision would be irrelevant. Wherever needed, the values shown in Table 6, which were taken from an International Agency for Research on Cancer (IARC) monograph, were used in the derivations. The following summaries outline the derivation of Table 4.

TABLE 6. Values Used in Calculating Potencies in Appendix B

Species	Weight (kg)	Lifetime (yr)	Food consumption (g/d)	Water consumption (ml/d)	Air breathed (l/d)
Mouse	0.025	1.75	5	5	40
Rat	0.25	2	15	25	200
Dog	10	10	250	500	15,000
Human	70	70	1500	2500	15,000

Acrylonitrile

A continuing Dow Chemical Co. lifetime feeding study in rats (Food and Drug Administration Hearing, 1977) shows at 13 mo a risk of 4×10^{-4} per ppm acrylonitrile (AN) in the water supply (Wilson, 1977a). Extrapolation to a full lifetime gives a risk of 6×10^{-3} per ppm AN in the water supply, although subsequent (still incomplete) analysis of this experiment suggests that this may be an overestimate. This is equivalent to 0.1 mg/kg·d, giving a potency of 0.06 kg·d/mg. The data of Maltoni et al. (1974) are for lower doses and are not statistically significant, although they correspond to a potency of 0.05 kg·d/mg for ingestion and ~ 0.2 kg·d/mg for inhalation.

The data for humans come from a study of 470 DuPont employees who worked in AN concentrations averaging 20 ppm over the working day. Although only a few of these workers have developed cancer, the incidence is twice normal. This is not very significant and certainly not proved to be caused by AN; the preponderance of lung cancer suggests that cigarette smoking is the cause. The upper limit to the lifetime cancer risk is taken by assuming that they are all caused by AN; the lifetime cancer incidence is 0.15, which was used to obtain the potency given in Table 4, using the human inhalation figures of Table 6.

Aflatoxin B_1

This is a considerable literature on aflatoxin, and the animal data are not entirely consistent. For this comparison the average outlined by Meselson and Russell (1977) is taken. For the human data the risk was evaluated on a linear basis by Piers and Linsell (1973) and used by the FDA in their analysis of aflatoxin in milk, peanut butter, and corn (Bureau of Foods, 1978).

Arsenic

The carcinogenicity of As has been reviewed elsewhere (International Agency for Research on Cancer, 1973; National Institute of Occupational Safety and Health, 1975; American Industrial Health Council, 1978). In

endeavoring to derive a potency from human epidemiology, we note here four fairly clear-cut cases.

The prevalence of skin cancers attributed to (high) levels of As in the water supply in an area of Taiwan is described in Tseng et al. (1968). Analysis of their data leads to a potency for skin cancer for As ingestion of 4–8 kg·d/mg. No search was made for other cancers.

Investigations of cancer incidence in a British sheep dip factory (Hill and Faning, 1948; Perry et al., 1948) allow an estimate of potency of ~110 kg·d/mg for all cancers and ~35 kg·d/mg for lung cancer only for inhalation of arsenical dusts. These may be up to a factor of 5 too high, because we have assumed that only 20% of the dust could pass the crude dust marks worn, although >20% of the dust was in the size range $<5\ \mu m$.

Pinto et al. (1977) related mortality in a group of 527 men to an exposure index that could be directly correlated with the current As exposure (by inhalation), using a measured correlation between urinary As and airborne As concentrations. The observed linear trend of standardized mortality ratio for respiratory cancer with exposure index translates, in our terms, to a potency of 20 kg·d/mg for lung cancer if air concentrations in the past were the same as current concentrations. Scattered measurements suggest that past concentrations may have been a factor of 5–10 higher, so 20 kg·d/mg may be regarded as an upper bound, the actual value being 5–10 times lower. The figures reported by Lee and Fraumeni (1969) agree with this, if the data on airborne As concentrations reported in the *Federal Register* (1978) for the period of this study are used.

There have been at least 40 attempts to produce cancer in animals. The inhalation studies were too short to provide useful information at potencies comparable to those estimated above. Three long-term experiments on As ingestion in animals provided evidence of low potency. Byron et al. (1967) reported no carcinogenic effect of sodium arsenite or sodium arsenate fed for 2 yr to Osborne-Mendel rats at levels up to 250 and 400 ppm, respectively, the latter corresponding to ~7.6 and ~6.1 mg/kg·d As in females and males, respectively. Kroes et al. (1974) reported a similar lifetime experiment on Wistar rats, feeding 416 ppm sodium arsenate in the diet; again, no carcinogenic effect was noted. If we assume that these experiments could detect any effect in 10% of the rats, we get an upper limit on the potency of AS of $\sim 10^{-2}$ kg·d/mg (for ingestion by rats). This clearly disagrees with the potencies estimated above for humans. There is a similar disagreement with Schroeder et al. (1958), who found no carcinogenic effect in rats fed 0.46 ppm As in their diet and 5 ppm As in their water.

In mice, carcinogenic activity of As has been observable, and at least

one study (Osswald and Goerttler, 1971) allows estimates of the potency for sc injection of 1.5–30 mg/kg·d. However, the control animals did not receive any injections. We summarize the various results as follows:

Location and reference	Species	Application	Tumor	Potency (mg/kg·d)	Error
Taiwan (Tseng et al., 1968)	Human	Imbibition	Skin cancer	4–8	(~ × 3)
U.K. sheep dip factory (Hill and Faning, 1948)	Human	Inhalation	Total cancer Lung cancer	< 110 < 35	Up to five times lower
U.S. copper smelter (Pinto et al., 1977)	Human	Inhalation	Lung cancer	2–20	(~ × 3)
U.S. copper smelter (Holland et al., 1959)	Human	Inhalation	Lung cancer	15	(~ × 3)
(Bryon et al., 1967; Kroes et al., 1974)	Rat	Ingestion	Any cancer	< 0.01	
(Osswald and Goerttler, 1971)	Mouse	Sc injection	Leukemia	1.5–30	

Benzene

There is a great deal of human data on benzene, based mainly on European exposures (in Turkey and Italy) to very high levels in the workplace. Leukemia is produced at high doses but has only been observed together with a toxic effect—aplasia of the bone marrow. The leukemia could be a secondary consequence of the toxic effect, in which case there would be a threshold for the carcinogenic effect just as is believed to exist for the toxic effect.

There are some early data on animals exposed to benzene; until recently, the only lifetime inhalation studies were at exposure levels (10 ppm) where no carcinogenic effect would be expected with the sensitivity available. However, a preliminary report has been made available of a high-dose study on rats and mice (New York University Medical Center, 1977). Leukemias were observed, but only in conjunction with aplasia. Whether or not such a comparison means anything for the leukemia hazard of low-level exposures to benzene, it is interesting to make the comparison at the high level.

The animal data yield a leukemia incidence of ~ 2% for the exposure range 200–400 ppm; this must be corrected upward because the experiment is ongoing and the rats and mice were not all dead at the time of the preliminary report. This might give a 16% lifetime risk for 200 ppm in the air or a risk of 8×10^{-4} for 1 ppm. This corresponds to a risk of 8×10^{-4} for 1 mg/kg daily or a potency of 0.0008 kg·d/mg.

For humans, a total risk of 3.5×10^{-6} yearly or a lifetime total risk of 2.5×10^{-4} for 1 ppm benzene in the air was estimated (Wilson, 1977b)

by a proportional extrapolation to low levels of the Turkish and Italian experience. A level of 1 ppm in the air corresponds to a daily intake of 0.25 mg/kg, giving a lifetime risk of 10^{-3} per 1 mg/kg daily intake or a potency of 10^{-3} kg·d/mg.

Benzidine

Data for sc injection in the rat and mouse were summarized by Meselson and Russell (1977). Data for humans are exemplified by those of Zavon et al. (1973), which show that 13 of 25 workers occupationally exposed to benzidine got bladder cancer; the workers were often exposed to dust levels of >5 mg/m^3 in the air, and an average of 0.1 mg/m^3 seems likely over a lifetime. This gives a potency of 34 kg·d/mg. In table 5 of the NAS (1975) report the lifetime accumulated dose is estimated to be 10 times lower, but they note that they may be underestimating the exposure.

Ingestion data are available for animals. Boyland et al. (1954) found tumors in female Wistar rats fed 0.017% benzidine (10 mg/kg·d) in the diet; there was no control experiment. This gives an upper bound on the potency of ~ 0.02. If we make a correction for full lifetime exposure (a factor of ~ 5-25), the bound becomes 0.1-0.5 kg·d/mg. On the other hand, Griswold et al. (1968) administered benzidine by gavage to female Sprague-Dawley rats. With total dose of only 12 mg, 50% of the rats developed mammary tumors; this leads to a potency of ~ 7 kg·d/mg, or 130-2500 kg·d/mg if a correction is made for observation for 24 mo instead of the 9 mo they were actually observed before sacrifice.

3,3'-Dichlorobenzidine

Dichlorobenzidine (DCB) was shown to be carcinogenic when ingested by hamster (Sellakmmar et al., 1969), rat (Pliss, 1959; Stula et al., 1971), mouse (Pliss, 1959), and dog (Stula, 1974). Although the rats and mice were fed DCB for only 12 and 11 mo, respectively, they were observed for a full lifetime. We therefore obtain the potency simply by using a lifetime average dose and the results of these experiments.

The chemical similarities of DCB and benzidine and the many bladder cancers attributed to the latter prompted extensive epidemiologic studies at DCB plants (Gerarde and Gerarde, 1974; MacIntyre, 1975), but no excess bladder or other cancer was found among 175 workers in Haleden, N.J., and 225 workers in Britain. We therefore assume a lifetime risk of $<1\%$ in these cases. Although no extensive personnel monitoring was done, DCB levels of 70 μg/m^3 were observed at a DCB plant in Buffalo in 1939, corresponding to an average intake of ~ 5 μg/kg·d, or ~ 2 μg/kg·d averaged over a lifetime if the whole working life was spent at the plant. This gives a potency, with very wide error margins, of <5 kg·d/mg.

Saccharin

There have been numerous animal tests with saccharin, many of which are reviewed in a report by the Office of Technology Assessment (1977). From this we estimate potencies of $\sim 3 \times 10^{-4}$ and $\lesssim 5 \times 10^{-5}$ kg·d/mg for male and female rats, respectively.

For humans, we use the results of Howe et al. (1977), even though the interpretation may be somewhat ambiguous. They reported a risk ratio for bladder cancer in males of 1.6, independent of length of time of consumption, for <2500 tablets per year. Assume that an average of 1500 tablets per year ≈ 200 mg/d ≈ 3 mg/kg·d gives a risk ratio of 1.6. (This implies a risk that increases more rapidly than linearly with dose.) The risk of bladder cancer averaged over the U.S. male population is $\sim 1.9 \times 10^{-4}$ yr^{-1}, so the excess risk caused by saccharin consumption will be 1.1×10^{-4} yr^{-1} or $\sim 8 \times 10^{-3}$ in a lifetime, giving a potency of $\sim 3 \times 10^{-3}$ kg·d/mg. This estimate is subject to considerable uncertainty. Indeed, Miller and Howe (1978) present a fairly extreme model that corresponds to a potency of ~ 0.04 kg·d/mg, although that model has the lifetime risk increasing much more rapidly than linearly with lifetime saccharin consumption. We take this as an upper bound (50 mg per tablet is assumed throughout).

Smoking (Cigarettes)

We use directly the figures quoted in the NAS (1975) report.

Vinyl Chloride

We have the risk analysis of Kuzmack and McGaughy (1975) based on the work of Maltoni et al. (1974). The animal studies show a total lifetime carcinogenic risk of $4.9 \times 10^{-3}d$ [where d is the lifetime average dose in air (ppm)] for liver angiosarcomas and $10^{-2}d$ for all tumors. (Kuzmack and McGaughy actually calculated for 4 h/d, 5 d/wk, for half a lifetime.) A rat breathes 0.14 l/min = 200 l/d $\approx$ 220 g/d, so 1 ppm in air gives 1 mg/kg vinyl chloride daily.

The best indication of human incidence is given in appendix D4 of Kuzmack and McGaughy. This gives an average lifetime risk of 0.13 for 20 ppm or $6 \times 10^{-3}d$, where d is the average dose (ppm). For a human who breathes 15 m^3 of air per day or 18 kg/d, 1 ppm in air is 0.25 mg/kg·d. This procedure gives a higher human risk than the procedure used by the NAS (1975) committee, who (quoting the IARC) take a lower average angiosarcoma incidence in a larger population. This may indicate a nonlinear dose-response relationship, but could be an overestimate of exposure for the low-exposure members of the group.

Radiation

The doses here are expressed in terms of rads or rems. These are doses per unit volume, so it is unnecessary to divide by body weight. Numbers

for humans come from the BEIR report (Committee on the Biological Effects of Ionizing Radiation, 1972), which states that at an exposure of 0.1 rem/yr, 3000–4000 extra cancer deaths probably result out of a total of 2,000,000 deaths. The potency is thus ~ 0.020 yr/rem. The data for mice are taken from a United Nations (1977) report that 15% leukemia incidence arises from a 100-rad total dose in mice. Allowing six times as many other cancers as leukemias (the factor for humans), the potency becomes 0.01 yr/rem.

Chloroform

For mouse and rat we use the NCI carcinogenesis bioassay results (Table 1).

Human epidemiology is limited and shows no effect. Daily ingestion for 10 yr of cough suppressant containing chloroform-codeine at dose levels estimated at 23–27 mg/kg·d for a 70-kg person showed only reversible hepatotoxicity (Tardiff, 1977). The average dose over a 50-yr span was then 5 mg/kg·d. The 10,000 yearly deaths caused by liver cancer represent 0.005 of all deaths, and in a small population a doubling of this rate could probably have been seen, so the excess probability of death caused by liver cancer in this group is ≤ 0.005, giving a potency ≤ 0.001 kg·d/mg.

Chlornaphazine

Figures are abstracted directly from the NAS (1975) report.

Ethylene Dibromide

Ethylene dibromide (EDB) has been shown (Olsen et al., 1973; Powers et al., 1975) to cause an increased incidence of gastric tumors in rats when administered by gavage. So many animals died, even at the low dose, that the experiment terminated at 61 wk, and attempting to directly fit Eq. (1) gives a very inaccurate determination of the potency. Using Eq. (2) and the times of death, the Carcinogenesis Assessment Group determined a value of $k = 5.9$ and a potency of 6 kg·d/mg (our units and notation). Mouse data from these experiments averaged over females and males (see Table 1) similarly give 6 kg·d/mg. If a new experiment were performed in which the rats and male mice were dosed at lower levels, a more precise determination of the potency would be possible.

Epidemiologic data from the Dow Chemical Co. on 161 employees exposed to EDB (Ott et al., 1977) were analyzed by Dow (Ramsey et al., 1978) and the EPA (Albert, 1977). On the basis of the EPA's estimate of potency, where the potency for rats (6 mg/kg·d) was multiplied by a surface area correction factor of 5, Ramsey et al. calculated an expected 85 malignant neoplasms where 8 were observed, and the expected background is 5.6. Thus we get $30 \times 2.4/85 \approx 0.8$ kg·d/mg for the potency.

Lead Acetate

Basic lead acetate was fed to rats, mice, and hamsters in controlled lifetime experiments (Boyland et al., 1962; van Esch et al., 1962; van Esch and Kroes, 1969). Renal tumors were found in rats and hamsters, but were below the level of significance in mice. The results of these experiments were used for the estimates in Table 4.

There have been extensive epidemiologic studies of mortality of Pb workers. Although in some cases excess cancers were observed (Cooper and Gaffey, 1974; Cooper, 1976), they were not related to Pb intake and cannot therefore be attributed to Pb. However, we use this increase to obtain an upper limit on the carcinogenic potency of Pb (Table 4).

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