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Target Organs in Chronic Bioassays of 533 Chemical Carcinogens

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A compendium of carcinogenesis bioassay results organized by target organ is presented for 533 chemicals that are carcinogenic in at least one species. This compendium is based primarily on experiments in rats or mice; results in hamsters, nonhuman primates, and dogs are also reported. The compendium can be used to identify chemicals that induce tumors at particular sites, and to determine whether target sites are the same for chemicals positive in more than one species. The Carcinogenic Potency Database (CPDB), which includes results of 3969 experiments, is used in the analysis. The published CPDB includes details on each test, and literature references. Chemical carcinogens are reported for 35 different target organs in rats or mice. More than 80% of the carcinogens in each of these species are positive in at least one of the 8 most frequent target sites: liver, lung, mammary gland, stomach, vascular system, kidney, hematopoietic system, and urinary bladder. An analysis is presented of how well one can predict the carcinogenic response in mice from results in rats, or vice versa. Among chemicals tested in both species, 76% of rat carcinogens are positive in mice, and 71% of mouse carcinogens are positive in rats. Prediction is less accurate to the same target site: 52% of rat carcinogens are positive in the same site in mice, and 48% of mouse carcinogens are positive in the same site in rats. The liver is the most frequent site in common between rats and mice.

Introduction

For a variety of research purposes, a compendium of carcinogenesis bioassay results organized by target organ is useful. A single resource that lists all test agents shown to induce tumors in a given species at each site can facilitate investigations of particular site-specific carcinogens, as well as comparisons of results in different species. This paper presents such a resource document (Table 1) based on the results of chronic, long-term experiments reported in the Carcinogenic Potency Database (CPDB). Several analyses of patterns of target sites in rats and mice are also presented.

The CPDB, in addition to providing an index of carcinogenic potency (*1–4*), is an exhaustive source of information on many aspects of bioassay design and results for 3969 species and sex-specific experiments on 1052 chemicals. The CPDB has been published in plot format in four papers in *Environmental Health Perspectives*. Used in combination, the published plots of the CPDB and the compendium by target organ in Table 1, together provide comprehensive detailed results on each experiment including tumor pathology and incidence rates, sex and strain tested, dose rates, shape of the dose-response curves, statistical significance of the slope of the dose-response curve, carcinogenic potency, author's opinion about carcinogenicity, and literature reference. As a resource, the compendium in this paper, organized by target organ, will be useful for a variety of research endeavors. For example, epidemiologists interested in a particular target tissue in humans may seek clues in animal models, and can use the compendium to obtain a list of substances found to induce tumors at the site of interest in rats, mice, hamsters, nonhuman primates, or dogs. Investigators interested in mechanism of carcinogenesis at a specific target site, or in chemical structure, can identify compounds that induce tumors at that target organ. As one feature of our summary table, we have indicated the carcinogens at each target site that have been tested in both rats and mice (by far the two most frequently used test animals), and that are positive in both versus only one of these species. Thus, comparative toxicologists can determine whether a chemical that is positive at a given site in the rat has been tested in the mouse and if so, whether it is positive in the mouse, and whether the target organ(s) is the same.

This paper also summarizes the number of chemicals that induce tumors at each site in rats and mice, and compares the common tumor sites in the two species.

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Many chemicals cause tumors at more than one site in a species (here termed "multiple-site carcinogens"), and we describe the frequency with which this occurs in rats and mice. In earlier work we examined the issue of extrapolation between species by assessing how well one can predict carcinogenicity from a rat to a mouse or from a mouse to a rat (*5*). We showed that a variety of factors affect the accuracy of prediction including chemical class, mutagenicity, toxicity of the chemical (measured by the administered high dose), and target organ. In this paper we use additional results included in the published CPDB for the subset of chemicals tested in both rats and mice, to update data on the frequency with which chemical carcinogens induce tumors at the same site in rats and mice. In a separate paper we will discuss the issue of mutagenicity of the test agent and target organ (Gold et al., in preparation).

Methods

Our analyses are based on the CPDB, which includes results of chronic exposure animal bioassays that were published either in the general literature through 1986 or in Technical Reports of the National Cancer Institute/National Toxicology Program (NCI/NTP) through June 1987 (*1–4*). All experiments in the CPDB meet a set of inclusion criteria that were designed to allow for estimation of carcinogenic potency; therefore, reasonable consistency in experimental protocols is assured. Experiments are included only if the test agent was administered alone rather than in combination with other substances; if the protocol included a control group, if the route of administration was either diet, water, gavage, inhalation, IV injection or IP injection; and if the length of the experiment in rodents was at least 1 year with dosing for at least 6 months. For the CPDB, evidence for carcinogenicity in an experiment is based on the evaluation of the published author; however, in addition, the statistical significance of the tumorigenic dose-response is calculated and reported for each tissue and tumor in the database (*1*). Some test agents are excluded from the CPDB because the route of administration was not one of those defined above (for example, some polycyclic aromatic hydrocarbons and inorganic chemicals) and some because they are chemical mixtures, particulates, or industrial processes. Among the 241 chemicals, mixtures, and particulates that have been evaluated by the International Agency for Research on Cancer (IARC) as having sufficient evidence for carcinogenicity in experimental animals (*6,7*), the CPDB includes data on 64%.

In the analyses below, we classify a target organ as positive on the basis of the author's opinion in the published paper. Experiments evaluated as "inadequate" by NCI/NTP are excluded. In some cases authors do not clearly state their evaluation, and in some NCI/NTP Technical Reports the evidence for carcinogenicity at a site is considered only "associated" with compound administration or "equivocal"; in our analyses we consider these experiments as lacking positive evidence of carcinogenicity. For NTP reports, the evaluations of "clear" or "some evidence" of carcinogenicity are both classified as positive, as they are by NTP. We use the author's opinion to determine positivity for an experiment because, in addition to statistical significance, it often takes into account historical control rates for particular sites, poor survival, tumor latency, and/or dose response. Positive target sites for a chemical are identified across experiments in a species using all results for a chemical from both the general literature and NCI/NTP bioassays. Hence, if a chemical has two target sites in a species, the results may represent two different experiments, although this occurs infrequently.

The compendium in Table 1 includes the 533 chemicals in the CPDB that are positive in at least one site in one test of one species, regardless of the number of tests in the database. In the CPDB, the number of experiments per chemical varies and some chemicals are more thoroughly tested than others. Among all chemicals in the CPDB, the percentages with one experiment, two experiments, and more than two experiments are 30%, 52%, and 18%, respectively, for rats and 12%, 56%, and 32%, respectively, for mice. The specific histopathology associated with each target site is not presented in this compendium but is reported in the published plots of the database using the nomenclature of the original author (*1–4*). The original reference of each experiment is listed under the chemical name on the right side of the plot of the CPDB and in the bibliography (*1–4*).

One feature of the CPDB is the inclusion of experiments with species other than rats and mice. Among the results reported in the compendium (Table 1) are those for 36 carcinogens in hamsters, 8 in nonhuman primates [aflatoxin B_1, methylazoxymethanol acetate and cycasin mixture, 2-naphthylamine, *N*-nitroso-*N*-methylurea, *N*-nitrosodiethylamine, *N*-nitrosopiperidine, procarbazine.*HCl*, and urethane], and 2 in dogs [3,3′-dichlorobenzidine and 4,4′-methylene-*bis*(2-chloroaniline)].

Description of Table 1: Carcinogenic Response by Target Organ for 533 Chemical Carcinogens

Table 1 lists all chemicals in the CPDB that induce tumors in each of 35 target organs in rats, mice, hamsters, monkeys, prosimians, or dogs. The table is organized alphabetically by site, species, and chemical. This compendium permits comparisons between species at a given target site; for example, if kidney is the target organ of interest, a list of kidney carcinogens ordered alphabetically for each species is presented: 1 chemical in the monkey, 12 in the mouse, and 45 in the rat. Because we have indicated with superscripts those chemicals that have been tested in both rats and mice, it is possible to see whether the kidney is a target organ in both species for a given chemical. For example, for the rat kidney, chloroform is listed with the symbol ‡

(text continues on page 241)

Table 1. Carcinogenic response by target organ for 533 chemicals classified as positive by author's opinion. A chemical is listed under each organ that is evaluated as positive in an experiment in that species by at least one author. Therefore, a chemical may be listed under several target organs and every chemical listed in the table is positive in at least one species. In order to compare results in rats and mice, the two most commonly tested species, symbols are applied to chemicals tested in both species. A ‡ indicates that the chemical is positive at some site in both species, and a † indicates that it was tested in both but positive in only one. Detailed information on each experiment is presented in the four published plots of the Carcinogenic Potency Database. N = the number of chemicals with at least one positive test at that site in that species.

Tissue	Species	N	Chemical names
Adrenal gland	Hamster	1	urethane‡
	Mouse	4	carbon tetrachloride‡; 4,4′-methylenedianiline.2*HCl*‡; *p*-rosaniline.*HCl*‡; 1,1,2-trichloroethane†
	Rat	7	acrylamide; 4-chloro-*m*-phenylenediamine‡; 1,2-dibromo-3-chloropropane‡,a; diethylstilbestrol‡,a; ethyl alcohol; 1,2-propylene oxide‡; reserpine‡
Bone	Monkey	2	aflatoxin B_1†; procarbazine.*HCl*‡
	Rat	3	acronycine; 1-(2-hydroxyethyl)-1-nitrosourea; *o*-toluidine.*HCl*‡
Central nervous system	Mouse	2	*N*-nitrosodimethylamine‡; procarbazine.*HCl*‡
	Rat	15	acrylamide; acrylonitrile; 2-amino-6-methyldipyrido[1,2-*a*:3′,2′-*d*]imidazole‡; 2-aminodipyrido[1,2-*a*:3′,2′-*d*]imidazole‡; chlorambucil‡; 1-(4-chlorophenyl)-1-phenyl-2-propynyl carbamate; cyclophosphamide‡; 1-ethyl-1-nitrosourea; ethylene oxide; R(-)-2-methyl-*N*-nitrosopiperidine; S(+)-2-methyl-*N*-nitrosopiperidine; 1-phenyl-3,3-dimethyltriazene; procarbazine.*HCl*‡; propane sultone; vinyl chloride‡
Clitoral gland	Mouse	2	acetaldehyde methylformylhydrazone; *N*-*N*-butyl-*N*-formylhydrazine
	Rat	7	2-amino-6-methyldipyrido[1,2-*a*:3′,2′-*d*]imidazole‡; 2-amino-3-methylimidazo[4,5-*f*]quinoline‡; 2-aminodipyrido[1,2-*a*:3′,2′-*d*]imidazole‡; 2,4-diaminoanisole sulfate‡; 1,5-naphthalenediamine‡; 5-nitro-*o*-anisidine‡; 5-nitroacenaphthene‡
Ear/Zymbal's gland	Mouse	2	benzene‡; cupferron‡
	Rat	30	acrylonitrile; 3-amino-9-ethylcarbazole.*HCl*‡; 2-amino-6-methyldipyrido[1,2-*a*:3′,2′-*d*]imidazole‡; 2-amino-3-methylimidazo[4,5-*f*]quinoline‡; 2-amino-3-methylimidazo[4,5-*f*]quinoline.*HCl*; 2-aminodipyrido[1,2-*a*:3′,2′-*d*]imidazole‡; benzene‡; *N*-*N*-butyl-*N*-nitrosourea; chlorambucil‡; cupferron‡; *N*-1-diacetamidofluorene; 2,4-diaminoanisole sulfate‡; 3,3′-dichlorobenzidine; 2,5-dimethoxy-4′-aminostilbene‡; *N*-(2-fluorenyl)-2,2,2-trifluoroacetamide; formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl]hydrazide‡; hydrazobenzene‡; 2-methoxy-3-aminodibenzofuran; *N*-(*N*-methyl-*N*-nitrosocarbamoyl)-*l*-ornithine; 4,4′-methylene-bis(2-chloroaniline); 5-nitro-*o*-anisidine‡; 5-nitroacenaphthene‡; *N*-(9-oxo-2-fluorenyl) acetamide; phenacetin‡; prednimustine; *p*-rosaniline.*HCl*‡; thio-TEPA‡; 4,4′-thiodianiline‡; β-thioguanine deoxyriboside; vinyl chloride‡
Esophagus	Hamster	2	AF-2‡; *N*-nitroso-*N*-methylurethan
	Monkey	2	methylazoxymethanol acetate and cycasin mixture; *N*-nitroso-*N*-methylurea
	Mouse	7	benzo(*a*)pyrene‡; 1,2-dibromoethane‡; *N*-ethyl-*N*′-nitro-*N*-nitrosoguanidine; *N*-hydroxy-2-acetylaminofluorene‡; 3-(5-nitro-2-furyl)-imidazo(1,2-α)pyridine‡; nitrosodibutylamine‡; *N*-nitrosohexamethyleneimine
	Rat	29	*N*-*N*-butyl-*N*-nitrosourea; dihydrosafrole‡; dimethylvinyl chloride‡; dinitrosohomopiperazine; *Z*-ethyl-*O*,*N*,*N*-azoxyethane; 3-(5-nitro-2-furyl)-imidazo(1,2-α)pyridine‡; *N*-nitroso-2,3-dihydroxypropyl-2-hydroxypropylamine; nitroso-2,3-dihydroxypropyl-2-oxopropylamine; *N*-nitroso-(2-hydroxypropyl)-(2-hydroxyethyl) amine; *N*-nitroso-*N*-methyl-4-fluoroaniline; nitroso-*N*-methyl-*N*-(2-phenyl) ethylamine; nitroso-1,2,3,6-tetrahydropyridine; *N*-nitroso(2,2,2-trifluoroethyl) ethylamine; *N*-nitrosoallyl-2,3-dihydroxypropylamine; *N*-nitrosoallyl-2-hydroxypropylamine; *N*-nitrosoallyl-2-oxopropylamine; nitrosoamylurethan; nitrosoanabasine; *N*-nitrosobis(2-hydroxypropyl) amine; *N*-nitrosodiethanolamine; *N*-nitrosodiethylamine; *N*-nitrosodipropylamine; nitrosoheptamethyleneimine; *N*-nitrosomethyl-2,3-dihydroxypropylamine; *N*-nitrosomethyl-2-hydroxypropylamine; 2-nitrosomethylaminopyridine; nitrosomethylaniline; *N*′-nitrosonornicotine-1-*N*-oxide; *N*-nitrosothiomorpholine
Gall bladder	Hamster	1	*N*-methyl-*N*-formylhydrazine
	Monkey	1	aflatoxin B_1†
	Mouse	3	*N*-ethyl-*N*-formylhydrazine; *N*-methyl-*N*-formylhydrazine; *N*-*N*′-propyl-*N*-formylhydrazine
Harderian gland	Mouse	6	benzene‡; benzidine.2*HCl*; cupferron‡; dichloroacetylene‡; gentian violet; 4,4′-oxydianiline‡
Hematopoietic system	Monkey	1	procarbazine.*HCl*‡
	Mouse	39	acetamide‡; aflatoxin, crude‡; allyl isovalerate‡; *trans*-5-amino-3[2-(5-nitro-2-furyl)vinyl- 1,2,4-oxadiazole; 2-amino-4-(*p*-nitrophenyl) thiazole; 2-aminoanthraquinone‡; benzene‡; benzoyl hydrazine; 1,3-butadiene; 1,2-di-*N*-butylhydrazine.2*HCl*; chlorambucil‡; chlorinated paraffins (*C*23, 43% chlorine)†; cyclophosphamide‡; dacarbazine‡; DDT‡; dibromodulcitol‡; dibromomannitol‡; estradiol mustard†; formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl]hydrazide‡; gentian violet; hexanamide†; 2-hydrazino-4-(*p*-aminophenyl) thiazole‡; 2-hydrazino-4-(*p*-nitrophenyl) thiazole‡; ICRF-159‡; isophosphamide‡; melphalan‡; 1-methyl-1,4-dihydro-7-[2-(5-nitrofuryl)vinyl]-4-oxo-1,8-naphthyridine-3-carboxylate, potassium; methyl methanesulfonate; 4,4′-methylenedianiline.2*HCl*‡; metronidazole‡; *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide‡; phenesterin‡; phorbol; procarbazine.*HCl*‡; strobane; thio-TEPA‡; *p*-tolylurea†; urethane‡; C.I. Vat Yellow 4†

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Table 1. ***Continued.***

Tissue	Species	N	Chemical names
	Rat	35	allyl isovalerate‡; 1-amyl-1-nitrosourea; benzidine; *N-N*-butyl-*N*-nitrosourea; chlorambucil‡; cyclophosphamide‡; dacarbazine‡; 1,3-dibutyl-1-nitrosourea; dichloroacetylene‡; 3,3′-dichlorobenzidine; dimethoxane; 3,3′-dimethoxybenzidine-4,4′-diisocyanate†; 2-(2,2-dimethylhydrazino)-4-(5-nitro-2-furyl) thiazole; dimethyl morpholinophosphoramidate†; ethylene oxide; formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl]hydrazide‡; FD & C Green No. 1†; FD & C Green No. 2†; hematoxylin; 2-hydrazino-4-(*p*-aminophenyl) thiazole‡; 1-(2-hydroxyethyl)-1-nitrosourea; lasiocarpine; metepa; l-5-morpholinomethyl-3-[(5-nitrofurfurylidene)amino]-2-oxazolidinone.*HCl*; nitrite, sodium†; *N*-[5-(5-nitro-2-furyl)-1,3,4-thiadiazol-2-yl]acetamide‡; 1-[(5-nitrofurfurylidene)amino]-2-imidazolidinone; nitroso-*N*-methyl-*N*-(2-phenyl) ethylamine; procarbazine.*HCl*‡; propane sultone; FD & C Red No. 2; FD & C Red No. 4†; tetrachloroethylene‡; thio-TEPA‡; 2,4,6-trichlorophenol‡
Kidney	Monkey	1	methylazoxymethanol acetate and cycasin mixture
	Mouse	12	1,2-di-*N*-butylhydrazine.2*HCl*; chloroform‡; daminozide‡; dichloroacetylene‡; *N*-hydroxy-2-acetylaminofluorene‡; lead acetate, basic‡; nitrilotriacetic acid‡; ochratoxin A†; phenacetin‡; streptozotocin‡; tris-(2,3-dibromopropyl) phosphate‡; vinylidene chloride†
	Rat	45	aflatoxin B_1†; 1-amino-2-methylanthraquinone‡; 2-amino-5-(5-nitro-2-furyl)-1,3,4-oxadiazole; 2-amino-5-(5-nitro-2-furyl)-1,3,4-thiadiazole; 2-amino-5-nitrothiazole†; *o*-anisidine.*HCl*‡; azoxymethane; bromate, potassium†; chlorinated paraffins (*C*12, 60% chlorine)‡; chloroform‡; chlorothalonil†; cinnamyl anthranilate‡; citrinin; dichloroacetylene‡; 1,4-dichlorobenzene‡; diethylacetamide; dimethoxane; 4,6-dimethyl-2-(5-nitro-2-furyl) pyrimidine; *N*-4-(4′-fluorobiphenyl) acetamide; formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl]hydrazide‡; hexachlorobutadiene; hexamethylmelamine; 2-hydrazino-4-(5-nitro-2-furyl) thiazole‡; isophorone†; lead acetate†; lead acetate, basic‡; 2-methoxy-3-aminodibenzofuran; *Z*-methyl-*O*,*N*,*N*-azoxyethane; *N*-(*N*-methyl-*N*-nitrosocarbamoyl)-*l*-ornithine; l-5-morpholinomethyl-3-[(5-nitrofurfurylidene)amino]-2-oxazolidinone.*HCl*; nitrilotriacetic acid‡; nitrilotriacetic acid, trisodium salt, monohydrate†; 3-(5-nitro-2-furyl)-imidazo(1,2-α)pyridine‡; *N*-([3-(5-nitro-2-furyl)-1,2,4-oxadiazole-5-yl]-methyl)acetamide; *N*-[5-(5-nitro-2-furyl)-1,3,4-thiadiazol-2-yl]acetamide‡; 1-nitroso-1-hydroxyethyl-3-chloroethylurea; *N*-nitrosodiethanolamine; *N*-oxydiethylene thiocarbamyl-*N*-oxydiethylene sulfenamide; phenacetin‡; phenazone; *o*-phenylphenate, sodium†; streptozotocin‡; tetrachloroethylene‡; tris(2,3-dibromopropyl) phosphate‡; vinyl chloride‡
Large intestine	Hamster	5	1,1-dimethylhydrazine; 1,2-dimethylhydrazine.2*HCl*; hydrazine‡; methylhydrazine; urethane‡
	Rat	15	aflatoxin B_1†; 2-amino-6-methyldipyrido[1,2-*a*:3′,2′-*d*]imidazole‡; 2-amino-3-methylimidazo[4,5-*f*]quinoline‡; 2-aminodipyrido[1,2-*a*:3′,2′-*d*]imidazole‡; amylopectin sulfate; azoxymethane; carrageenan, acid-degraded; chrysazin‡; dextran sulfate sodium (DS-M-1); *Z*-ethyl-*O*,*N*,*N*-azoxymethane; formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl]hydrazide‡; *N*-nitrosobis(2-oxopropyl) amine; phenazopyridine.*HCl*‡; 4,4′-thiodianiline‡; tris(2,3-dibromopropyl) phosphate‡
Liver	Bush baby	1	*N*-nitrosodiethylamine
	Dog	2	3,3′-dichlorobenzidine; 4,4′-methylene-bis(2-chloroaniline)
	Hamster	14	2-acetylaminofluorene‡; *p,p*′-DDE†; 1,2-dimethylhydrazine.2*HCl*; hexachlorobenzene‡; *N*-hydroxy-2-acetylaminofluorene‡; *N*-methyl-*N*-formylhydrazine; methylhydrazine; *N*-nitroso-1,3-oxazolidine; nitroso-2-oxopropylethanolamine; *N*-nitrosoallyl-2-oxopropylamine; *N*-nitrosoazetidine; *N*-nitrosomorpholine; *N*-nitrosopiperidine‡; *N*-nitrosopyrrolidine‡
	Monkey	5	aflatoxin B_1†; methylazoxymethanol acetate and cycasin mixture; *N*-nitrosodiethylamine; *N*-nitrosopiperidine‡; urethane‡
	Mouse	171	acetaminophen‡; 2-acetylaminofluorene‡; aldrin‡; 3-amino-1,4-dimethyl-5*H*-pyrido[4,3-*b*]indole acetate‡; 2-amino-3,4-dimethylimidazo[4,5-*f*]quinoline; 3-amino-9-ethylcarbazole.*HCl*‡; 2-amino-3-methyl-9*H*-pyrido-[2,3-*b*]-indole; 3-amino-1-methyl-5*H*-pyrido[4,3-*b*]indole acetate‡; 1-amino-2-methylanthraquinone‡; 2-amino-6-methyldipyrido[1,2-*a*:3′,2′-*d*]imidazole‡; 2-amino-3-methylimidazo[4,5-*f*]quinoline‡; 2-amino-9*H*-pyrido(2,3-*b*) indole; 2-aminoanthraquinone‡; 4-aminodiphenyl; 4-aminodiphenyl.*HCl*‡; 2-aminodiphenylene oxide; 2-aminodipyrido[1,2-*a*:3′,2′-*d*]imidazole‡; 3-aminotriazole‡; aramite‡; aroclor 1254†; auramine-*O*‡; benzidine.2*HCl*; benzyl acetate†; bis(2-chloro-1-methylethyl) ether†; bis-2-chloroethylether; bis-2-hydroxyethyldithiocarbamic acid, potassium; HC Blue No. 1‡; 1,3-butadiene; 1,1-di-*N*-butylhydrazine; captafol; carbazole; carbon tetrachloride‡; chloramben†; chlordane†; chlorendic acid‡; chlorinated paraffins (*C*12, 60% chlorine)‡; 1-chloro-2-nitrobenzene†; 1-chloro-4-nitrobenzene†; 4-chloro-*m*-phenylenediamine‡; 4-chloro-*o*-phenylenediamine‡; 5-chloro-*o*-toluidine†; [4-chloro-6-(2,3-xylidino)-2-pyrimiduinylthio]acetic acid‡; 4-chloro-6-(2,3-xylidino)-2-pyrimidinylthio(*N*-β- hydroxyethyl)acetamide‡; chlorobenzilate†; chlorodibromomethane†; chloroform‡; chrysazin‡; cinnamyl anthranilate‡; *p*-cresidine‡; cupferron‡; cyclamate, sodium†; cyclochlorotine; *p,p*′-DDD†; *p,p*′-DDE†; DDT‡; diallate; 2,4-diaminotoluene‡; 2,4-diaminotoluene.2*HCl*‡; 3,5-dichloro(*N*-1,1-dimethyl-2-propynyl) benzamide; 2,6-dichloro-*p*-phenylenediamine†; 1,4-dichlorobenzene‡; 1,2-dichloropropane†; dicofol†; dieldrin‡; diftalone; dihydrosafrole‡; 2,5-dimethoxy-4′-aminostilbene‡; 1,1-dimethylhydrazine; 1,4-dioxane‡; dipyrone†; estragole; DL-ethionine‡; *o*-ethoxybenzamide; *N*-ethyl-*N*-formylhydrazine; ethylene imine; ethylene thiourea‡; di(2-ethylhexyl) adipate†; di(2-ethylhexyl) phthalate‡; 4′-fluoro-4-aminodiphenyl; gentian violet; griseofulvin; HCDD mixture‡; heptachlor†; hexachlorobenzene‡; hexachlorocyclohexane; α-1,2,3,4,5,6-hexachlorocyclohexane‡; β-1,2,3,4,5,6-hexachlorocyclohexane; γ-1,2,3,4,5,6-hexachlorocyclohexane†; hexachloroethane†; hydrazine sulfate‡; hydrazobenzene‡; *N*-hydroxy-2-acetylaminofluorene‡; 1′-hydroxyestragole; 2-hydroxyethylhydrazine; 1′-hydroxysafrole‡; isoniazid‡; kepone‡; leupep-

Table 1. *Continued.*

Tissue	Species	N	Chemical names
			tin; luteoskyrin; malonaldehyde, sodium; 3-methoxy-4-aminoazobenzene; *N*-methyl-*N*-formylhydrazine; 4,4′-methylene-bis(2-chloroaniline).2*HCl*†; methylene chloride‡; 4,4′-methylenebis(*N*,*N*-dimethyl) benzenamine‡; 4,4′-methylenedianiline.2*HCl*‡; methylhydrazine; Michler's ketone‡; mirex†; 1,5-naphthalenediamine‡; 2-naphthylamine‡; nithiazide‡; 3-nitro-*p*-acetophenetide†; 5-nitro-*o*-anisidine‡; 2-nitro-*p*-phenylenediamine†; 5-nitro-*o*-toluidine†; 5-nitroacenaphthene‡; 6-nitrobenzimidazole†; nitrofen‡; nitrosodibutylamine‡; *N*-nitrosodimethylamine‡; *p*-nitrosodiphenylamine‡; *N*-nitrosohexamethyleneimine; *N*-nitrosopiperidine‡; ochratoxin A†; 4,4′-oxydianiline‡; pentachloroethane†; pentachloronitrobenzene†; phenazopyridine.*HCl*‡; phenobarbital†; phenobarbital, sodium‡; *o*-phenylenediamine.2*HCl*‡; piperonyl sulfoxide†; polybrominated biphenyl mixture‡; *N*-*N*′-propyl-*N*-formylhydrazine; D & C Red No. 5‡; rifampicin†; ripazepam†; *p*-rosaniline.*HCl*‡; safrole‡; selenium diethyldithiocarbamate; selenium sulfide‡; strobane; 2,3,7,8-tetrachlorodibenzo-*p*-dioxin‡; 1,1,1,2-tetrachloroethane†; 1,1,2,2-tetrachloroethane†; tetrachloroethylene‡; tetrachlorvinphos†; tetrafluoro-*m*-phenylenediamine.2*HCl*†; thioacetamide; 4,4′-thiodianiline‡; thiouracil; toluene diisocyanate, commercial grade (2,4 (80%)- and 2,6 (20%)-)‡; *m*-toluidine.*HCl*†; *o*-toluidine.*HCl*‡; *p*-toluidine.*HCl*†; toxaphene†; 2,4,6-trichloroaniline†; 1,1,2-trichloroethane†; trichloroethylene‡; 2,4,6-trichlorophenol‡; trifluralin†; 2,4,5-trimethylaniline‡; 2,4,5-trimethylaniline.*HCl*‡; 2,4,6-trimethylaniline.*HCl*‡; tris(2,3-dibromopropyl) phosphate‡; tris(2-ethylhexyl) phosphate†; urethane‡; 2,5-xylidine.*HCl*‡; C.I. Disperse Yellow 3‡; zearalenone†
	Rat	143	acetamide‡; acetaminophen‡; acetoxime; 2-acetylaminofluorene‡; aflatoxicol; aflatoxin B_1†; aflatoxin, crude‡; 3-amino-1,4-dimethyl-5*H*-pyrido[4,3-*b*]indole acetate‡; 3-amino-9-ethylcarbazole.*HCl*‡; 3-amino-1-methyl-5*H*-pyrido[4,3-*b*]indole acetate‡; 1-amino-2-methylanthraquinone‡; 2-amino-6-methyldipyrido[1,2-*a*:3′,2′-*d*]imidazole‡; 2-amino-3-methylimidazo[4,5-*f*]quinoline‡; 2-amino-3-methylimidazo-[4,5-*f*]quinoline.*HCl*; 2-aminoanthraquinone‡; *o*-aminoazotoluene†; 2-aminodipyrido[1,2-*a*:3′,2′-*d*]imidazole‡; 11-aminoundecanoic acid†; aramite‡; aroclor 1260; auramine-*O*‡; azoxymethane; benzidine; bromodichloromethane; carbon tetrachloride‡; chlorendic acid‡; chlorinated paraffins (*C*12, 60% chlorine)‡; 4-chloro-4′-aminodiphenylether‡; 2-chloro-5-(3,5-dimethylpiperidinosulphonyl)benzoic acid; [4-chloro-6-(2,3-xylidino)-2-pyrimidinylthio]acetic acid‡; 4-chloro-6-(2,3-xylidino)-2-pyrimidinylthio-(*N*-β-hydroxyethyl) acetamide‡; chlorobenzene†; chlorobenzene†; chloroform‡; ciprofibrate; clivorine; clofibrate; clophen A 30; *p*-cresidine‡; crotonaldehyde; cupferron‡; DDT‡; decabromodiphenyl oxide†; 2,4-diaminotoluene‡; 2,4-diaminotoluene.2*HCl*‡; 1,2-dibromoethane‡; dichloroacetylene‡; *N*,*N*-diethyl-4-(4′-[pyridyl-1′-oxide]azo) aniline; dimethoxane; *N*,*N*-dimethyl-4-aminoazobenzene; dimethylnitramine; dinitrosohomopiperazine; 1,4-dioxane‡; ethionine; DL-ethionine‡; ethyl alcohol; *Z*-ethyl-*O*,*N*,*N*-azoxyethane; *Z*-ethyl-*O*,*N*,*N*-azoxymethane; ethylene thiourea‡; di(2-ethylhexyl) phthalate‡; *N*-(2-fluorenyl)-2,2,2-trifluoroacetamide; formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl]hydrazide‡; FD & C Green No. 1†; HCDD mixture‡; hexachlorobenzene‡; α-1,2,3,4,5,6-hexachlorocyclohexane‡; hydrazine sulfate‡; hydrazobenzene‡; *N*-hydroxy-2-acetylaminofluorene‡; 1′-hydroxysafrole‡; isoniazid‡; kepone‡; lasiocarpine; methapyrilene.*HCl*; *Z*-methyl-*O*,*N*,*N*-azoxyethane; methyl clofenapate; 3′-methyl-4-dimethylaminoazobenzene; 2-methyl-1-nitroanthraquinone‡; 4-(4-*N*-methyl-*N*-nitrosaminostyryl) quinoline; 4,4′-methylene-bis(2-chloroaniline); 4,4′-methylene-bis(2-methylaniline); 4,4′-methylenedianiline.2*HCl*‡; metronidazole‡; Michler's ketone‡; monocrotaline; nitrite, sodium†; *N*-nitroso-bis-(4,4,4-trifluoro-*N*-butyl) amine; 1-nitroso-5,6-dihydrouracil; *N*-nitroso-2,3-dihydroxypropylethanolamine; 1-nitroso-1-hydroxyethyl-3-chloroethylurea; 1-nitroso-1-(2-hydroxypropyl)-3-chloroethylurea; *N*-nitroso-(2-hydroxypropyl)-(2-hydroxyethyl) amine; *N*-nitroso-*N*-methyl-*N*-dodecylamine; nitroso-*N*-methyl-*N*-(2-phenyl) ethylamine; *N*-nitroso-*N*-methyldecylamine; nitroso-2-oxopropylethanolamine; nitroso-1,2,3,6-tetrahydropyridine; *N*-nitrosoallyl-2-hydroxypropylamine; *N*-nitrosoallyl-2-oxopropylamine; *N*-nitrosoallylethanolamine; *N*-nitrosobis(2-oxopropyl) amine; nitrosodibutylamine‡; *N*-nitrosodiethanolamine; *N*-nitrosodiethylamine; *N*-nitrosodimethylamine‡; *p*-nitrosodiphenylamine‡; *N*-nitrosodipropylamine; nitrosododecamethyleneimine; *N*-nitrosoephedrine; nitrosoheptamethyleneimine; *N*-nitrosomethyl-2,3-dihydroxypropylamine; nitrosomethylundecylamine; *N*-nitrosopyrrolidine‡; *o*-nitrosotoluene; norlestrin‡; *N*-(9-oxo-2-fluorenyl) acetamide; 4,4′-oxydianiline‡; petasitenine; phenobarbital, sodium‡; 1-phenylazo-2-naphthol†; *o*-phenylenediamine.2*HCl*‡; polybrominated biphenyl mixture‡; pyrilamine maleate; D & C Red No. 5‡; D & C Red No. 9†; FD & C Red No. 1; *p*-rosaniline.*HCl*‡; safrole‡; selenium sulfide‡; senkirkine; sterigmatocystin‡; symphytine; Telone II‡; 3,3′,4,4′-tetraaminobiphenyl.4*HCl*‡; 2,3,7,8-tetrachlorodibenzo-*p*-dioxin‡; 4,4′-thiodianiline‡; toluene diisocyanate, commercial grade (2,4 (80%)- and 2,6 (20%)-)‡; 2,4,5-trimethylaniline‡; 2,4,5-trimethylaniline.*HCl*‡; 2,4,6-trimethylaniline.*HCl*‡; vinyl acetate; vinyl bromide; vinyl chloride‡; C.I. Disperse Yellow 3‡
	Tree shrew	1	aflatoxin B_1†
Lung	Hamster	2	nitroso-2,6-dimethylmorpholine; 1-nitroso-3,4,5-trimethylpiperazine
	Mouse	83	acetaldehyde methylformylhydrazone; *N*′-acetyl-4-(hydroxymethyl) phenylhydrazine; 1-acetyl-2-isonicotinoylhydrazine; allylhydrazine.*HCl*; 2-amino-3-methylimidazo[4,5-*f*]quinoline‡; arecoline.*HCl*; benzene‡; benzoyl hydrazine; benzylhydrazine.2*HCl*; bis(2-chloro-1-methylethyl) ether†; bis-(chloromethyl) ether‡; 1,3-butadiene; *N*-*N*-butyl-*N*-formylhydrazine; butylated hydroxytoluene†; 1,1-di-*N*-butylhydrazine; *N*-butylhydrazine.*HCl*; 1,2-di-*N*-butylhydrazine.2*HCl*; carbamyl hydrazine.*HCl*; 1-carbamyl-2-phenylhydrazine; chlorambucil‡; cyclophosphamide‡; dacarbazine‡; daminozide‡; *p*,*p*′-DDD†; 1,1-diallylhydrazine; 1,2-diallylhydrazine.2*HCl*; dibenz(*a*,*h*) anthracene; 1,2-dibromo-3-chloropropane‡; dibromodulcitol‡; 1,2-dibromoethane‡; dibromomannitol‡; 1,2-dichloroethane‡; 1,2-diformylhydrazine; dihydrosafrole‡; 2,5-dimethoxy-4′-aminostilbene‡; 1,1-dimethylhydrazine; 1,2-dimethylhydrazine.2*HCl*; estradiol mustard†; *N*-ethyl-*N*-formylhydrazine; ethylene imine; ethylhydrazine.*HCl*; formylhydrazine; hydrazine‡; hydrazine sulfate‡; isoniazid‡; isonicotinic acid vanillylidenehydrazide; melphalan‡; 1-methyl-1,4-dihydro-7-[2-(5-nitrofuryl)vinyl]-4-oxo-1,8-naphthyridine-3-carboxylate, potassium; *N*-methyl-*N*-formylhydrazine; methyl methanesulfonate; methylene chloride‡; methylhydrazine; methylhydrazine sulfate;

(Continued on next page)

Table 1. ***Continued.***

Tissue	Species	N	Chemical names
			(*N*-6)-(methylnitroso) adenine; (*N*-6)-(methylnitroso) adenosine; metronidazole‡; monoacetyl hydrazine; 1,5-naphthalenediamine‡; nicotinic acid hydrazide; *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide‡; 3-nitro-3-hexene‡; nitrosodibutylamine‡; *N*-nitrosodimethylamine‡; *N*-nitrosopiperidine‡; *N*-pentylhydrazine.*HCl*; phenesterin‡; phenylethylhydrazine sulfate; procarbazine.*HCl*‡; *N*-*N*′-propyl-*N*-formylhydrazine; propylhydrazine.*HCl*; selenium sulfide‡; streptozotocin‡; sulfallate‡; Telone II‡; 3,3′,4,4′-tetraaminobiphenyl.4*HCl*‡; trichloroethylene‡; trifluralin†; 2,4,5-trimethylaniline.*HCl*‡; tris(2,3-dibromopropyl) phosphate‡; urethane‡; vinyl chloride‡; vinylidene chloride†; 2,4-xylidine.*HCl*†
	Rat	31	2-amino-5-(5-nitro-2-furyl)-1,3,4-oxadiazole; 2-amino-5-(5-nitro-2-furyl)-1,3,4-thiadiazole; 2-amino-5-nitrothiazole†; bis-(chloromethyl) ether‡; HC Blue No. 1‡; 1,2-dibromoethane‡; dimethyl hydrogen phosphite†; *trans*-2-[(dimethylamino)methylimino]-5-[2-(5-nitro-2-furyl)vinyl]-1,3,4-oxadiazole; hydrazine‡; hydrazine sulfate‡; 1-(2-hydroxyethyl)-1-nitrosourea; isoniazid‡; 4,4′-methylene-bis(2-chloroaniline); *N*-{[3-(5-nitro-2-furyl)-1,2,4-oxadiazole-5-yl]-methyl}acetamide; *N*-[5-(5-nitro-2-furyl)-1,3,4-thiadiazol-2-yl] acetamide‡; 3-nitro-3-hexene‡; 5-nitroacenaphthene‡; *N*-nitroso-bis-(4,4,4-trifluoro-*N*-butyl) amine; *N*-nitroso-*N*-methyl-*N*-dodecylamine; *N*-nitroso-*N*-methyl-*N*-tetradecylamine; *N*-nitroso-*N*-methyldecylamine; *N*-nitrosobis(2-hydroxypropyl) amine; *N*-nitrosobis(2-oxopropyl) amine; nitrosodibutylamine‡; *N*-nitrosoephedrine; *N*-nitrosomethyl-2,3-dihydroxypropylamine; nitrosomethylundecylamine; 2,3,7,8-tetrachlorodibenzo-*p*-dioxin‡; 2,4,5-trimethylaniline‡; 2,4,6-trimethylaniline.*HCl*‡; vinyl chloride‡
Mammary gland	Hamster	1	vinyl chloride‡
	Mouse	14	benzene‡; 1,3-butadiene; 1,2-dibromoethane‡; 1,2-dichloroethane‡; diethylstilbestrol‡; estradiol; isoniazid‡; isonicotinic acid vanillylidenehydrazide; (*N*-6)-(methylnitroso) adenosine; reserpine‡; sulfallate‡; vinyl chloride‡; vinylidene chloride†; vitamin D_2
	Rat	73	4-acetylaminobiphenyl; 2-acetylaminofluorene‡; acronycine; acrylamide; acrylonitrile; AF-2‡; 2-amino-3-methylimidazo[4,5-*f*]quinoline.*HCl*; 2-amino-5-(5-nitro-2-furyl)-1,3,4-oxadiazole; 2-amino-5-(5-nitro-2-furyl)-1,3,4-thiadiazole; 2-amino-5-nitrothiazole†; 4-aminodiphenyl.*HCl*‡; 1-amyl-1-nitrosourea; benzidine; 4-bis(2-hydroxyethyl)amino-2-(5-nitro-2-thienyl) quinazoline; carbon tetrachloride‡; carboxymethylnitrosourea; chlorambucil‡; cytembena†; dacarbazine‡; *N*-1-diacetamidofluorene; 4,6-diamino-2-(5-nitro-2-furyl)-*S*-triazine; 2,4-diaminoanisole sulfate‡; 2,4-diaminotoluene‡; 1,2-dibromo-3-chloropropane‡; 1,2-dibromoethane‡; dibromomannitol‡; 1,3-dibutyl-1-nitrosourea; 3,3′-dichlorobenzidine; 1,2-dichloroethane‡; 4,6-dimethyl-2-(5-nitro-2-furyl) pyrimidine; 1,2-dimethyl-5-nitroimidazole; *trans*-2-[(dimethylamino)methylimino]-5-[2-(5-nitro-2-furyl)vinyl]- 1,3,4-oxadiazole; 2-(2,2-dimethylhydrazino)-4-(5-nitro-2-furyl) thiazole; *N*-(2-fluorenyl)-2,2,2-trifluoroacetamide; formic acid 2-(4-methyl-2-thiazolyl) hydrazide; formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl]hydrazide‡; hexamethylmelamine; 2-hydrazino-4-(*p*-aminophenyl) thiazole‡; 2-hydrazino-4-(5-nitro-2-furyl) thiazole‡; 2-hydrazino-4-(*p*-nitrophenyl) thiazole‡; hydrazobenzene‡; 1-(2-hydroxyethyl)-3-[(5-nitrofurfurylidene)amino]-2-imidazolidinone; isoniazid‡; 2-methoxy-3-aminodibenzofuran; 4-methyl-1-[(5-nitrofurfurylidene)amino]-2-imidazolidinone; *N*-(*N*-methyl-*N*-nitrosocarbamoyl)-*l*-ornithine; 3-methylcholanthrene; 4,4′-methylene-bis(2-chloroaniline); 4,4′-methylene-bis(2-methylaniline); methylene chloride‡; metronidazole‡; l-5-morpholinomethyl-3-[(5-nitrofurfurylidene)amino]-2-oxazolidinone.*HCl*; nithiazide‡; 5-nitro-2-furaldehyde semicarbazone; 3-(5-nitro-2-furyl)-imidazo(1,2-α)pyridine‡; 4-(5-nitro-2-furyl) thiazole; *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]acetamide; *N*,*N*′-[6-(5-nitro-2-furyl)-*S*-triazine-2,4-diyl]bisacetamide; 5-nitroacenaphthene‡; 1-[(5-nitrofurfurylidene)amino]-2-imidazolidinone; norlestrin‡; *N*-(9-oxo-2-fluorenyl) acetamide; phenacetin‡; phenesterin‡; procarbazine.*HCl*‡; propane sultone; sulfallate‡; 4,4′-sulfonylbisacetanilide; toluene diisocyanate, commercial grade (2,4 (80%)- and 2,6 (20%))-‡; *o*-toluidine.*HCl*‡; 2,2,2-trifluoro-*N*-[4-(5-nitro-2-furyl)-2-thiazolyl]acetamide‡; vinyl chloride‡; FD & C Violet No. 1†
Mesovarium	Rat	2	salbutamol; terbutaline
Myocardium	Mouse	2	estradiol mustard†; phenesterin‡
Nasal cavity[b]	Bush baby	1	*N*-nitrosodiethylamine
	Hamster	10	acetaldehyde; diallylnitrosamine; dimethylcarbamyl chloride; hydrazine‡; nitroso-2,6-dimethylmorpholine; *N*-nitrosoallyl-2-oxopropylamine; *N*-nitrosomethyl-2,3-dihydroxypropylamine; *N*-nitrosomorpholine; *N*′-nitrosonornicotine; *N*-nitrosopiperidine‡
	Mouse	4	1,2-dibromo-3-chloropropane‡; 1,2-dibromoethane‡; formaldehyde‡; 1,2-propylene oxide‡
	Rat	33	acetaldehyde; acrylonitrile; benzene‡; bis-(chloromethyl) ether‡; *p*-cresidine‡; diallylnitrosamine; 1,2-dibromo-3-chloropropane‡; 1,2-dibromoethane‡; dimethylvinyl chloride‡; dinitrosohomopiperazine; 1,4-dioxane‡; *Z*-ethyl-*O*,*N*,*N*-azoxyethane; ethylnitrosocyanamide; formaldehyde‡; hydrazine‡; *N*-nitroso-*N*-methyldecylamine; di(*N*-nitroso)-perhydropyrimidine; *N*-nitroso(2,2,2-trifluoroethyl) ethylamine; 1-nitroso-3,4,5-trimethylpiperazine; *N*-nitrosoallyl-2,3-dihydroxypropylamine; *N*-nitrosoallyl-2-hydroxypropylamine; *N*-nitrosoallylethanolamine; *N*-nitrosobis(2-hydroxypropyl) amine; *N*-nitrosobis(2-oxopropyl) amine; *N*-nitrosodiethanolamine; *N*-nitrosodipropylamine; *N*-nitrosomethyl-2,3-dihydroxypropylamine; *N*-nitrosomethyl-2-hydroxypropylamine; *N*′-nitrosonornicotine-1-*N*-oxide; phenacetin‡; phenylglycidyl ether; 1,2-propylene oxide‡; vinyl chloride‡
Oral[c] cavity	Hamster	2	acetaldehyde; nitroso-2,6-dimethylmorpholine
	Monkey	1	*N*-nitroso-*N*-methylurea
	Mouse	1	*N*-nitrosohexamethyleneimine
	Rat	16	acrylamide; acrylonitrile; 2-amino-3-methylimidazo[4,5-*f*]quinoline‡; benzene‡; 1,2-dibromo-3-chloropropane‡; dimethylvinyl chloride‡; dinitrosohomopiperazine; *N*-nitroso-2,3-dihydroxypropyl-2-hydroxypropylamine; nitroso-2,3-dihydroxypropyl-2-oxopropylamine; nitroso-*N*-methyl-*N*-(2-phenyl) ethyl-

Table 1. *Continued.*

Tissue	Species	N	Chemical names
			amine; nitrosoamylurethan; *N*-nitrosodiethylamine; nitrosoheptamethyleneimine; 1-nitrosohydantoin; *N*-nitrosothiomorpholine; 2,3,7,8-tetrachlorodibenzo-*p*-dioxin‡
Ovary	Mouse	4	benzene‡; 1,3-butadiene; 5-nitroacenaphthene‡; 4-vinylcyclohexene
Pancreas	Hamster	3	nitroso-2,3-dihydroxypropyl-2-oxopropylamine; nitroso-2,6-dimethylmorpholine; nitroso-2-oxopropyl-ethanolamine
	Monkey	2	aflatoxin B_1†; methylazoxymethanol acetate and cycasin mixture
	Rat	9	2-amino-3-methylimidazo[4,5-*f*]quinoline.*HCl*; azaserine; chlorendic acid‡; cinnamyl anthranilate‡; clofibrate; ethyl alcohol; *N*-(*N*-methyl-*N*-nitrosocarbamoyl)-*l*-ornithine; nitrofen‡; toluene diisocyanate, commercial grade (2,4 (80%)- and 2,6 (20%)-)‡,d
Peritoneal cavity[c]	Mouse	7	bis-1,2-(chloromethoxy) ethane; bis-1,4-(chloromethoxy)-*p*-xylene; bis-(chloromethyl) ether‡; *trans*-1,4-dichlorobutene-2; dimethylcarbamyl chloride; phenoxybenzamine.*HCl*‡; tris-1,2,3-(chloromethoxy) propane
	Rat	17	acronycine; acrylamide; actinomycin D; aniline.*HCl*†; bromate, potassium†; chlorozotocin; cytembena†; dapsone†; 1,2-dibromoethane‡; dibromomannitol‡; ethylene oxide; melphalan‡; *N*-methyl-*N*,4-dinitroso-aniline; mitomycin-C; *N*-nitroso-2,2,4-trimethyl-1,2-dihydroquinoline polymer; phenoxybenz-amine.*HCl*‡; *o*-toluidine.*HCl*‡
Pituitary gland	Mouse	4	enovid; norlestrin‡; propylthiouracil‡; zearalenone†
	Rat	7	acrylamide; 3-aminotriazole‡; 1,2-dibromoethane‡; diethylstilbestrol‡; ethyl alcohol; metronidazole‡; norlestrin‡
Preputial gland	Mouse	7	acetaldehyde methylformylhydrazone; benzene‡; *N*-*N*-butyl-*N*-formylhydrazine; dimethylvinyl chloride‡; *N*-ethyl-*N*-formylhydrazine; *N*-*N*′-propyl-*N*-formylhydrazine; thio-TEPA‡
	Rat	2	2,4-diaminoanisole sulfate‡; isophorone†
Prostate	Rat	2	*N*-nitrosobis(2-hydroxypropyl) amine; *N*-nitrosobis(2-oxopropyl) amine
Skin	Hamster	2	urethane‡; vinyl chloride‡
	Mouse	1	thio-TEPA‡
	Rat	20	2-acetylaminofluorene‡; 3-amino-9-ethylcarbazole.*HCl*‡; 2-amino-3-methylimidazo[4,5-*f*]quinoline‡; ben-zene‡; carboxymethylnitrosourea; 2,4-diaminoanisole sulfate‡; dibromodulcitol‡; dibromomannitol‡; di-methoxane; 2,5-dimethoxy-4′-aminostilbene‡; 3,3′-dimethoxybenzidine-4,4′-diisocyanate†; dimethylvinyl chloride‡; lasiocarpine; *N*-(*N*-methyl-*N*-nitrosocarbamoyl)-*l*-ornithine; 5-nitro-*o*-anisidine‡; *p*-ros-aniline.*HCl*‡; thio-TEPA‡; thiourea†; vinyl chloride‡; FD & C Violet No. 1†
Small intestine	Monkey	2	methylazoxymethanol acetate and cycasin mixture; urethane‡
	Mouse	3	captafol; *N*-ethyl-*N*′-nitro-*N*-nitrosoguanidine; hydrogen peroxide
	Rat	21	acrylonitrile; 3-amino-1-methyl-5*H*-pyrido[4,3-*b*]indole acetate‡; 2-amino-6-methyldipyrido[1,2-*a*:3′,2′-*d*]imidazole‡; 2-amino-3-methylimidazo[4,5-*f*]quinoline‡; 2-aminodipyrido[1,2-*a*:3′,2′-*d*]imidazole‡; 4-bis-(2-hydroxyethyl)amino-2-(5-nitro-2-thienyl) quinazoline; carboxymethylnitrosourea; 1-(4-chlorophenyl)-1-phenyl-2-propynyl carbamate; 2,5-dimethoxy-4′-aminostilbene‡; 4,6-dimethyl-2-(5-nitro-2-furyl) pyrimidine; *trans*-2-[(dimethylamino)methylimino]-5-[2-(5-nitro-2-furyl)vinyl]-1,3,4- oxadiazole; *Z*-ethyl-*O*,*N*,*N*-azoxymethane; 1-ethyl-1-nitrosourea; formic acid 2-[4-(5-nitro-2-furyl)-2-thia-zolyl]hydrazide‡; lasiocarpine; *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine; *N*-[5-(5-nitro-2-furyl)-1,3,4-thiadi-azol- 2-yl]acetamide‡; *N*-nitroso-*N*-isobutylurea; nitrosoethylurethan; propane sultone; quercetin†
Spleen	Rat	6	aniline.*HCl*†; azobenzene†; dapsone†; *o*-nitrosotoluene; D & C Red No. 9†; *o*-toluidine.*HCl*‡
Stomach	Hamster	15	AF-2‡; 1,4-dinitroso-2,6-dimethylpiperazine; formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl]hydrazide‡; hydrazine‡; *N*-hydroxy-2-acetylaminofluorene‡; *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]acetamide; *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide‡; *N*-nitroso-2,3-dihydroxypropyl-2-hydroxypropylamine; nitroso-2,3-dihydroxypropyl-2-oxopropylamine; nitroso-5-methyloxazolidone; *N*-nitroso-*N*-methylurethan; *N*-nitroso-1,3-oxazolidine; 1-nitroso-3,4,5-trimethylpiperazine; urethane‡; vinyl chloride‡
	Mouse	42	acetaldehyde methylformylhydrazone; AF-2‡; 2-amino-3,4-dimethylimidazo[4,5-*f*]quinoline; 2-amino-3-methylimidazo[4,5-*f*]quinoline‡; 2-amino-4-(5-nitro-2-furyl) thiazole‡; *trans*-5-amino-3[2-(5-nitro-2-furyl)vinyl-1,2,4-oxadiazole; arecoline.*HCl*; benzyl acetate†; benzyl chloride†; bromoethanol; 1,3-butadiene; 1,1-di-*N*-butylhydrazine; captafol; carbazole; 3-chloro-2-methylpropene, technical grade (con-taining 5% dimethylvinyl chloride)‡; 3-(chloromethyl)pyridine.*HCl*‡; 2-chloropropanal; 1-chloropropene; 1,1-diallylhydrazine; 1,2-dibromo-3-chloropropane‡; 1,2-dibromoethane‡; diglycidyl resorcinol ether, technical grade‡; dimethylvinyl chloride‡; dinitrosopiperazine; estradiol mustard†; ethyl acrylate‡; formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl]hydrazide‡; 2-hydrazino-4-(5-nitro-2-furyl) thiazole‡; *N*-hydroxy-2-acetylaminofluorene‡; 1-methyl-1,4-dihydro-7-[2-(5-nitrofuryl)vinyl]-4-oxo-1,8-naphthyridine-3-carboxylate, potassium; 3-(5-nitro-2-furyl)-imidazo(1,2-α)pyridine‡; *N*-[5-(5-nitro-2-furyl)-1,3,4-thiadi-azol-2-yl]acetamide‡; *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide‡; nitrosodibutylamine‡; *N*-nitroso-hexamethyleneimine; *N*-nitrosopiperidine‡; β-propiolactone‡; styrene oxide‡; Telone II‡; 2,2,2-trifluoro-*N*-[4-(5-nitro-2-furyl)-2-thiazolyl]acetamide‡; trifluralin†; tris(2,3-dibromopropyl) phosphate‡

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Table 1. *Continued.*

Tissue	Species	N	Chemical names
	Rat	60	acetone[4-(5-nitro-2-furyl)-2-thiazolyl]hydrazone; 1′-acetoxysafrole†; acrylonitrile; 2-amino-5-(5-nitro-2-furyl)-1,3,4-oxadiazole; 2-amino-5-(5-nitro-2-furyl)-1,3,4-thiadiazole; 2-amino-4-(5-nitro-2-furyl) thiazole‡; 1-amyl-1-nitrosourea; benzene‡; benzo(*a*)pyrene‡; *N*-*N*-butyl-*N*-nitrosourea; butylated hydroxyanisole; β-butyrolactone; 3-chloro-2-methylpropene, technical grade (containing 5% dimethylvinyl chloride)‡; 4-chloro-*o*-phenylenediamine‡; 3-(chloromethyl)pyridine.*HCl*‡; cupferron‡; 1,2-dibromo-3-chloropropane‡; 1,2-dibromoethane‡; 1,2-dichloroethane‡; diglycidyl resorcinol ether, technical grade‡; 2,5-dimethoxy-4′-aminostilbene‡; dimethyl hydrogen phosphite†; 4,6-dimethyl-2-(5-nitro-2-furyl) pyrimidine; *trans*-2-[(dimethylamino)methylimino]-5-[2-(5-nitro-2-furyl)vinyl]-1,3,4-oxadiazole; dimethylvinyl chloride‡; epichlorohydrin†; ethyl acrylate‡; ethylene oxide; fluorocarbon 31; 1-(2-hydroxyethyl)-1-nitrosourea; 1′-hydroxysafrole‡; *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine; *N*-methyl-*N*-nitrosobenzamide; methylnitrosocyanamide; 3-(5-nitro-2-furyl)-imidazo(1,2-α)pyridine‡; *N*-[5-(5-nitro-2-furyl)-1,3,4-thiadiazol-2-yl]acetamide‡; 4-(5-nitro-2-furyl) thiazole; 8-nitroquinoline; nitroso-Baygon; *N*-nitroso-2,3-dihydroxypropyl-2-hydroxypropylamine; nitroso-2,3-dihydroxypropyl-2-oxopropylamine; 1-nitroso-3,5-dimethyl-4-benzoylpiperazine; *N*-nitroso-*N*-methyl-*N*-dodecylamine; nitroso-*N*-methyl-*N*-(2-phenyl) ethylamine; *N*-nitroso-*N*-methyldecylamine; nitroso-1,2,3,6-tetrahydropyridine; *N*-nitrosobenzthiazuron; nitrosodibutylamine‡; *N*-nitrosodiethylamine; *N*-nitrosoephedrine; nitrosoethylurethan; phenacetin‡; pivalolactone†; β-propiolactone‡; *N*-propyl-*N*′-nitro-*N*-nitrosoguanidine; 1,2-propylene oxide‡; styrene oxide‡; sulfallate‡; Telone II‡; 2,4,6-trimethylaniline.*HCl*‡
Subcutaneous	Mouse	1	1,2-dibromoethane‡
	Rat	10	2,4-diaminotoluene.2*HCl*‡; 1,2-dichloroethane‡; dimethoxane; 4,4′-methylene-bis(2-methylaniline); *o*-nitrosotoluene; *p*-rosaniline.*HCl*‡; toluene diisocyanate, commercial grade (2,4 (80%)- and 2,6 (20%))-‡; *o*-toluidine.*HCl*‡; 2,4,5-trimethylaniline.*HCl*‡; 2,5-xylidine.*HCl*‡
Testes	Mouse	1	reserpine‡
	Rat	6	*N*-butyl-*N*-(4-hydroxybutyl) nitrosamine; fluorocarbon 133a; metronidazole‡; *N*-nitrosodimethylamine‡; trichloroethylene‡; vinyl chloride‡
Thyroid gland	Hamster	4	hexachlorobenzene‡; hydrazine‡; methylthiouracil; urethane‡
	Mouse	10	3-amino-4-ethoxyacetanilide†; HC Blue No. 1‡; chlorinated paraffins (*C*12, 60% chlorine)‡; 2,4-diaminoanisole sulfate‡; ethionamide†; 4,4′-methylenedianiline.2*HCl*‡; 1,5-naphthalenediamine‡; 4,4′-oxydianiline‡; 2,3,7,8-tetrachlorodibenzo-*p*-dioxin‡; 4,4′-thiodianiline‡
	Rat	20	3-aminotriazole‡; *o*-anisidine.*HCl*‡; chlorinated paraffins (*C*12, 60% chlorine)‡; 2,4-diaminoanisole sulfate‡; *N*,*N*′-diethylthiourea†; 1-ethyl-1-nitrosourea; ethylene thiourea‡; methimazole; 4,4′-methylene-bis(*N*,*N*-dimethyl) benzenamine‡; 4,4′-methylenedianiline.2*HCl*‡; mirex, photo-; *N*-nitrosobis(2-oxopropyl) amine; 4,4′-oxydianiline‡; propylthiouracil‡; *p*-rosaniline.*HCl*‡; 2,3,7,8-tetrachlorodibenzo-*p*-dioxin‡; 4,4′-thiodianiline‡; trimethylthiourea†; vinyl acetate; zinc dimethyldithiocarbamate†
Urinary bladder	Dog	2	3,3′-dichlorobenzidine; 4,4′-methylene-bis(2-chloroaniline)
	Hamster	3	formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl]hydrazide‡; *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]acetamide; *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide‡
	Monkey	1	2-naphthylamine‡
	Mouse	12	2-acetylaminofluorene‡; 4-aminodiphenyl; 4-aminodiphenyl.*HCl*‡; 2-aminodiphenylene oxide; *o*-anisidine.*HCl*‡; 4-chloro-4′-aminodiphenylether‡; *p*-cresidine‡; 4-ethylsulphonylnaphthalene-1-sulfonamide; *N*-hydroxy-2-acetylaminofluorene‡; *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide‡; phenacetin‡; Telone II‡
	Rat	37	acetaminophen‡; allyl isothiocyanate†; 2-amino-3-methylimidazo[4,5-*f*]quinoline.*HCl*; 2-amino-4-(5-nitro-2-furyl)thiazole‡; 4-amino-2-nitrophenol†; 11-aminoundecanoic acid†; *o*-anisidine.*HCl*‡; C.I. Disperse Blue 1†; *N*-butyl-*N*-(4-hydroxybutyl) nitrosamine; 4-chloro-*o*-phenylenediamine‡; *m*-cresidine†; *p*-cresidine‡; cyclophosphamide‡; diethylene glycol; melamine†; 2-methoxy-3-aminodibenzofuran; 2-naphthylamine‡; nitrilotriacetic acid‡; nitrilotriacetic acid, trisodium salt, monohydrate†; *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide‡; *N*-nitroso-*N*-methyl-*N*-dodecylamine; *N*-nitroso-*N*-methyl-*N*-tetradecylamine; *N*-nitroso-*N*-methyldecylamine; *N*-nitrosobis(2-oxopropyl) amine; nitrosodibutylamine‡; *N*-nitrosodiphenylamine†; *o*-nitrosotoluene; *N*-oxydiethylene thiocarbamyl-*N*-oxydiethylene sulfenamide; phenacetin‡; phenazone; *o*-phenylphenate, sodium†; *o*-phenylphenol†; quercetin†; *p*-quinone dioxime†; saccharin, sodium†; *o*-toluenesulfonamide; *o*-toluidine.*HCl*‡
Uterus	Mouse	5	dacarbazine‡; 1,2-dichloroethane‡; (*N*-6)-(methylnitroso) adenosine; procarbazine.*HCl*‡; trimethylphosphate†
	Rat	11	3-amino-9-ethylcarbazole.*HCl*‡; dacarbazine‡; daminozide‡; 3,3′-dimethoxybenzidine-4,4′-diisocyanate†; fluorocarbon 133a; ICRF-159‡; isophosphamide‡; 1,5-naphthalenediamine‡; norlestrin‡; 4,4′-thiodianiline‡; vinyl acetate
Vagina	Rat	1	*N*-*N*-butyl-*N*-nitrosourea
Vascular system	Hamster	3	1,2-dimethylhydrazine.2*HCl*; hexachlorobenzene‡; vinyl chloride‡
	Monkey	2	aflatoxin B_1†; procarbazine.*HCl*‡
	Mouse	47	*N*′-acetyl-4-(hydroxymethyl) phenylhydrazine; 1-acetyl-2-phenylhydrazine; allylhydrazine.*HCl*; 2-amino-3-methyl-9*H*-pyrido-[2,3-*b*]-indole; 2-amino-6-methyldipyrido[1,2-*a*:3′,2′-*d*]imidazole‡; 2-amino-9*H*-py-

Table 1. ***Continued.***

Tissue	Species	N	Chemical names
			rido(2,3-*b*) indole; 4-aminodiphenyl.*HCl*‡; 2-aminodipyrido[1,2-*a*:3′,2′-*d*]imidazole‡; arecoline.*HCl*[f]; benzidine.2*HCl*; 2-biphenylamine.*HCl*†; 1,3-butadiene; captafol; carbamyl hydrazine.*HCl*; 4-chloro-4′-aminodiphenylether‡; 1-chloro-4-nitrobenzene†; 5-chloro-*o*-toluidine†; 4-chloro-*o*-toluidine.*HCl*†; cupferron‡; dacarbazine‡; daminozide‡; 2,4-diaminotoluene.2*HCl*‡; 1,2-dibromoethane‡; diftalone; 7,12-dimethylbenz(*a*)anthracene; 1,1-dimethylhydrazine; 1,2-dimethylhydrazine.2*HCl*; *N*-ethyl-*N*-formylhydrazine; ethylhydrazine.*HCl*; 1′-hydroxysafrole‡; *N*-methyl-*N*-formylhydrazine; 2-methyl-1-nitroanthraquinone‡; Michler's ketone‡; 5-nitro-*o*-toluidine†; nitrofen‡; *N*-pentylhydrazine.*HCl*; phenylethylhydrazine sulfate; phenylhydrazine.*HCl*; sterigmatocystin‡; toluene diisocyanate, commercial grade (2,4 (80%)- and 2,6 (20%)-)‡; *o*-toluidine.*HCl*‡; 2,4,6-trichloroaniline†; 2,4,5-trimethylaniline.*HCl*‡; 2,4,6-trimethylaniline.*HCl*‡; vinyl chloride‡; vinylidene chloride†,f; 2,5-xylidine.*HCl*‡
	Rat	26	3-amino-1-methyl-5*H*-pyrido[4,3-*b*]indole acetate‡; 2-amino-3-methylimidazo[4,5-*f*]quinoline.*HCl*; aniline.*HCl*†; azobenzene†; benzene‡,f; clivorine; cupferron‡; 1,2-dibromoethane‡; 1,2-dichloroethane‡; 4,6-dimethyl-2-(5-nitro-2-furyl) pyrimidine; *Z*-ethyl-*O*,*N*,*N*-azoxyethane; *Z*-ethyl-*O*,*N*,*N*-azoxymethane; lasiocarpine; 4,4′-methylene-bis(2-chloroaniline); *N*-[5-(5-nitro-2-furyl)-1,3,4-thiadiazol-2-yl]acetamide‡; *N*-nitroso-(2-hydroxypropyl)-(2-hydroxyethyl) amine; nitroso-1,2,3,6-tetrahydropyridine; *N*-nitrosobis(2-oxopropyl) amine; *N*-nitrosodimethylamine‡; *N*-nitrosopyrrolidine‡; petasitenine; sterigmatocystin‡; symphytine; *o*-toluidine.*HCl*‡; vinyl bromide; vinyl chloride‡

†Adequately tested in both mice and rats, but positive in only one of them.
‡Positive in both mice and rats.
[a]Cortical adenomas were induced by these chemicals.
[b]Nasal cavity includes tissues of the nose, nasal turbinates, paranasal sinuses and trachea. If the author used the term "respiratory system" to define the above tissues without including lung and the bronchioles, it was included in this category.
[c]Oral cavity includes tissues of the mouth, oropharynx, pharynx, and larynx.
[d]Islet-cell adenomas were induced in females and acinar cell adenomas were induced in males.
[e]Peritoneal cavity includes mesotheliomas seen in either multiple organs, peritoneal cavity, peritoneum, abdominal cavity or abdomen.
[f]Vascular tumors were induced only in liver.

indicating that it has been tested in both rats and mice and is positive in both species at some target site. Since chloroform is also listed under kidney for mice, both species have been shown to induce tumors at that site. In contrast 1,4-dichlorobenzene is listed under kidney for the rat with the same symbol ‡, indicating that it is positive in the mouse as well, but it is not listed under kidney for the mouse; therefore, kidney is not a target in the mouse. Another example under rat kidney is chlorothalonil which has the symbol †, indicating that it has been tested in both rats and mice, but is positive only in one of them: in this case, the rat. For azoxymethane, however, there is no superscript, indicating that it has not been tested in the mouse. When a chemical is listed with superscripts, the information applies only to rats and mice. Sometimes the superscripts appear for a chemical listed under a different species; for example, under thyroid gland for hamsters, urethane is listed with the symbol ‡, indicating that the chemical is a carcinogen in both rats and mice, but the superscript does not apply to results in hamsters. In Table 1 under thyroid gland, urethane is not listed for either rats or mice, and therefore it is not a target organ for either species.

While Table 1 provides an exhaustive overview by target site of the CPDB, full details on each experiment are given in our published plots, including references to the published papers, results of negative tests, and the sex and strain in each test. The four plots of the CPDB analyze the results of published papers chronologically, and appear in *Environmental Health Perspectives* (*1–4*). Experiments of a given chemical may appear in more than one plot, and the reader can locate all tests by referring to Appendix 14 in reference (*4*). This appendix lists all 1052 chemicals that appear in any of the four plots, indicating which plot(s) contains results on each chemical; the appendix is ordered alphabetically by chemical name and common synonym. Thus, for any target organ of interest, using Table 1 in conjunction with the published plots of the CPDB will provide detailed information on each experiment (see "Introduction"). For example, the CPDB includes experiments of 96 mouse strains and 71 rat strains. A combined plot of the entire CPDB, that merges results from all four plots and is organized by chemical, can be obtained from the first author. A computer readable (SAS) database is also obtainable.

Based on Table 1, the frequency of carcinogenic response by site in rats and mice is tabulated in Table 2. Twenty-eight sites are identified as positive target organs in the mouse and 31 in the rat. In both species, the liver is the most common target site, and it is the predominant site in the mouse. The second most common sites are the mouse lung and the rat mammary gland. In the subset of NCI/NTP bioassays, which use an extensive and standardized pathology protocol, these same sites are the most frequent in each species, although the rat stomach is identified as frequently as the rat mammary gland. Chemical carcinogens thus induce tumors in a wide variety of target organs. As shown in Table 2, each of eight sites is a target for at least 10% of the carcinogens in either rats or mice: liver, lung, mammary gland, stomach, vascular system, kidney, hematopoietic system, and urinary bladder.

Table 2. Frequency of positive target sites for chemicals classified as positive by author's opinion.

	Number positive at site (%)[a]	
	Chemicals evaluated as carcinogenic in rats (n = 354)[b]	Chemicals evaluated as carcinogenic in mice (n = 299)[b]
Liver	143 (40%)	171 (57%)
Lung	31 (9%)	83 (28%)
Mammary gland	73 (21%)	14 (5%)
Stomach	60 (17%)	42 (14%)
Vascular system	26 (7%)	47 (16%)
Kidney/ureter	45 (13%)	12 (4%)
Hematopoietic system	35 (10%)	39 (13%)
Urinary bladder/ urethra	37 (10%)	12 (4%)
Nasal cavity/ turbinates	33 (9%)	4 (1%)
Ear/Zymbal's gland	30 (9%)	2
Esophagus	29 (8%)	7 (2%)
Small intestine	21 (6%)	3 (1%)
Thyroid gland	20 (6%)	10 (3%)
Skin	20 (6%)	1
Peritoneal cavity	17 (5%)	7 (2%)
Oral cavity	16 (5%)	1
Large intestine	15 (4%)	
Central nervous system	15 (4%)	2
Uterus	11 (3%)	5 (2%)
Subcutaneous tissue	10 (3%)	1
Pancreas	9 (3%)	
Adrenal gland	7 (2%)	4 (1%)
Pituitary gland	7 (2%)	4 (1%)
Clitoral gland	7 (2%)	2
Preputial gland	2	7 (2%)
Testes	6 (2%)	1
Harderian gland		6 (2%)
Spleen	6 (2%)	
Ovary		4 (1%)
Gall bladder		3 (1%)
Bone	3	
Mesovarium	2	
Myocardium		2
Prostate	2	
Vagina	1	

[a] Percentages are not given when fewer than 1% of the carcinogens were active at a given site.

[b] Chemicals have been excluded for which the only positive results in the CPDB are for "all tumor bearing animals," i.e., there is no reported target site.

Multiple Target Sites for a Chemical

It is common for a chemical to induce tumors at more than one site in a species. This is demonstrated in Table 2 where the summation of the percentages of chemicals that are positive in the various organs for each species is far greater than 100%. Table 2 also indicates that in rats compared to mice, a larger number of organs are target sites for a higher percentage of the carcinogens, e.g., in rats each of 16 sites is a target organ for at least 5% of the compounds compared to only six sites in the mouse.

Overall, in rats, 176 of 328 carcinogens (54%) cause tumors at multiple sites; for mice, 43% (122/283) are multiple-site carcinogens. Fewer chemicals are included in this analysis than are shown in Table 2 because multiple-site carcinogenesis cannot be measured for experiments that restrict histopathological examination or report data for only a few selected tissues. Although we have defined multiple-site carcinogenesis in this analysis as target sites in any of the experiments on a chemical (multiple sites across experiments), the results are similar if multiple-site carcinogen is defined as two or more target organs *within* a single experiment (at least one experiment of the chemical has two or more target sites): in rats, 51% (167/328) are multiple-site carcinogens, and in mice 39% (109/283).

The liver is the most frequent target site in both species and the predominant site in the mouse (Tables 1 and 2). We have investigated whether the pattern of single versus multiple-site carcinogenesis in the mouse is unusual for liver carcinogens compared to the pattern for other mouse carcinogens or for rat carcinogens. Figure 1 shows the distribution of carcinogens in each species by whether or not they are positive in the liver at all, and whether there is only one target site, two target sites, or three or more. The pattern of target sites differs in the two species. Overall, fewer carcinogens in the mouse than the rat are multiple-site and many fewer in the mouse have three or more target organs. However, this difference between species is not due to the frequency of single-site carcinogenesis in the mouse liver. Figure 1 indicates that in the mouse the frequency of single-site carcinogenesis is similar for chemicals that are positive in the liver and for mouse carcinogens that are positive only at other sites. In rats, however, liver carcinogens are most often multiple-site carcinogens, and particularly are more often positive at three or more target sites, whereas the pattern of single-site carcinogenesis among chemicals that are positive only at sites other than the liver is similar to the mouse carcinogens. Thus, there is a similar distribution of single-site carcinogenesis for mouse liver carcinogens, other mouse carcinogens, and rat carcinogens that are positive only at sites other than the liver. In comparison, rat liver carcinogens are more frequently positive at multiple sites. Similar results are obtained for NCI/NTP bioassays alone and for the subset of chemicals that are positive in both rats and mice.

Despite the wide variety of target organs in each species, due to the frequency of multiple-site carcinogenesis, most carcinogens in rats and mice can be identified by just the eight most common sites: liver, lung, mammary gland, stomach, vascular system, kidney, hematopoietic system, and urinary bladder. Overall, 94% (266/283) of mouse carcinogens and 83% (273/328) of rat carcinogens are positive in at least one of these eight sites. The chemicals that do not induce tumors in one of these sites are primarily single-site carcinogens that are positive only in a less common target organ; there are more of such chemicals in rats than in mice, and this explains the lower percentage of rat carcinogens that are identified by the top eight sites.

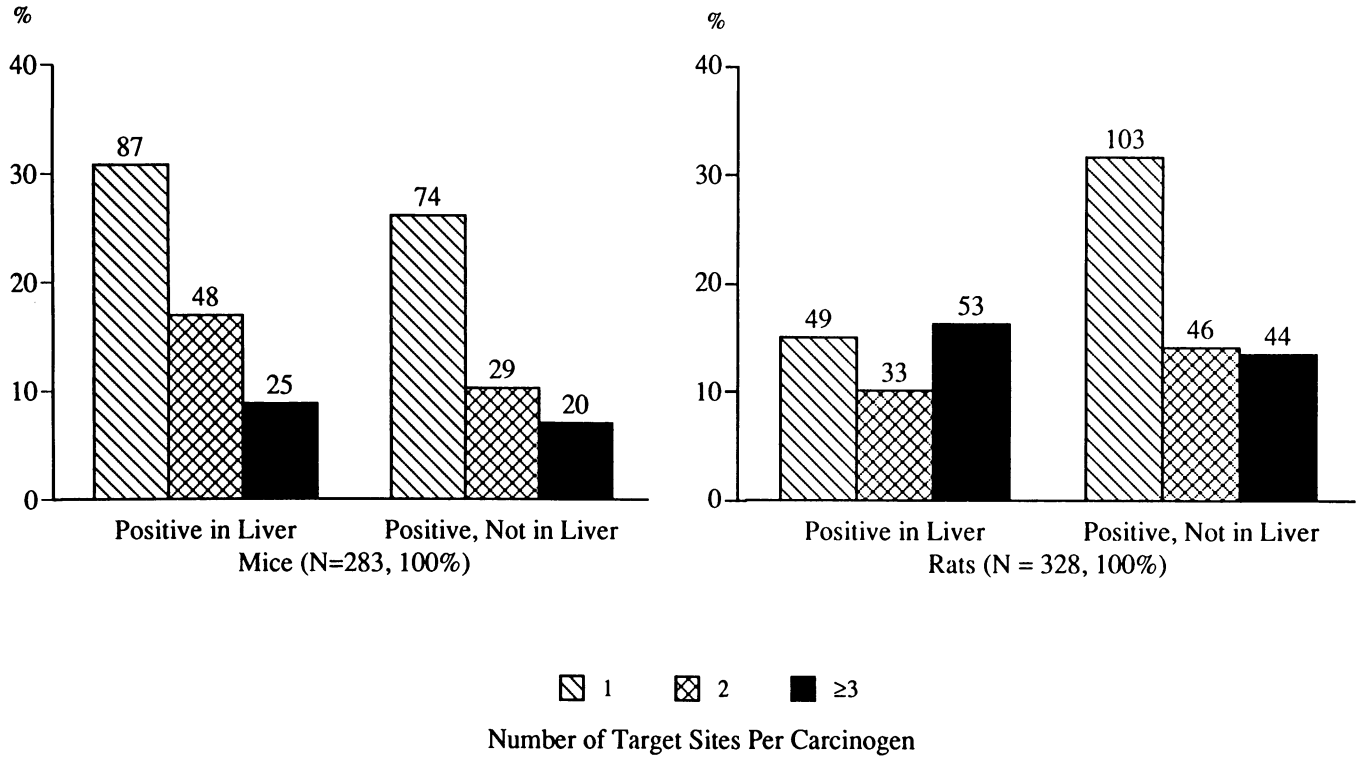

FIGURE 1. Distribution of carcinogens by number of target sites in rats and mice.

Prediction of Carcinogenicity and Target Organ, from Rats to Mice and from Mice to Rats for Chemicals Tested in Both Species

Results from rodent bioassays are often used to predict whether a chemical is a potential human carcinogen. Ideally, one would like to know the accuracy of prediction from rats or mice to humans, but because epidemiologic data are usually lacking and experiments cannot be conducted in humans, this knowledge is not available. Data are available, however, on the accuracy of prediction between the two closely related species, rats and mice. These data reflect results obtained under similar experimental conditions, including administration of estimated maximum tolerated doses (MTD) and laboratory diets fed *ad libitum*. Thus, qualitative prediction from one rodent species to another (prediction of positivity and prediction of target organ) can be examined without simultaneously having to address the issue of high to low dose extrapolation (*5*). One would expect that prediction of positivity and target organ from rats to mice tested under similar conditions, would be at least as good, and likely much better than prediction from rats or mice to humans exposed at much lower doses.

Table 3 reports the comparison of carcinogenic response in rats and mice for 427 chemicals tested in both species. Overall, prediction from rats to mice indicates

Table 3. Comparison of carcinogenic response for 427 chemicals tested in both rats and mice.

Not positive in either rats or mice	172
Positive in rats only	46
Positive in mice only	61
Positive in both rats and mice, no common target site	47
Positive in both rats and mice at same target site	101[a]

[a] For 56 of these 101 chemicals there is a site other than the liver in common between rats and mice.

that 194 chemicals (46+47+101) are carcinogenic in rats, and 148 (47+101) of the 194 are also carcinogenic in mice: 76%. The predictive value from mice to rats is similar. Of the 209 chemicals (61+47+101) carcinogenic in mice, 148 (47+101) are also carcinogenic in rats: 71%. Prediction is less accurate from target site to target site because some chemicals are positive only at different sites in the two species. Among 194 rat carcinogens, 24% (46) are negative in mice, 24% (47) are positive in mice but only at a different target site, and 52% (101) are positive at the same site; the corresponding values for predicting from mice to rats among the 209 mouse carcinogens are 29% (61) negative in rats, 22% (47) positive only at a different site, and 48% (101) positive at the same site.

To investigate how well a carcinogenic response at a particular site in one species predicts carcinogenicity in a second species, we have examined results in rats and mice for 10 frequent sites that are targets for more than

15 carcinogens in either the rat or the mouse (Table 4). The analysis is based on the 255 chemicals that have been tested in both species and are reported in Table 3 as positive, in either or both species (46 + 61 + 47 + 101). Table 4 is an update of work we published earlier for a smaller number of compounds (*5*), and reports *a*) the number of carcinogens at each of 10 frequent sites in rats or mice; for each site, we also give *b*) the number and proportion that are positive at some site in the second species, and *c* the number that are positive at the same site in both species. Most individual sites are good predictors of carcinogenicity at some site in the other species. The least accurate predictors are the urinary bladder in the rat (48%) and the liver in the mouse (65%).

Table 4 also indicates that there is a wide range in the predictive value of carcinogenicity to the same site in the other species: for the two most frequent sites in the mouse 56 of the 131 mouse liver carcinogens (43%) are positive in the rat liver, and only 8/45 (18%) mouse lung carcinogens are positive in the rat lung. For the two most frequent sites in the rat, 56 of the 79 rat liver carcinogens (71%) are positive in the mouse liver, and only 5/35 (14%) rat mammary gland carcinogens are positive in the mouse mammary gland. These results are similar to those we discussed earlier (*5*). Among the 101 chemicals with a site in common between rats and mice, 56 are positive in the liver of both species. We examined these 56 in detail and found that 11 had an additional site in common. Thus, for 45 of the 101 chemicals the one site in common is the liver, and for 56 chemicals there is at least one different site in common.

Discussion

This paper presents both a compendium of bioassay results organized by target site, and analyses of target site in rats and mice. We have shown some similarities in the results for the two species: there is a wide variety of target sites in both the rat and the mouse; the liver is the most common site in both species; and more than 80% of the carcinogens in each species are positive in at least one of the eight most frequent sites: liver, lung, mammary gland, stomach, vascular system, kidney, hematopoietic system, and urinary bladder. We have also shown some differences in the results for the two species: a chemical is more likely to induce tumors at two or more sites in rats than in mice; and some sites are frequent targets in one species and not the other, e.g., mammary gland, Zymbal's gland, and skin in the rat.

The liver is the most frequent site in both rats and mice. In mice, it is the predominant site. In an earlier paper (*5*) we showed for chemicals that were tested in both rats and mice that: *a*) when results in both species are taken into account, there are relatively few rodent carcinogens that are positive only in the mouse liver and not in either another mouse site or at all in the rat (14%) (termed "single-site mouse liver carcinogens"); and *b*) excluding chlorinated compounds, the single-site mouse liver carcinogens do not differ from other mouse liver carcinogens in the frequency with which they are mutagenic in Salmonella (*5*). In this paper, we have shown that carcinogens in the mouse liver are similar to mouse carcinogens that are not positive in the liver, in terms of how frequently there is only a single target site. In rats there is a similar pattern for chemicals that are not positive in the liver. In comparison, carcinogens that affect the rat liver also commonly affect another site (Fig. 1). These results are consistent with our earlier findings (*5*).

Rats and mice are two closely related species that are studied under similar experimental conditions; in particular, both receive doses at or near the MTD for the species. In comparison, humans are less closely re-

Table 4. Predictive value of target sites in one species for carcinogenicity in a second species: rats and mice. Chemicals tested in both rats and mice and evaluated as positive in at least one experiment.

	Rats		Mice		
Target site[a]	Total number positive at site[b]	Number positive at site in rats that are also positive at some site in mice	Total number positive at site	Number positive at site in mice that are also positive at some site in rats	Number positive at same site in rat and mouse
Liver	79	70 (89%)	131	85 (65%)	56
Lung	16	14 (88%)	45	38 (84%)	8
Mammary gland	35	32 (91%)	9	8 (89%)	5
Stomach	29	25 (86%)	27	23 (85%)	14
Hematopoietic system	18	12 (67%)	29	24 (83%)	8
Vascular system	13	11 (85%)	27	20 (74%)	5
Kidney/ureter	26	18 (69%)	11	9 (82%)	7
Urinary bladder/urethra	25	12 (48%)	9	9 (100%)	4
Ear/Zymbal's gland	18	18 (100%)	2	2 (100%)	2
Skin	16	13 (81%)	1	1 (100%)	1
At leasts one site[c]	194	148 (76%)	209	148 (71%)	101

[a] Target sites reported in the table are those affected by more than 15 chemicals in at least one species.
[b] Numbers add to more than total for "at least one site" because there is often more than one target site per chemical per species.
[c] Includes all target sites, including those not shown in this table.

lated to rodents, and the levels of human exposure are usually orders of magnitude lower than the MTD. Thus, there may be qualitative as well as quantitative species differences between humans and either rats or mice. The practice of extrapolating rodent results to humans should be judged by the accuracy of extrapolation between rodent species, since the predictive value from a rodent species to humans would be expected to be lower than that between two rodent species at the MTD (*5,8*). We have shown above and previously (*5*) that it cannot be assumed that a chemical positive in rats will be positive at the same site in the mouse, or visa versa. Overall, knowing that a chemical is positive in one of the species predicts positivity at some site in the other species about 75% of the time. This result is similar to results reported earlier for smaller numbers of chemicals (*5,8–10*). The overall predictive values between rats and mice provide some confidence in interspecies extrapolation; however, since a high proportion of test chemicals are positive, by chance alone we would expect a positive predictive value between species of about 50% (*5*).

Site-specific prediction between rats and mice is less accurate than overall prediction of positivity. Knowing that a chemical is positive at any site in one species gives about a 50% chance that it will be positive at the same site in the other species. Since many chemicals induce tumors at multiple sites, there is often more than one target site that is potentially a common site for the two species. Among the 101 chemicals with a site in common, 56 have a common site other than the liver.

In order to examine further the issue of similarity of target sites between species, we have also compared results for the limited number of compounds tested in hamsters and rats, or hamsters and mice. Prediction from rats to hamsters or from mice to hamsters is similar to, but slightly less accurate than, prediction between rats and mice. Overall, 64% (21/33) of rat carcinogens are positive in hamsters, and 61% (17/28) of mouse carcinogens are positive in hamsters. Knowing that a chemical is positive at a specific site in the rat gives a 45% chance that it will be positive in the same site in the hamster, and for mouse to hamster the chance is 48%.

Ultimately, one wants to know whether chemicals that have been shown to be carcinogenic in experimental animals are also carcinogenic in humans. This question cannot be answered by reversing the question (i.e., by asking whether chemicals that are human carcinogens are also carcinogenic in a rodent species) because even if most human carcinogens are rodent carcinogens, the converse does not necessarily follow, as can be demonstrated by a simple probabilistic argument (*11*). However, some additional evidence about interspecies extrapolation can be obtained by asking how good a model the human is for the rat or the mouse, even though this will not provide direct evidence about how good a model the rat or mouse is for the human. The evaluations of the IARC list 53 known human carcinogens including industrial processes, therapeutic combinations, single chemicals, and mixtures such as tobacco smoke (*6,7, 12*). For 33 of these, data in experimental animals have been evaluated by IARC (*12*). The CPDB includes only results of experiments on single chemicals, administered by routes expected to result in whole body exposure, that meet specified experimental-design criteria (described in "Methods"). A search of the CPDB indicates that results are included for 16 human carcinogens tested in rats, and for 13 tested in mice. Using only these CPDB results, the overall predictive value from humans to rats is 75% (12/16) and from humans to mice is 77% (10/13). For some human carcinogens with only negative results in the CPDB, positive results have been obtained in experiments not meeting CPDB inclusion criteria (*7*).* Prediction based on target organ is 44% (7/16) from humans to rats and 31% (4/13) from humans to mice. Thus, the overall predictive values are similar to those reported above between rats and mice for the CPDB; the value for target organ is slightly lower for mice.

Based on this experimental evidence from the CPDB involving prediction from rats to mice, from rats or mice to hamsters, and from humans to rats or mice, we conclude that one cannot assume that if a chemical induces tumors at a given site in one species it will also induce tumors at the same site in a second species; the likelihood is at most 52%.

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REFERENCES

1. Gold, L. S., Sawyer, C. B., Magaw, R., Backman, G. M., de Veciana, M., Levinson, R., Hooper, N. K., Havender, W. R., Bernstein, L., Peto, R., Pike, M. C., and Ames, B. N. A Carcinogenic Potency Database of the standardized results of animal bioassays. Environ. Health Perspect. 58: 9–319 (1984).
2. Gold, L. S., de Veciana, M., Backman, G. M., Magaw, R., Lopipero, P., Smith, M., Blumenthal, M., Levinson, R., Bernstein, L., and Ames, B. N. Chronological supplement to the Carcinogenic Potency Database: standardized results of animal bioassays published through December 1982. Environ. Health Perspect. 67: 161–200 (1986).

*The four human carcinogens with only negative results in rats in the CPDB are arsenic compounds, azathioprine, myleran, and nickel or nickel compounds. All but nickel or nickel compounds are evaluated by IARC as having limited, not sufficient, evidence in experimental animals; for rats, IARC does not report evidence of carcinogenicity for either arsenic or myleran (*12*). The three human carcinogens with only negative results in mice in the CPDB are aflatoxin B_1, arsenic compounds, and nickel or nickel compounds. The exclusion of some experiments on these five chemicals from the CPDB that IARC discusses in its evaluations is based on route of exposure (e.g., skin painting, subcutaneous injection, intratracheal instillation), nonchronic dosing, use of infant animals, lack of controls, cocarcinogenesis tests, and Strain A mouse assays.

3. Gold, L. S., Slone, T. H., Backman, G. M., Magaw, R., Da Costa, M., Lopipero, P., Blumenthal, M., and Ames, B. N. Second chronological supplement to the Carcinogenic Potency Database: standardized results of animal bioassays published through December 1984 and by the National Toxicology Program through May 1986. Environ. Health Perspect. 74: 237–329 (1987).
4. Gold, L. S., Slone, T. H., Backman, G. M., Eisenberg, S., Da Costa, M., Wong, M., Manley, N. B., Rohrbach, L., and Ames, B. N. Third chronological supplement to the Carcinogenic Potency Database: standardized results of animal bioassays published through December 1986 and by the National Toxicology Program through June 1987. Environ. Health Perspect. 84: 215–286 (1990).
5. Gold, L. S., Bernstein, L., Magaw, R., and Slone, T. H. Interspecies extrapolation in carcinogenesis: prediction between rats and mice. Environ. Health Perspect. 81: 211–219 (1989).
6. IARC. Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, Vol. 1–47. International Agency for Research on Cancer, Lyon, France, 1971–1989.
7. IARC. Overall Evaluations of Carcinogenicity, Suppl. 7. International Agency for Research on Cancer, Lyon, France, 1987.
8. Zeiger, E. Carcinogenicity of mutagens: predictive capability of the *Salmonella* mutagenesis assay for rodent carcinogenicity. Cancer Res. 27: 1287–1296 (1987).
9. Haseman, J. K., Huff, J. E., Zeiger, E., and McConnell, E. E. Comparative results of 327 chemical carcinogenicity studies. Environ. Health Perspect. 74: 229–235 (1987).
10. Purchase, I. F. H. Inter-species comparisons of carcinogenicity. Br. J. Cancer 41: 454–468 (1980).
11. Freedman, D. A., and Zeisel, H. From mouse to man: the quantitative assessment of cancer risks. Statistical Science 3: 3–56 (1988).
12. Tomatis, L., Aitio, A., Wilbourn, J., and Shuker, L. Human carcinogens so far identified. Jpn. J. Cancer Res. 80: 795–807 (1989).