

## REVIEW ARTICLE

# Compendium of Chemical Carcinogens by Target Organ: Results of Chronic Bioassays in Rats, Mice, Hamsters, Dogs, and Monkeys

LOIS SWIRSKY GOLD,<sup>1,2</sup> NEELA B. MANLEY,<sup>1</sup> THOMAS H. SLONE,<sup>1</sup> AND JERROLD M. WARD<sup>3</sup>

<sup>1</sup>*Division of Biochemistry and Molecular Biology, University of California, Berkeley, California 94720-3202*

<sup>2</sup>*Life Sciences Division, Mail Stop: 946, Ernest Orlando Lawrence Berkeley National Laboratory, Berkeley, California 94720, and*

<sup>3</sup>*Veterinary and Tumor Pathology Section, Center for Cancer Research, National Cancer Institute, Frederick, MD 21702-1201*

### ABSTRACT

A compendium of carcinogenesis bioassay results organized by target organ is presented for 738 chemicals that are carcinogenic in chronic-exposure, long-term bioassays in at least 1 species. This compendium is based primarily on experiments in rats or mice; results in hamsters, monkeys, 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 1 species. The source of information is the Carcinogenic Potency Database (CPDB), which includes results of 6073 experiments on 1458 chemicals (positive or negative for carcinogenicity) that have been reported in Technical Reports of the National Cancer Institute/National Toxicology Program or in papers in the general published literature. The published CPDB includes detailed analyses of each test and citations. The CPDB is publicly available in several formats (<http://potency.berkeley.edu>). Chemical carcinogens are reported for 35 different target organs in rats or mice. Target organs in humans are also summarized for 82 agents that have been evaluated as human carcinogens at a particular target site by the International Agency for Research on Cancer (IARC). Comparisons are provided of target organs for mutagens versus nonmutagens and rats versus mice.

**Keywords.** Human carcinogen; tumor site; animal cancer test; Carcinogenic Potency Database; species comparisons; mutagenicity; monkeys.

### INTRODUCTION

For many research issues in carcinogenesis, it is valuable to have quick access to a list of chemicals that have been found in chronic bioassays to induce tumors at each target site in various species. Researchers interested in carcinogenesis in a particular target organ, for example, or epidemiologists interested in a particular cancer in humans, can use such results to compare species or seek clues in animal models. Comparison of target sites in several species is possible for work on interspecies extrapolation. Investigations of chemical structure or mechanism of carcinogenesis at a specific target site can identify chemicals that induce tumors in that organ.

This paper presents a compendium of results of chronic, long-term cancer tests that is organized by the target organ of carcinogenesis (Table 1). Results are presented for 738 chemicals that have been evaluated by the published author of experimental data as carcinogenic in at least one experiment in the Carcinogenic Potency Database (CPDB) (2, 3, 6), <http://potency.berkeley.edu/database.html>. Results are organized by each of 35 target sites and within each

site by the chemicals that induce tumors in each species. The compendium includes results of chronic bioassays in rats, mice, hamsters, monkeys, and dogs. Comparative toxicological analyses are facilitated by indicating whether a chemical that is positive at a given site in the rat has been tested in the mouse, whether results are also positive in the mouse, and whether the target organs are the same in the 2 species. By cross-referencing a chemical of interest to the published plots of the CPDB (2, 3, 6), details of each experiment can be obtained, including the number of experiments and strains tested as well as the following details on each experiment: citation of the original published paper, strain and sex of test animal, route of chemical administration, dose rate, tumor types, tumor incidence, the tumorigenic potency (TD<sub>50</sub>), statistical significance, and author's opinion. Target organs in humans are also summarized for 82 agents that have been evaluated as human carcinogens at a particular target site by the International Agency for Research on Cancer (IARC) (10, 15, 16). Comparisons of target organs for mutagens versus nonmutagens, and for rats versus mice are also provided.

### METHODS

The CPDB (2, 3, 6), a systematic and unifying analysis of chronic, long-term animal cancer tests, is the source of

Address correspondence to: Lois Swirsky Gold, Mail Stop 946, E. O. Lawrence Berkeley National Laboratory, Berkeley, California 94720. Fax: (510) 547-7073. E-mail: [lois@potency.berkeley.edu](mailto:lois@potency.berkeley.edu)

results included in the compendium (Table 1). The CPDB includes 1,381 papers published in the general literature through 1996 and 430 Technical Reports of the National Cancer Institute/National Toxicology Program (NCI/NTP) published through 1998. Results are reported for 6,073 experiments on 1,458 chemicals, of which 738 induce tumors in 1 or more experiments.

A word of caution is necessary about the limitations of the CPDB. Only long-term experiments meeting a set of criteria designed to measure tumorigenic dose-rate ( $TD_{50}$ ) are included; therefore, the CPDB does not cover all cancer tests. Additionally, for the identification of target sites for the compendium, we do not personally evaluate whether a compound induced tumors at a given site; rather, the opinion of the published author is used. For published opinions that are not clear, even after personal communication with the published author, the site is not considered a target and is not reported in the compendium.

Results of all NCI/NTP Technical Reports are included in the CPDB except a few, for which no whole body exposure in mg/kg/day could be calculated because the test agent was a particulate or the route of administration was dermal (12, 13) [<http://ntp-server.niehs.nih.gov/>]. In the compendium, a site is classified as a target in an NCI/NTP bioassay if the evaluation in the Technical Report was "carcinogenic," "clear," or "some" evidence of carcinogenic activity. Sites that were evaluated as "equivocal" are not included (9).

In the general literature, experimental designs as well as the authors' choice of information to report are quite diverse, and bioassays have been included only if they meet all of the following conditions:

1. Animals on test were mammals.
2. Administration was begun early in life (100 days of age or less for rats, mice, and hamsters).
3. Route of administration was diet, water, gavage, inhalation, intravenous or intraperitoneal injection (ie, where the whole body was more likely to have been exposed rather than only a specific site, as with subcutaneous injection or skin painting).
4. Test agent was administered alone, rather than in combination with other chemicals.
5. Exposure was chronic, with not more than 7 days between administrations.
6. Duration of exposure was at least one fourth the standard life span for that species. For rodents the standard life span is 2 years.
7. Duration of experiment was at least half the standard life span for that species.
8. Research design included a concurrent control group.
9. Research design included at least 5 animals per group.
10. Surgical intervention was not performed.
11. Pathology data were reported for the number of animals with tumors rather than the total number of tumors.
12. Results reported were original data, rather than secondary analyses of experiments already reported by other authors.

More details on inclusion criteria can be found in Gold and coworkers (6) and <http://potency.berkeley.edu/text/methods.html>.

Because we have adhered strictly to the standard inclusion criteria, bioassays of particulate or fibrous matters are not in the compendium, eg, asbestos, cigarette smoke, and dusts. There are no studies using a single administration of the test agent, no experiments by skin painting, subcutaneous injection, or in utero exposure, and no cocarcinogenesis experiments. For a series of NCI long-term studies in monkeys, some of the inclusion rules have been relaxed; details are reported in Appendix 1 of Gold et al, 1999 (2).

There is great diversity in results for different chemicals in the CPDB, eg, in the number of times a chemical has been tested: among the 1,148 chemicals tested in rats, 25% have only 1 test in the CPDB and 50% have 2 tests; however, 25 chemicals have 10 or more tests. For the 938 chemicals tested in mice, the parallel numbers are 11% with 1 test, 57% with 2 tests, and 15 chemicals with more than 10 tests. Of the 738 carcinogens reported here, 54% (397/738) have been tested in more than 1 species. In the compendium (Table 1), a target site is identified by a positive result in any one experiment in the species; thus, different target sites may be identified from the same or different experiments. Chemicals that are tested more often have a greater chance of finding multiple target sites. Results on chemicals that have not been evaluated as carcinogenic are ignored in the target organ compendium (Table 1); however, detailed results of those experiments are reported in the plot of the CPDB (2, 3, 6); <http://potency.berkeley.edu/>.

#### *Guide to the Compendium of Target Organs for 738 Carcinogens*

Table 1 reports results on 738 chemicals in the CPDB that induce tumors in at least 1 of 35 target organs in rats, mice, hamsters, monkeys, or dogs. The table is organized alphabetically by target site and within each site, by species and chemical. Our previously unpublished analyses of experimental results that will be published in a forthcoming plot of the CPDB are included (3).

To facilitate use of the compendium, the features are described below using the example of adrenal gland, which is the first of 35 target sites in Table 1. Under adrenal gland, 1 chemical is listed in hamsters, 8 in mice, and 16 in rats. If a chemical name is followed by a superscript (either † or ‡), this indicates that the CPDB includes test results in both rats and mice, for example, under adrenal gland in rats 2-mercaptobenzothiazole but not isomazole, has a superscript. Because isomazole has no superscript, it only has tests in the CPDB in the species reported, in this case rats. The superscript † for 2-mercaptobenzothiazole, indicates that the chemical has been tested in both rats and mice but induced tumors only in the reported species, in this case rats. The superscript ‡ for 1,2-dibromo-3-chloropropane (DBCP) indicates that DBCP is carcinogenic at some target site in both rats and mice. Although the superscript ‡ does not indicate whether DBCP induced tumors at the *same* target site in both rats and mice, this can easily be determined by looking at mice under adrenal gland for the chemical name DBCP. Because it is not there, DBCP induced tumors in mice only at sites other than the adrenal gland. In contrast, pentachloroanisole<sup>‡</sup> induced adrenal tumors in both species, because it is listed under that site for both species. By comparing the chemicals with superscripts listed under each

TABLE 1.—Summary of Carcinogenic Potency Database by target organ.

Target site	Species	N	Chemicals that induce tumors at each site
Adrenal gland	Hamster	1	Urethane <sup>†</sup>
	Mouse	8	Carbon tetrachloride <sup>†</sup> ; Furan <sup>†</sup> ; 4,4'-Methylene dianiline.2 HCl <sup>†</sup> ; Pentachloroanisole <sup>†</sup> ; 2,3,4,5,6-Pentachlorophenol (Dowicide EC-7) <sup>†</sup> ; 2,3,4,5,6-Pentachlorophenol, technical grade <sup>†</sup> ; <i>p</i> -Rosaniline.HCl <sup>†</sup> ; 1,1,2-Trichloroethane <sup>†</sup>
Bone	Rat	16	Bromoethane <sup>†</sup> ; 4-Chloro- <i>m</i> -phenylenediamine <sup>†</sup> ; Cobalt sulfate heptahydrate <sup>†</sup> ; 1,2-Dibromo-3-chloropropane <sup>†</sup> ; Diethylstilbestrol <sup>†</sup> ; Ethyl alcohol <sup>†</sup> ; Indolizidine <sup>†</sup> ; Isomazole <sup>†</sup> ; 2-Mercaptobenzothiazole <sup>†</sup> ; Mirex <sup>†</sup> ; Pentachloroanisole <sup>†</sup> ; Phenolphthalein <sup>†</sup> ; 1,2-Propylene oxide <sup>†</sup> ; C.I. pigment red 3 <sup>†</sup> ; Reserpine <sup>†</sup> ; Retinol acetate
	Rat	5	Acronyline <sup>†</sup> ; Deflazacort; <i>N,N</i> -Dimethylaniline <sup>†</sup> ; 1-(2-Hydroxyethyl)-1-nitrosourea <sup>†</sup> ; <i>o</i> -Toluidine.HCl <sup>†</sup>
Clitoral/preputial gland	Mouse	11	Acetaldehyde methylformylhydrazine; Benzene <sup>†</sup> ; 1,3-Butadiene <sup>†</sup> ; <i>N-n</i> -Butyl- <i>N</i> -formylhydrazine; Dimethylvinyl chloride <sup>†</sup> ; <i>N</i> -Ethyl- <i>N</i> -formylhydrazine; Hexanal methylformylhydrazine; 3-Methylbutanal methylformylhydrazine; Pentanal methylformylhydrazine;
	Rat	21	<i>N,N'</i> -Propyl- <i>N</i> -formylhydrazine; Thio-tepa <sup>†</sup>
Ear/Zymbal's gland	Mouse	3	Acrylamide; C.I. direct blue 15; 2,4-Diaminoanisole sulfate <sup>†</sup> ; 3,3'-Dimethoxybenzidine.2HCl; 3,3'-Dimethylbenzidine.2HCl <sup>†</sup> ; Glu-P-1 <sup>†</sup> ;
	Rat	41	Glu-P-2 <sup>†</sup> ; Glycidol <sup>†</sup> ; IQ <sup>†</sup> ; Isophorone <sup>†</sup> ; MeQx <sup>†</sup> ; 2-Mercaptobenzothiazole <sup>†</sup> ; Nalidixic acid <sup>†</sup> ; 1,5-Naphthalenediamine <sup>†</sup> ; 5-Nitro- <i>o</i> -anisidine <sup>†</sup> ; 5-Nitroacenaphthene <sup>†</sup> ; <i>p</i> -Nitrobenzoic acid <sup>†</sup> ; 1-Nitropyrene; C.I. acid red 114; 1,2,3-Trichloropropane <sup>†</sup> ; Trp-P-2 acetate <sup>†</sup>
Esophagus	Hamster	2	Benzene <sup>†</sup> ; Chloroprene <sup>†</sup> ; Cupferron <sup>†</sup>
	Mouse	8	Acrylonitrile; 3-Amino-9-ethylcarbazole mixture <sup>†</sup> ; Azoxymethane; Benzene <sup>†</sup> ; 2,2-Bis(bromomethyl)-1,3-propanediol, technical grade <sup>†</sup> ; C.I. direct blue 15; <i>N-n</i> -Butyl- <i>N</i> -nitrosourea; Chlorambucil <sup>†</sup> ; Cupferron <sup>†</sup> ; <i>N</i> -1-Diacetamidofluorene; 2,4-Diaminoanisole sulfate <sup>†</sup> ; 3,3'-Dichlorobenzidine; 2,5-Dimethoxy-4'-aminostilbene <sup>†</sup> ; 3,3'-Dimethoxybenzidine.2HCl; 3,3'-Dimethylbenzidine.2HCl <sup>†</sup> ; <i>N</i> -(2-Fluorenyl)-2,2,2-trifluoroacetamide; Formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl]hydrazide <sup>†</sup> ; Glu-P-1 <sup>†</sup> ; Glu-P-2 <sup>†</sup> ; Glycidol <sup>†</sup> ; Hydrazobenzene <sup>†</sup> ; IQ <sup>†</sup> ; IQ.HCl; MeQx <sup>†</sup> ; 2-Methoxy-3-aminodibenzofuran; 8-Methoxypsoralen; <i>N</i> -( <i>N</i> -Methyl- <i>N</i> -nitrosocarbonyl)- <i>l</i> -ornithine; 4,4'-Methylenebis(2-chloroaniline); 5-Nitro- <i>o</i> -anisidine <sup>†</sup> ; 5-Nitroacenaphthene <sup>†</sup> ; <i>N</i> -(9-Oxo-2-fluorenyl)acetamide; Phenacetin <sup>†</sup> ; Prednimustine; C.I. acid red 114; <i>p</i> -Rosaniline.HCl <sup>†</sup> ; Thio-tepa <sup>†</sup> ; 4,4'-Thiodianiline <sup>†</sup> ; $\beta$ -Thioguanine deoxyriboside <sup>†</sup> ; 1,2,3-Trichloropropane <sup>†</sup> ; Vinyl chloride <sup>†</sup> ; Vinyl fluoride <sup>†</sup>
Gall bladder	Hamster	1	AF-2 <sup>†</sup> ; <i>N,N</i> -Nitroso- <i>N</i> -methylurethane
	Mouse	4	Benzo( <i>o</i> )pyrene <sup>†</sup> ; 1,2-Dibromoethane <sup>†</sup> ; <i>N</i> -Ethyl- <i>N'</i> -nitro- <i>N</i> -nitrosoguanidine; <i>N</i> -Hydroxy-2-acetylaminofluorene <sup>†</sup> ;
Harderian gland	Monkey	1	3-(5-Nitro-2-furyl)-imidazo(1,2- $\alpha$ )pyridine <sup>†</sup> ; Nitrosodibutylamine <sup>†</sup> ; <i>N</i> -Nitrosohexamethylenimine; Vinyl acetate <sup>†</sup>
	Rat	36	2,2-Bis(bromomethyl)-1,3-propanediol, technical grade <sup>†</sup> ; Bis(2,3-dibromopropyl)phosphate, magnesium salt; <i>N-n</i> -Butyl- <i>N</i> -nitrosourea; Dihydrosofrole <sup>†</sup> ; Dimethylvinyl chloride <sup>†</sup> ; Dinitrosomopiperazine; Z-Ethyl- <i>O,N</i> -azoxyethane; <i>N</i> -Methyl- <i>N'</i> -nitro- <i>N</i> -nitrosoguanidine <sup>†</sup> ;
Hematopoietic system	Hamster	1	3-(5-Nitro-2-furyl)-imidazo(1,2- $\alpha$ )pyridine <sup>†</sup> ; <i>N</i> -Nitroso-2,3-dihydroxypropylamine; Nitroso-2,3-dihydroxypropyl-2-oxopropylamine;
	Mouse	53	<i>N</i> -Nitroso-(2-hydroxypropyl)-(2-hydroxyethyl)amine; <i>N</i> -Nitroso- <i>N</i> -methyl-4-fluoroaniline; Nitroso- <i>N</i> -methyl- <i>N</i> -(2-phenyl)ethylamine; Nitroso-1,2,3,6-tetrahydropyridine; <i>N</i> -Nitroso(2,2,2-trifluoroethyl)ethylamine; <i>N</i> -Nitrosoallyl-2,3-dihydroxypropylamine; <i>N</i> -Nitrosoallyl-2-hydroxypropylamine; <i>N</i> -Nitrosoallyl-2-oxopropylamine; Nitrosoamylurethane; Nitrosohexamethylenimine; <i>N</i> -Nitrosoethanalamine; <i>N</i> -Nitrosodiethylamine; <i>N</i> -Nitrosodipropylamine; Nitrosoethylurethane; Nitrosoheptamethylenimine; <i>N</i> -Nitrosomethyl-2,3-dihydroxypropylamine; <i>N</i> -Nitrosomethyl-2-hydroxypropylamine; <i>N</i> -Nitrosomethyl(2-oxopropyl)amine; 2-Nitrosomethylaminopyridine; Nitrosomethylamine; <i>N</i> -Nitrosomethyl-1- <i>N</i> -oxide; <i>N</i> -Nitrosopiperidine <sup>†</sup> ; <i>N</i> -Nitrosothialdine; <i>N</i> -Nitrosothiomorpholine
Harderian gland	Hamster	1	<i>N</i> -Methyl- <i>N</i> -formylhydrazine
	Monkey	1	<i>N</i> -Ethyl- <i>N</i> -formylhydrazine; <i>N</i> -Methylbutanal methylformylhydrazine; <i>N</i> -Propyl- <i>N</i> -formylhydrazine
Hematopoietic system	Mouse	19	Aflatoxin B <sub>1</sub> <sup>†</sup>
	Mouse	53	Benzene <sup>†</sup> ; Benzidine.2HCl; 2,2-Bis(bromomethyl)-1,3-propanediol, technical grade <sup>†</sup> ; 1,3-Butadiene <sup>†</sup> ; Captafol <sup>†</sup> ; Chloroprene <sup>†</sup> ; Cupferron <sup>†</sup> ; Dichloroacetylene <sup>†</sup> ; Ethylene oxide <sup>†</sup> ; Gentian violet; Glycidol <sup>†</sup> ; Iodinated glycerol <sup>†</sup> ; Isoprene; <i>N</i> -Methylolacrylamide <sup>†</sup> ; Nitromethane <sup>†</sup> ; 4,4'-Oxydianiline <sup>†</sup> ; 1,2,3-Trichloropropane <sup>†</sup> ; 2,4,6-Trinitro-1,3-dimethyl-5- <i>tert</i> -butylbenzene; Vinyl fluoride <sup>†</sup>

(Continued on next page)

TABLE 1.—Summary of Carcinogenic Potency Database by target organ. (Continued)

Target site	Species	N	Chemicals that induce tumors at each site
Kidney	Monkey	1	Procabazine.HCl†
	Rat	56	Allyl isovalerate‡; 1-Amyl-1-nitrosourea; Atrazine†; Benzidine; 2,2-Bis(bromomethyl)-1,3-propanediol, technical grade‡; C.I. direct blue 15; <i>N</i> - <i>n</i> -Butyl- <i>N</i> -nitrosourea; Cadmium chloride; Chlorambucil†; Cyclophosphamide‡; Dacarbazin†; 1,3-Dibutyl-1-nitrosourea; Dichloroacetylene‡; 3,3'-Dichlorobenzidine; Dichlorvos‡; Dimethoxane; 3,3'-Dimethoxybenzidine-4,4'-diisocyanate‡; 3,3'-Dimethoxybenzidine.2HCl; Dimethyl morpholinophosphoramide‡; 2-(2,2-Dimethylhydrazino)-4-(5-nitro-2-furyl)thiazole; Ethylene oxide‡; Formaldehyde‡; Formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl]hydrazide‡; Furan†; Glycidol†; Furan†; Glycidol†; FD & C green no. 1†; FD & C green no. 2†; Hematoxylin; 2-Hydrazino-4-( <i>p</i> -aminophenyl)thiazole‡; Hydroquinone‡; 1-(2-Hydroxyethyl)-1-nitrosourea‡; Iodinated glycerol‡; Lasciocarpine; 2-Mercaptobenzothiazole‡; Metepa; Methyl <i>tert</i> -butyl ether†; Mirex‡; 1-(5-Morpholinomethyl)-3-[(5-nitrofurfurylidene)amino]-2-oxalidione.HCl; Nitrite, sodium†; <i>N</i> -[5-(Nitro-2-furyl)-1,3,4-thiadiazol-2-yl]acetamide‡; <i>o</i> -Nitroanisole‡; 1-[5-(Nitrofurfurylidene)amino]-2-imidazolidione; 1-Nitropyrene; Nitroso- <i>N</i> -methyl- <i>N</i> -(2-phenyl)ethylamine; <i>N</i> -Nitrosodithanolamine; PIP.HCl†; Procabazine.HCl†; Propane sulfone; <i>N</i> -Propyl- <i>N</i> -nitrosourea; FD & C red no. 2; FD & C red no. 4†; Tetrachloroethylene‡; Tetrafluoroethylene‡; Thio-tepat‡; 2,4,6-Trichlorophenol‡; Trp-P-2 acetate‡
Kidney	Hamster	1	Bromate, potassium†
	Mouse	26	<i>o</i> -Benzyl- <i>p</i> -chlorophenol†; 2,2-Bis(bromomethyl)-1,3-propanediol, technical grade‡; Bromate, potassium†; Bromodichloromethane‡; 1,3-Butadiene‡; 1,2-di- <i>n</i> -Butylhydrazine.2HCl; Caffeic acid‡; Chloroform‡; Chloroprene‡; Daminozide‡; 2,4-Diaminophenol.2HCl†; Dichloroacetylene‡; 2,4-Dinitrotoluene (containing 1.0-1.5% 2,6-dinitrotoluene); Hydroquinone‡; <i>N</i> -Hydroxy-2-acetylaminofluorene‡; 3-Hydroxy- <i>p</i> -butylphenetidine; Lead acetate, basic‡; Mercury methyl chloride; Nitrolic acid‡; Ochratoxin A†; Phenacetin‡; C.I. pigment red 3†; Streptozotocin‡; Tris(2-chloroethyl)phosphate‡; Tris(2,3-dibromopropyl) phosphate‡; Vinylidene chloride
Kidney	Monkey	1	Cycasin and methylazoxymethanol acetate
	Rat	86	Aflatoxin B <sub>1</sub> †; 1-Amino-2,4-dibromoanthraquinone‡; 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-4-nitrophenol†; 2-Amino-5-nitrothiazole‡; <i>o</i> -Anisidine.HCl†; Aristolochic acid, sodium salt (77% AAL, 21% AAID); Azoxymethane; Barbitol, sodium; Benzofuran†; Bromate, potassium†; Bromodichloromethane‡; <i>tert</i> -Butyl alcohol†; Caffeic acid‡; Captafol†; Captan†; Chlorinated paraffins (C <sub>12</sub> , 60% chlorine)‡; Chloroform‡; 3-( <i>p</i> -Chlorophenyl)-1,1-dimethylurea†; Chloroprene‡; Chloroethanol†; Cinnamyl anthranilate‡; Citrinin; Coumarin†; Dichloroacetylene‡; 1,4-Dichlorobenzene‡; Diethylacetamide; 3,4-Dihydrocoumarin†; Dimethoxane; Dimethyl methylphosphonate‡; 4,6-Dimethyl-2-(5-nitro-2-furyl)pyrimidine; <i>N</i> -4-(4'-Fluorobiphenyl)acetamide; Formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl]hydrazide‡; Glycine; Hexachlorobutadiene; Hexachloroethane‡; Hexamethylmelamine; 2-Hydrazino-4-(5-nitro-2-furyl)thiazole‡; Hydroquinone‡; 1-(2-Hydroxyethyl)-1-nitrosourea‡; Isophorone‡; Lead acetate†; Lead acetate, basic†; <i>d</i> -Limonene‡; 2-Methoxy-3-aminodibenzofuran; 8-Methoxypsoralen; <i>Z</i> -Methyl- <i>O,N,N</i> -azoxyethane; Methyl <i>tert</i> -butyl ether†; <i>N</i> -( <i>N</i> -Methyl- <i>N</i> -nitrosocarbamoyl)-1-ornithine; $\alpha$ -Methylbenzyl alcohol†; Mirex‡; 1-(5-Morpholinomethyl)-3-[(5-nitrofurfurylidene)amino]-2-oxazolidione.HCl; Nitrolic acid‡; Nitrolic acid†; 1-(5-Nitro-2-furyl)-1,3,4-thiadiazole; 2-(5-Nitro-2-furyl)-imidazo[1,2- <i>o</i> ]pyridine‡; <i>N</i> [(3-(5-Nitro-2-furyl)-1,2,4-oxadiazole-5-yl)methyl]acetamide; <i>N</i> [(5-(5-Nitro-2-furyl)-1,3,4-thiadiazol-2-yl)acetamide]; <i>o</i> -Nitroanisole‡; Nitrobenzene‡; 2-Nitrofluorene; 1-[5-(Nitrofurfurylidene)amino]hydantoin‡; 1-Nitroso-1-hydroxyethyl-3-chloroethylurea; <i>N</i> -Nitrosodithanolamine; <i>N</i> -Nitrosodiethylamine; <i>N</i> -Nitrosodimethylamine†; <i>N</i> -Nitrosopyrrolidine†; Ochratoxin A†; C.I. acid orange 3†; <i>N</i> -Oxydiethylene thiocarbonyl- <i>N</i> -oxydiethylene sulfenamide; Phenacetin†; Phenazone; Phenolphthalein†; Phenylbutazone‡; <i>o</i> -Phenylphenate, sodium†; Quercetin†; Salicylazosulfapyridine‡; Streptozotocin‡; Tetrachloroethylene‡; Tetrafluoroethylene‡; Tetrahydrofuran†; 1,2,3-Trichloropropane‡; Tris(2-chloroethyl)phosphate‡; Tris(2,3-dibromopropyl) phosphate†; Vinyl chloride†
Large intestine	Hamster	5	1,1-Dimethylhydrazine‡; 1,2-Dimethylhydrazine.2HCl; Hydrazine‡; Methylhydrazine; Urethane†
	Mouse	1	Capsaicin
Large intestine	Rat	32	Aflatoxin B <sub>1</sub> †; 1-Allyl-1-nitrosourea; 1-Amino-2,4-dibromoanthraquinone‡; Amylopectin sulfate; Azoxymethane; 2,2-Bis(bromomethyl)-1,3-propanediol, technical grade‡; C.I. direct blue 15; Bromodichloromethane‡; <i>N,N</i> -Butyl- <i>n</i> -nitrosourea; Carrageenan, acid-degraded; Chrysozin†; Dextran sulfate sodium (DS-M-1); 3,3'-Dimethoxybenzidine.2HCl†; 3,3'-Dimethylbenzidine.2HCl†; <i>Z</i> -Ethyl- <i>O,N,N</i> -azoxymethane; 1-Ethylnitroso-3-(2-oxopropyl)-urea; Formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl]hydrazide‡; Glu-P-1†; Glu-P-2†; Glycidol†; <i>N</i> -Hexyl nitrosourea; 1-Hydroxyanthraquinone; 1-(2-Hydroxyethyl)-1-nitrosourea‡; IQ†; <i>o</i> -Nitroanisole‡; <i>N</i> -Nitrosobis(2-oxopropyl)amine; Phenazopyridine.HCl†; PIP.HCl†; C.I. acid red 114; 4,4'-Thiodianiline‡; Tribromomethane†; Tris(2,3-dibromopropyl)phosphate†
	Dog	2	3,3'-Dichlorobenzidine; 4,4'-Methylene-bis(2-chloroaniline)
Liver	Hamster	16	2-Acetylaminofluorene‡; <i>p,p'</i> -DDE†; 1,2-Dimethylhydrazine.2HCl; Hexachlorobenzene‡; Hydrazine sulfate‡; <i>N</i> -Hydroxy-2-acetylaminofluorene‡; <i>N</i> -Methyl- <i>N</i> -formylhydrazine; Methylhydrazine; Methyl nitrosamino- <i>N,N</i> -dimethylethylamine; <i>N</i> -Nitroso-1,3-oxazolidione; Nitroso-2-oxopropylethanolamine; <i>N</i> -Nitrosoallyl-2-oxopropylamine; <i>N</i> -Nitrosoazetidine; <i>N</i> -Nitrosomorpholine; <i>N</i> -Nitrosopyrrolidine‡; <i>N</i> -Nitrosopyrrolidine†
	Mouse	231	<i>A</i> - $\alpha$ -C; Acetaminophen†; 2-Acetylaminofluorene‡; Acifluorfen†; Aldrin†; 1-Amino-2,4-dibromoanthraquinone‡; 3-Amino-9-ethylcarbazole mixture‡; 1-Amino-2-methylanthraquinone‡; 2-Aminoanthraquinone‡; 4-Aminodiphenyl†; 2-Aminodiphenyl oxide; 3-Aminotriazole‡; Aramite‡; Aroclor 1254†; Auramine- <i>O</i> †; Benzidine.2HCl; Benzofuran†; Benzyl acetate†; 3-Benzylisodone-4-acetamide‡; Bis(2-chloro-1-methylethyl)ether, technical grade‡; Bis-2-chloroethyl ether; Bis-2-hydroxyethylidithiocarbamic acid, potassium; C.I. direct black 38; C.I. direct blue 218†; HC blue no. 1†; HC blue no. 1 (purified); Bromodichloromethane‡; 1,3-Butadiene‡; Butylated hydroxytoluene†; 1,1-di- <i>n</i> -Butylhydrazine; Captafol†; Carbazole; Carbon tetrachloride‡; Chloral hydrate; Chloramben†; Chlordane, technical grade‡; Chlorendic acid†; Chlorinated paraffins (C <sub>12</sub> , 60% chlorine)‡; 1-Chloro-2-nitrobenzene†; 1-Chloro-4-nitrobenzene†; 4-Chloro- <i>m</i> -phenylenediamine‡; 4-Chloro- <i>o</i> -phenylenediamine†; 5-Chloro- <i>o</i> -toluidine†;





Rat	102	4-Acetylamino-biphenyl; 2-Acetylamino-fluorene <sup>‡</sup> ; Acronycine; Acrylamide; Acrylonitrile; AF-2 <sup>‡</sup> ; 1-Allyl-1-nitrosourea; 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 <sup>‡</sup> ; 4-Aminodiphenyl.HCl; 1-Amyl-1-nitrosourea; 2-Amino-5-(5-nitro-2-furyl)-1,3,4-benzidine; 2,2-Bis(bromomethyl)-1,3-propanediol, technical grade <sup>‡</sup> ; 4-Bis(2-hydroxyethyl)amino-2-(5-nitro-2-thienyl)quinazoline; 1,3-Butadiene <sup>‡</sup> ; <i>N-n</i> -Butyl- <i>N</i> -nitrosourea; Captafol <sup>‡</sup> ; Carbon tetrachloride <sup>‡</sup> ; Carboxymethylnitrosourea; Chlorambucil <sup>‡</sup> ; Chloroprene <sup>‡</sup> ; Cytembena <sup>‡</sup> ; Dacarbazine <sup>‡</sup> ; <i>N</i> -1-Diacetamidofluorene; 4,6-Diamino-2-(5-nitro-2-furyl)- <i>S</i> -triazine; 2,4-Diaminotoluene <sup>‡</sup> ; 1,2-Dibromo-3-chloropropane <sup>‡</sup> ; 1,2-Dibromooethane <sup>‡</sup> ; Dibromomannitol <sup>‡</sup> ; 1,3-Dibutyl-1-nitrosourea; 3,3'-Dichlorobenzene <sup>‡</sup> ; 1,2-Dichloroethane <sup>‡</sup> ; 3,3'-Dimethoxybenzidine.2HCl; 1,2-Dibromobenzene.2HCl; 4,6-Dimethyl-2-(5-nitro-2-furyl)pyrimidine; 1,2-Dimethyl-5-nitroimidazole; trans-2-[(Dimethylamino)methyl]imino-5-[2-(5-nitro-2-furyl)vinyl]-1,3,4-oxadiazole; Dimethylaminoethyl nitrosoethylurea, nitrite salt; 3,3'-Dimethylbenzidine.2HCl <sup>‡</sup> ; 2-(2,2-Dimethylhydrazino)-4-(5-nitro-2-furyl)thiazole <sup>‡</sup> ; 2,4-Dinitrotoluene (containing 1.0-1.5% 2,4-Dioxane <sup>‡</sup> ); 1-Ethyl-1-nitroso-3-(2-hydroxyethyl)-urea; 1-Ethyl-1-nitroso-3-(2-oxopropyl)-urea; 6-dinitrotoluene <sup>‡</sup> ; <i>N</i> -(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 <sup>‡</sup> ; Glycidol <sup>‡</sup> ; Hexamethylmelamine; <i>N</i> -Hexylnitrosourea; 2-Hydrazino-4-( <i>p</i> -aminophenyl) thiazole <sup>‡</sup> ; 2-Hydrazino-4-(5-nitro-2-furyl)thiazole <sup>‡</sup> ; 2-Hydrazino-4-( <i>p</i> -nitrophenyl)thiazole <sup>‡</sup> ; Hydrazobenzene <sup>‡</sup> ; 1-(2-Hydroxyethyl)-3-[(5-nitrofururylidene)amino]-2-imidazolidinone; 1-(2-Hydroxyethyl)-nitroso-3-ethylurea; 1-(2-Hydroxyethyl)-1-nitrosourea <sup>‡</sup> ; Indomethacin; IQ <sup>‡</sup> ; IQ.HCl; Isoniazid <sup>‡</sup> ; 2-Methoxy-3-aminodibenzofuran; 4-Methyl-1-[(5-nitrofururylidene)amino]-2-imidazolidinone; <i>N</i> -( <i>N</i> -Methyl- <i>N</i> -nitrosocarbamoyl)- <i>l</i> -ornithine; 3-Methylcholanthrene; 4,4'-Methylene-bis(2-chloroaniline); 4,4'-Methylene-bis(2-methylamine); Methylene chloride <sup>‡</sup> ; Metronidazole <sup>‡</sup> ; 1,5-Morpholinomethyl-3-[(5-nitrofururylidene)amino]-2-oxazolidinone.HCl; Nithiazide <sup>‡</sup> ; 5-Nitro-2-furaldehyde semicarbazone <sup>‡</sup> ; 3-(5-Nitro-2-furyl)-imidazo[1,2- <i>α</i> ]pyridine <sup>‡</sup> ; 4-(5-Nitro-2-furyl)thiazole <sup>‡</sup> ; <i>N</i> -[4-(5-Nitro-2-furyl)-2-thiazolyl]acetamide; <i>N,N'</i> -[6-(5-Nitro-2-furyl)-5-triazine-2,4-diy]bisacetamide; 5-Nitroacenaphthene <sup>‡</sup> ; 1-[1-(5-Nitrofururylidene)amino]-2-imidazolidinone; Nitromethane <sup>‡</sup> ; 1-Nitropyrene; Nortestrin <sup>‡</sup> ; Ochratoxin A <sup>‡</sup> ; <i>N</i> -(9-Oxo-2-fluorenyl)acetamide; Phenacetin <sup>‡</sup> ; Phenesterin <sup>‡</sup> ; PhIP.HCl <sup>‡</sup> ; Procabazine.HCl <sup>‡</sup> ; Propane sulfone; 1,2-Propylene oxide <sup>‡</sup> ; Styrene <sup>‡</sup> ; Sulfallate <sup>‡</sup> ; 4,4'-Sulfonylbisacetamide; Toluene diisocyanate, commercial grade (2,4 (80%)- and 2,6 (20%)-) <sup>‡</sup> ; <i>o</i> -Toluidine.HCl <sup>‡</sup> ; 1,2,3-Trichloropropane <sup>‡</sup> ; 2,2,2-Trifluoro- <i>N</i> -[4-(5-nitro-2-furyl)-2-thiazolyl]acetamide <sup>‡</sup> ; Trp-P-2 acetate <sup>‡</sup> ; Vinyl chloride <sup>‡</sup> ; FD & C violet no. 1
Mesovarium	2	Salbutamol; Terbutaline
Myocardium	2	Estradiol mustard <sup>‡</sup> ; Phenesterin <sup>‡</sup>
Nasal cavity <sup>b</sup>	1	<i>N</i> -Nitrosodiethylamine
	11	Acetaldehyde; Diallylnitrosamine; Dimethylcarbamyl chloride; Hydrazine <sup>‡</sup> ; Methylnitrosamino- <i>N,N</i> -dimethylethylamine; Nitroso-2,6-dimethylmorpholine; <i>N</i> -Nitrosoallyl-2-oxopropylamine; <i>N</i> -Nitrosoethyl-2,3-dihydroxypropylamine; <i>N</i> -Nitrosomorpholine; <i>N</i> -Nitrosomorpholine; <i>N</i> -Nitrosopiperidine <sup>‡</sup>
	6	Allyl glycidyl ether <sup>‡</sup> ; 1,2-Dibromo-3-chloropropane <sup>‡</sup> ; 1,2-Dibromoethane <sup>‡</sup> ; Formaldehyde <sup>‡</sup> ; <i>N</i> -Nitrosohexamethylenimine; 1,2-Propylene oxide <sup>‡</sup>
	43	Acetaldehyde; Acrylonitrile; 1-Azoxopropane; Benzene <sup>‡</sup> ; Bis-(chloromethyl)ether <sup>‡</sup> ; <i>p</i> -Cresidine <sup>‡</sup> ; Diallylnitrosamine; 1,2-Dibromo-3-chloropropane <sup>‡</sup> ; 1,2-Dibromooethane <sup>‡</sup> ; Dimethylnitramine; Dimethylvinyl chloride <sup>‡</sup> ; Dinitrosomorphazine; 1,4-Dioxane <sup>‡</sup> ; 1,2-Epoxybutane <sup>‡</sup> ; <i>Z</i> -Ethyl- <i>O,N,N</i> -azoxyethane; Ethylbenzene; Ethylnitrosocyanamide; Formaldehyde <sup>‡</sup> ; Hexamethylphosphoramide; Hydrazine <sup>‡</sup> ; <i>N</i> -Nitroso- <i>N</i> -methyldecylamine; di( <i>N</i> -Nitroso)-perhydroprimidine; <i>N</i> -Nitroso(2,2,2-trifluoroethyl)ethylamine; 1-Nitrosourea <sup>‡</sup> ; Hexamethylphosphoramide; Hydrazine <sup>‡</sup> ; <i>N</i> -Nitrosoallyl-2,3-dihydroxypropylamine; <i>N</i> -Nitrosoallyl-2-hydroxypropylamine; <i>N</i> -Nitrosolethanolamine; <i>N</i> -Nitrosobis(2-hydroxypropyl)amine; <i>N</i> -Nitrosobis(2-oxopropyl)amine; <i>N</i> -Nitrosodietanolamine; <i>N</i> -Nitrosodipropylamine; Nitrosoethylmethylamine; <i>N</i> -Nitrosoethyl-2,3-dihydroxypropylamine; <i>N</i> -Nitrosomethyl-(2-hydroxyethyl)amine; <i>M</i> -Nitrosomethyl-2-hydroxypropylamine; <i>N</i> -Nitrosomethyl-(2-oxopropyl)amine; <i>N</i> -Nitrosomorpholine; <i>N</i> -Nitrosomethyl-1,2,3-trichloropropane <sup>‡</sup> ; Phenacetin <sup>‡</sup> ; Phenylglycidyl ether; 1,2-Propylene oxide <sup>‡</sup> ; Vinyl acetate <sup>‡</sup> ; Vinyl chloride <sup>‡</sup>
Nervous system	3	1,3-Butadiene <sup>‡</sup> ; <i>N</i> -Nitrosodimethylamine <sup>‡</sup> ; Procabazine.HCl <sup>‡</sup>
	21	Acrylamide; Acrylonitrile; Bromoethane <sup>‡</sup> ; Chlorambucil <sup>‡</sup> ; 1-(4-Chlorophenyl)-1-phenyl-2-propynyl carbamate; Cyclophosphamide <sup>‡</sup> ; 1-Ethyl-1-nitrosourea; Ethylencoxide <sup>‡</sup> ; 1-Ethyl-1-nitroso-3-(2-oxopropyl)-urea; Glu-P-1 <sup>‡</sup> ; Glu-P-2 <sup>‡</sup> ; Glycidol <sup>‡</sup> ; <i>R</i> ( $\rightarrow$ )-2-Methyl- <i>N</i> -nitrosopiperidine; <i>S</i> ( $\leftarrow$ )-2-Methyl- <i>N</i> -nitrosopiperidine; Methylnitramine; <i>N</i> -Nitroso- <i>N</i> -methylurea <sup>‡</sup> ; <i>N</i> -Nitrosodietanolamine; 1-Phenyl-3,3-dimethyltriazen; Procabazine.HCl <sup>‡</sup> ; Propane sulfone; Vinyl chloride <sup>‡</sup>
	4	Acetaldehyde; Nitroso-2,6-dimethylmorpholine; <i>N</i> -Nitrosomorpholine; <i>N</i> -Nitrosopiperidine <sup>‡</sup>
	3	<i>N</i> -Nitrosohexamethylenimine; 1,2,3-Trichloropropane <sup>‡</sup> ; Vinyl acetate <sup>‡</sup>
	32	Acrylamide; Acrylonitrile; Benzene <sup>‡</sup> ; 2,2-Bis(bromomethyl)-1,3-propanediol, technical grade <sup>‡</sup> ; C.I. direct blue 15; C.I. direct blue 218 <sup>‡</sup> ; Chloroprene <sup>‡</sup> ; 3-Diazoxyamine.HCl; 1,2-Dibromo-3-chloropropane <sup>‡</sup> ; 3,3'-Dimethoxybenzidine.2HCl; 3,3'-Dimethylbenzidine.2HCl <sup>‡</sup> ; Dimethylvinyl chloride <sup>‡</sup> ; Dinitrosomorphazine; Glycidol <sup>‡</sup> ; IQ <sup>‡</sup> ; Me- $\alpha$ -C acetate <sup>‡</sup> ; <i>N</i> -Nitroso-2,3-dihydroxypropyl-2-hydroxypropylamine; Nitroso-2,3-dihydroxypropyl-2-oxopropylamine; Nitroso- <i>N</i> -methyl- <i>N</i> -(2-phenylethyl)amine; Nitrosoamylurethan; <i>N</i> -Nitrosodietylamine; Nitrosoethylurethan; Nitrosoheptamethylenimine; 1-Nitrosobutanolamine; <i>N</i> -Nitrosomethyl-(2-oxopropyl)amine; <i>N</i> -Nitrososulfadiazine; <i>N</i> -Nitrososulfamorpholine; C.I. acid red 114; 2,3,7,8-Tetrachlorodibenzo- <i>p</i> -dioxin <sup>‡</sup> ; Toluene <sup>‡</sup> ; 1,2,3-Trichloropropane <sup>‡</sup> ; Xylene mixture ( <i>m</i> -xylene, <i>o</i> -xylene, <i>p</i> -xylene)
Ovary	10	Benzene <sup>‡</sup> ; 1,3-Butadiene <sup>‡</sup> ; Diethylstilbestrol <sup>‡</sup> ; <i>N</i> -Methylolacrylamide <sup>‡</sup> ; 5-Nitro-2-furaldehyde semicarbazone <sup>‡</sup> ; 5-Nitroacenaphthene <sup>‡</sup> ; 1-[1-(5-Nitrofururylidene)amino]hydantoin <sup>‡</sup> ; Phenolphthalein <sup>‡</sup> ; Tamoxifen citrate <sup>‡</sup> ; 4-Vinylcyclohexene
	3	Nitroso-2,3-dihydroxypropyl-2-oxopropylamine; Nitroso-2,6-dimethylmorpholine; Nitroso-2-oxopropylmethanolamine
Pancreas	1	Urethane <sup>‡</sup>
	22	2-Amino-5-nitrophenol <sup>‡</sup> ; 1-(Aminomethyl)cyclohexanecarboxylic acid; Azaserine; Butyl benzyl phthalate <sup>‡</sup> ; Chlorendic acid <sup>‡</sup> ; Cinnamyl anthranilate <sup>‡</sup> ; Clofibrate <sup>‡</sup> ; Dichlorvos <sup>‡</sup> ; Ethyl alcohol <sup>‡</sup> ; Hydrochlorofluorocarbon 123; IQ.HCl; Malonaldehyde, sodium salt <sup>‡</sup> ; Me- $\alpha$ -C acetate <sup>‡</sup> ; 2-Mercaptothiazole <sup>‡</sup> ; Methyl clofenapate <sup>‡</sup> ; <i>N</i> -( <i>N</i> -Methyl- <i>N</i> -nitrosocarbamoyl)- <i>l</i> -ornithine; 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol; 4-(Methylnitrosamino)-1-(3-pyridyl)-1-(butanone); Nafencopin; Nitrofen <sup>‡</sup> ; Toluene diisocyanate, commercial grade (2,4 (80%)- and 2,6 (20%)-) <sup>‡</sup> ; 1,2,3-Trichloropropane <sup>‡</sup> ; Bis-1,2-(chloromethoxy)ethane; Bis-1,4-(chloromethoxy)- <i>p</i> -xylene; Bis-(chloromethyl)ether <sup>‡</sup> ; Chloroprene <sup>‡</sup> ; trans-1,4-Dichlorobutene-2; Dimethylcarbamyl chloride; Phenoxycarbamine.HCl <sup>‡</sup> ; Tris-1,2,3-(chloromethoxy)propane
Peritoneal cavity	8	Acronycine; Acrylamide; Actinomycin D; Aniline.HCl <sup>‡</sup> ; 2,2-Bis(bromomethyl)-1,3-propanediol, technical grade <sup>‡</sup> ; Bromate, potassium <sup>‡</sup> ; Chlorozotocin; Cytembena <sup>‡</sup> ; Dapsone <sup>‡</sup> ; 1,2-Dibromooethane <sup>‡</sup> ; Dibromomannitol <sup>‡</sup> ; 3,3'-Dimethylbenzidine.2HCl <sup>‡</sup> ; 1,4-Dioxane <sup>‡</sup> ; Ethylene oxide <sup>‡</sup> ; 1-Ethyl-1-nitroso-3-(2-oxopropyl)-urea; Glycidol <sup>‡</sup> ; Melphalan <sup>‡</sup> ; <i>N</i> -Methyl- <i>N</i> , <i>N</i> -dinitrosamine; Mitomycin-C; <i>N</i> -Nitroso-2,2,4-trimethyl-1,2-dihydroquinoline polymer; Phenoxybenzamine.HCl <sup>‡</sup> ; <i>o</i> -Toluidine.HCl <sup>‡</sup>
	22	

(Continued on next page)



Subcutaneous tissue	4	Mouse	2,2-Bis(bromomethyl)-1,3-propanediol, technical grade <sup>†</sup> ; 1,2-Dibromoethane <sup>†</sup> ; <i>N</i> ,2- $\gamma$ -Glutamyl- <i>p</i> -hydrazinobenzotriazole; acid; Glycidol <sup>†</sup>
Testis	13	Rat	2,2-Bis(bromomethyl)-1,3-propanediol, technical grade <sup>†</sup> ; 2,4-Diaminotoluene.2HCl <sup>†</sup> ; 1,2-Dichloroethane <sup>†</sup> ; Dimethoxane; 1,4-Dioxane <sup>†</sup> ; MeA- <i>o</i> -C acetate <sup>†</sup> ; 4,4'-Methylene-bis(2-methyl-aniline); <i>o</i> -Nitrosotoluene; <i>p</i> -Rosaniline.HCl <sup>†</sup> ; Toluene diisocyanate, commercial grade (2,4 (80%) and 2,6 (20%)) <sup>†</sup> ; <i>o</i> -Toluidine.HCl <sup>†</sup> ; 2,4,5-Trimethylamine.HCl <sup>†</sup> ; 2,5-Xylylene.HCl <sup>†</sup>
	4	Mouse	Diethylstilbestrol <sup>†</sup> ; Flinasteride; Reserpine <sup>†</sup> ; Tamoxifen citrate <sup>†</sup>
Thyroid gland	18	Rat	5-Azacytidine <sup>†</sup> ; 2,2-Bis(bromomethyl)-1,3-propanediol, technical grade <sup>†</sup> ; 1,3-Butadiene <sup>†</sup> ; <i>N</i> -Butyl- <i>N</i> -(4-hydroxybutyl)nitrosamine; Cadmium chloride; 2-Chloro-1,1,1-trifluoroethane; 1,1-Dichloro-1-fluoroethane; Hydrochlorofluorocarbon 123; Methyl <i>tert</i> -butyl ether <sup>†</sup> ; Methyl clofenapate <sup>†</sup> ; Metronidazole <sup>†</sup> ; <i>N</i> -Nitrosodimethylamine <sup>†</sup> ; Oxolinic acid <sup>†</sup> ; SDZ 200-110; 1,1,1,2-Tetrafluoroethane <sup>†</sup> ; Trichloroethylene <sup>†</sup> ; Trinitroglycerin; Vinyl chloride <sup>†</sup>
	4	Hamster	Hexachlorobenzene <sup>†</sup> ; Hydrazine <sup>†</sup> ; Methylthiourea; Urethane <sup>†</sup>
Urinary bladder	18	Mouse	3-Amino-4-ethoxyacetamide <sup>†</sup> ; HC blue no. 1 <sup>†</sup> ; <i>tert</i> -Butyl alcohol <sup>†</sup> ; Chlorinated paraffins (C <sub>12</sub> , 60% chlorine) <sup>†</sup> ; 2,4-Diaminoanisole sulfate <sup>†</sup> ; Diethylstilbestrol <sup>†</sup> ; Doxylamine succinate <sup>†</sup> ; Ethionamide <sup>†</sup> ; Ethylene thiourea <sup>†</sup> ; 4,4'-Methylenedianiline.2HCl <sup>†</sup> ; 1,5-Naphthalenediamine <sup>†</sup> ; Nitrobenzene <sup>†</sup> ; Oxazepam <sup>†</sup> ; 4,4'-Oxydianiline <sup>†</sup> ; C.I. pigment red 3 <sup>†</sup> ; Sulfamethazine; 2,3,7,8-Tetrachlorodibenzo- <i>p</i> -dioxin <sup>†</sup> ; 4,4'-Thiodianiline <sup>†</sup>
	33	Rat	Acrylamide; 3-Aminotriazole <sup>†</sup> ; <i>o</i> -Anisidine.HCl <sup>†</sup> ; Bemitradine; 2,2-Bis(bromomethyl)-1,3-propanediol, technical grade <sup>†</sup> ; Bromate, potassium <sup>†</sup> ; Chlorinated paraffins (C <sub>12</sub> , 60% chlorine) <sup>†</sup> ; Chloroprene <sup>†</sup> ; 2,4-Diaminoanisole sulfate <sup>†</sup> ; <i>N,N'</i> -Diethylthiourea <sup>†</sup> ; 1-Ethyl-1-nitrosourea; Ethylene thiourea <sup>†</sup> ; 1-Ethyl-1-nitroso-3-(2-oxopropyl)-urea; Fluvastatin; Glycidol <sup>†</sup> ; Iodinated glycerol <sup>†</sup> ; Isobutene <sup>†</sup> ; Malonaldehyde; sodium salt <sup>†</sup> ; Methimazole; 4,4'-Methylenebis( <i>N,N</i> -dimethyl)benzenamine <sup>†</sup> ; 4,4'-Methylenedianiline.2HCl <sup>†</sup> ; Mirex, photo-; Nitrobenzene <sup>†</sup> ; <i>N</i> -Nitrosobis(2-oxopropyl)amine; 4,4'-Oxydianiline <sup>†</sup> ; Propylthiourea <sup>†</sup> ; <i>p</i> -Rosaniline.HCl <sup>†</sup> ; 2,3,7,8-Tetrachlorodibenzo- <i>p</i> -dioxin <sup>†</sup> ; 4,4'-Thiodianiline <sup>†</sup> ; Thiourea <sup>†</sup> ; Trimethylthiourea <sup>†</sup> ; Vinyl acetate <sup>†</sup> ; Zinc dimethyldithiocarbamate <sup>†</sup>
Uterus	2	Dog	3,3'-Dichlorobenzidine; 4,4'-Methylene-bis(2-chloroaniline)
	3	Hamster	Formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl]hydrazide <sup>†</sup> ; <i>N</i> -[4-(5-Nitro-2-furyl)-2-thiazolyl]acetamide; <i>N</i> -[4-(5-Nitro-2-furyl)-2-thiazolyl]formamide <sup>†</sup>
Vagina	12	Mouse	2-Acetylaminofluorene <sup>†</sup> ; 4-Aminodiphenyl; 2-Aminodiphenylene oxide; <i>o</i> -Anisidine.HCl <sup>†</sup> ; 4-Chloro-4'-aminodiphenylether <sup>†</sup> ; <i>p</i> -Cresidine <sup>†</sup> ; 4-Ethylsulphonylnaphthalene-1-sulfonamide; <i>N</i> -Hydroxy-2-acetylaminofluorene <sup>†</sup> ; <i>N</i> -[4-(5-Nitro-2-furyl)-2-thiazolyl]formamide <sup>†</sup> ; Phenacetin <sup>†</sup> ; Telone II, technical grade <sup>†</sup> ; Uraclil <sup>†</sup>
	1	Monkey	2-Naphthylamine <sup>†</sup>
Uterus	49	Rat	Acetaminophen <sup>†</sup> ; Allyl isothiocyanate <sup>†</sup> ; 1-Amino-2,4-dibromonanthraquinone <sup>†</sup> ; 2-Amino-4-(5-nitro-2-furyl)thiazole <sup>†</sup> ; 4-Amino-2-nitrophenol <sup>†</sup> ; 11-Aminoundecanoic acid <sup>†</sup> ; <i>o</i> -Anisidine.HCl <sup>†</sup> ; Aristolochic acid, sodium salt (77% AAI, 21% AAII); 2,2-Bis(bromomethyl)-1,3-propanediol, technical grade <sup>†</sup> ; C.I. disperse blue 1 <sup>†</sup> ; <i>N</i> -Butyl- <i>N</i> -(4-hydroxybutyl)nitrosamine; 4-Chloro- <i>o</i> -phenylenediamine <sup>†</sup> ; <i>m</i> -Cresidine <sup>†</sup> ; <i>p</i> -Cresidine <sup>†</sup> ; Cyclophosphamide <sup>†</sup> ; Diethylene glycol; Dimethylarsinic acid <sup>†</sup> ; Fosetyl Al; IQ.HCl; MeA- <i>o</i> -C acetate <sup>†</sup> ; Melamine <sup>†</sup> ; 2-Methoxy-3-aminodibenzofuran; 2-Naphthylamine <sup>†</sup> ; Nitrotriacetic acid <sup>†</sup> ; Nitrotriacetic acid, trisodium salt, monohydrate <sup>†</sup> ; <i>N</i> -[4-(5-Nitro-2-furyl)-2-thiazolyl]formamide <sup>†</sup> ; <i>o</i> -Nitroanisole <sup>†</sup> ; <i>N</i> -Nitroso- <i>N</i> -methyl- <i>N</i> -dodecylamine; <i>N</i> -Nitroso- <i>N</i> -methyl- <i>N</i> -tetradecylamine; <i>N</i> -Nitroso- <i>N</i> -methyldecylamine; <i>N</i> -Nitrosobis(2-oxopropyl)amine; Nitrosodibutylamine <sup>†</sup> ; <i>N</i> -Nitrosodiphenylamine <sup>†</sup> ; <i>o</i> -Nitrosotoluene; <i>N</i> -Oxydiethylene thiocarbonyl- <i>N</i> -oxydiethylene sulfenamide; Phenacetin <sup>†</sup> ; Phenazone; <i>o</i> -Phenylphenate, sodium <sup>†</sup> ; <i>o</i> -Phenylphenol <sup>†</sup> ; Potassium bicarbonate; Purpurin; Quercetin <sup>†</sup> ; <i>p</i> -Quinone dioxime <sup>†</sup> ; Saccharin, sodium <sup>†</sup> ; Saliylazosulfapyridine <sup>†</sup> ; <i>o</i> -Toluenesulfonamide; <i>o</i> -Toluidine.HCl <sup>†</sup> ; Trp-P-2 acetate <sup>†</sup> ; Uraclil <sup>†</sup>
	1	Hamster	<i>N</i> -Nitroso-ethylhydroxyethylurea
Uterus	12	Mouse	Bromoethane <sup>†</sup> ; Chloroethane <sup>†</sup> ; Dacarbazine <sup>†</sup> ; 1,2-Dichloroethane <sup>†</sup> ; Diethylstilbestrol <sup>†</sup> ; Ethylene oxide <sup>†</sup> ; Glycidol <sup>†</sup> ; ( <i>N</i> -6)-(Methylnitroso) adenosine; Procabazine.HCl <sup>†</sup> ; 1,2,3-Trichloropropane <sup>†</sup> ; Trimethylphosphate <sup>†</sup> ; Vinyl acetate <sup>†</sup>
	26	Rat	Acrylamide; 1-Allyl-1-nitrosourea; 3-Amino-9-ethylcarbazole mixture <sup>†</sup> ; 1-Amyl-1-nitrosourea; Atrazine <sup>†</sup> ; C.I. direct blue 15; Bromocriptine mesylate <sup>†</sup> ; <i>N</i> - <i>n</i> -Butyl- <i>N</i> -nitrosourea; Calcium valproate; Captan <sup>†</sup> ; 2-Chloro-1,1,1-trifluoroethane; Dacarbazine <sup>†</sup> ; Daminozide <sup>†</sup> ; 3,3'-Dimethoxybenzidine-4,4'-diisocyanate <sup>†</sup> ; 3,3'-Dimethoxybenzidine.2HCl; Dimethylaminoethylnitrosoethylurea, nitrite salt; 1-Ethyl-1-nitroso-3-(2-hydroxyethyl)-urea; 1-Ethyl-1-nitroso-3-(2-oxopropyl)-urea; <i>N</i> -Hexyl nitrosourea; ICRF-159 <sup>†</sup> ; Isophosphamide <sup>†</sup> ; 1,5-Naphthalenediamine <sup>†</sup> ; Nitrobenzene <sup>†</sup> ; Norlestrin <sup>†</sup> ; 4,4'-Thiodianiline <sup>†</sup> ; Vinyl acetate <sup>†</sup>
Vagina	1	Mouse	AZT <sup>†</sup>
	2	Rat	AZT <sup>†</sup> ; <i>N</i> - <i>n</i> -Butyl- <i>N</i> -nitrosourea

(Continued on next page)

TABLE 1.—Summary of Carcinogenic Potency Database by target organ. (Continued)

Target site	Species	N	Chemicals that induce tumors at each site
Vascular system	Hamster	9	1,2-Dimethylhydrazine.2HCl; Glycidol <sup>†</sup> ; Hexachlorobenzene <sup>†</sup> ; <i>N</i> -Nitroso-ethyl-2-oxopropylurea; <i>N</i> -Nitroso-ethylhydroxyethylurea; <i>N</i> -Nitroso-oxopropylurea; <i>N</i> -Nitroso-oxopropylurea; <i>N</i> -Nitroso-2-phenylethylurea; Vinyl chloride <sup>†</sup>
	Mouse	59	A- $\alpha$ -C; <i>N</i> -Acetyl-4-(hydroxymethyl)phenylhydrazine; 1-Acetyl-2-phenylhydrazine; Allylhydrazine.HCl; Arecoline.HCl; Azathioprine; Benzidine.2HCl; 2-Biphenylamine.HCl <sup>†</sup> ; 1,3-Butadiene <sup>†</sup> ; Captafol <sup>†</sup> ; Carbamyl hydrazine.HCl; 4-Chloro-4'-aminodiphenylether <sup>†</sup> ; 1-Chloro-4-nitrobenzene <sup>†</sup> ; 5-Chloro- <i>o</i> -toluidine <sup>†</sup> ; 4-Chloro- <i>o</i> -toluidine.HCl <sup>†</sup> ; <i>p</i> -Chloroaniline.HCl <sup>†</sup> ; Chloroprene <sup>†</sup> ; Cupferon <sup>†</sup> ; Dacarbazine <sup>†</sup> ; Diaminazole <sup>†</sup> ; 2,4-Diaminotoluene.2HCl <sup>†</sup> ; 1,2-Dibromoethane <sup>†</sup> ; Diftalone; 7,12-Dimethylbenz(a)anthracene; 1,1-Dimethylhydrazine <sup>†</sup> ; 1,2-Dimethylhydrazine.2HCl; <i>N</i> -Ethyl- <i>N</i> -formylhydrazine; Ethylhydrazine.HCl; Glu-P-1 <sup>†</sup> ; Glu-P-2 <sup>†</sup> ; <i>p</i> -Hydrazinobenzoic acid.HCl; 1'-Hydroxysafrole <sup>†</sup> ; Isoprene; MeA- $\alpha$ -C acetate <sup>†</sup> ; <i>N</i> -Methyl- <i>N</i> -formylhydrazine; 2-Methyl-1-nitroanthraquinone <sup>†</sup> ; Michler's ketone <sup>†</sup> ; 5-Nitro- <i>o</i> -toluidine <sup>†</sup> ; Nitrofen <sup>†</sup> ; <i>N</i> -Nitroso- <i>N</i> -methylurea <sup>†</sup> ; Pentachloroanisole <sup>†</sup> ; 2,3,4,5,6-Pentachlorophenol (Dowicide EC-7) <sup>†</sup> ; 2,3,4,5,6-Pentachlorophenol, technical grade <sup>†</sup> ; <i>n</i> -Pentylhydrazine.HCl; Phenylethylhydrazine sulfate; Phenylhydrazine.HCl; Sterigmatocystin <sup>†</sup> ; Tetrafluoroethylene <sup>†</sup> ; Toluene diisocyanate, commercial grade (2,4 (80%)-and 2,6 (20%)-) <sup>†</sup> ; <i>o</i> -Toluidine.HCl <sup>†</sup> ; 2,4,6-Trichloroaniline <sup>†</sup> ; 2,4,5-Trimethylamine.HCl <sup>†</sup> ; 2,4,6-Trimethylamine.HCl <sup>†</sup> ; Urethane <sup>†</sup> ; Vinyl carbamate; Vinyl chloride <sup>†</sup> ; Vinyl fluoride <sup>†</sup> ; Vinylidene chloride <sup>†</sup> ; 2,5-Xylylidine.HCl <sup>†</sup>
	Monkey	2	Aflatoxin B <sub>1</sub> <sup>†</sup> ; Urethane <sup>†</sup>
	Rat	32	Aniline.HCl <sup>†</sup> ; Azobenzene <sup>†</sup> ; Benzene <sup>†</sup> ; Clivorine; Cupferon <sup>†</sup> ; 1,2-Dibromoethane <sup>†</sup> ; 4,6-Dimethyl-2-(5-nitro-2-furyl)pyrimidine; Z-Ethyl- <i>O,N,N</i> -azoxyethane; Z-Ethyl- <i>O,N,N</i> -azoxymethane; IQ.HCl; Lasiocarpine; 4,4'-Methylene-bis(2-chloroaniline); <i>N</i> -[5-(5-Nitro-2-furyl)-1,3,4-thiadiazol-2-yl]acetamide <sup>†</sup> ; <i>N</i> -Nitroso-(2-hydroxypropyl)-(2-hydroxyethyl)amine; Nitroso-1,2,3,6-tetrahydropyridine; <i>N</i> -Nitrosobis(2-oxopropyl)amine; <i>N</i> -Nitrosodiethanolamine; <i>N</i> -Nitrosodimethylamine; <i>N</i> -Nitrosodimethylamine <sup>†</sup> ; <i>N</i> -Nitrosomethyl-(2-tosyloxyethyl)amine; <i>N</i> -Nitrosomorpholine; <i>N</i> -Nitrosopyrrolidine <sup>†</sup> ; Petasitenine; Sterigmatocystin <sup>†</sup> ; Symphytine; Tetrafluoroethylene <sup>†</sup> ; <i>o</i> -Toluidine.HCl <sup>†</sup> ; Trp-P-2 acetate <sup>†</sup> ; Vinyl bromide; Vinyl chloride <sup>†</sup> ; Vinyl fluoride <sup>†</sup>

<sup>a</sup> There was no reported target site in 1 species (rats or mice) for 5 chemicals with superscripts, but the chemical was evaluated by the published author as a carcinogen: aldrin<sup>†</sup>, dieldrin<sup>†</sup>, *N*-nitrosopyrrolidine<sup>†</sup>; 2,3,4,5,6-pentachlorophenol (Dowicide EC-7)<sup>†</sup>; and urethane<sup>†</sup>.

<sup>b</sup> Nasal cavity includes tissues of the nose, nasal turbinates, paranasal sinuses, and trachea.

<sup>c</sup> Oral cavity includes tissues of the mouth, oropharynx, pharynx, and larynx.

A chemical is listed under each organ evaluated as positive in an experiment in that species by at least 1 author. Therefore, a chemical may be listed under several target organs and every chemical listed in the table is positive in at least 1 species. In order to compare results in rats and mice, symbols follow chemicals tested in both species: a <sup>†</sup> indicates that the chemical is positive at some site in both species, and a <sup>†</sup> indicates that it was tested in both but positive in only 1. <sup>a</sup> N = the number of chemicals with at least 1 positive test at that site in that species. Because many chemicals induce tumors at more than 1 site in a given species, many chemicals appear more than once in the table.

species, the reader can determine that pentachloroanisole is the only chemical that induced adrenal tumors in both rats and mice. The superscripts † and ‡ apply only to results in rats and mice; for example, hamsters are reported under adrenal gland for urethane with the symbol ‡, indicating that urethane was positive at some site in rats and mice; however, the superscript does not indicate anything about hamsters.

#### RESULTS IN RATS AND MICE

For rats and mice, Table 2 summarizes the proportion of carcinogens that are positive at each target organ, based on the results presented in the compendium (Table 1). In Table 2, the target sites are ordered by how frequently the site is positive in either rats or mice. A summary of the compendium is given under the headings "All Chemicals" for rats ( $N = 526$ ) and mice ( $N = 412$ ). Additionally, for the subset of carcinogens that have been tested in *Salmonella* ( $N = 459$ ), results in each species are reported separately for mutagens and nonmutagens. A chemical is classified as mutagenic in the *Salmonella* assay if it was evaluated as either "mutagenic" or "weakly mutagenic" by Zeiger (17) or as "positive" by the Gene-Tox Program (11, 14) and A. Auletta (personal communication April 1990). This summary table permits simple comparisons between species and between mutagens and nonmutagens.

#### All Carcinogens in Rats or Mice

Among rodent carcinogens, it is common for a chemical to induce tumors at more than one site in a species, and this is reflected in Table 2 where many chemicals are counted under more than one site. Multiple-site carcinogenesis is more common in rats (52%, 247/471) than mice (45%, 171/384), with 3 or more target sites also more common in rats (31%, 148/471 compared to 19%, 72/384 in mice). Fewer chemicals are included in the multiple-site analysis than the totals in Table 2 because multiple-site carcinogenesis cannot be measured for experiments that restrict histopathological examination or report data for only a couple of selected tissues. Results are similar when experiments with restricted analyses are included.

The liver is the most frequent target site in mice (56%) and rats (39%) (Table 2). The second most common sites are the mouse lung (28%) and the rat mammary gland (19%). Among the 44 carcinogens in hamsters, the most frequent sites are stomach and liver. For the 11 carcinogens in monkeys, liver is the most frequent target site.

Despite the wide variety of target organs in rats and mice (Tables 1 and 2), due to (a) the frequency of multiple-site carcinogenesis and (b) the frequency of tumorigenesis in a few common sites like liver, most chemical carcinogens in rats and mice can be identified by just the 8 most common

TABLE 2.—Frequency of target organs by mutagenicity in *Salmonella* for 526 carcinogens in rats and 412 carcinogens in mice in the Carcinogenic Potency Database.

Target organ	Chemicals evaluated as carcinogenic in:					
	Rats			Mice		
	All chemicals <sup>a</sup> ( $N = 526$ ) <sup>b</sup>	Mutagens ( $N = 214$ )	Nonmutagens ( $N = 126$ )	All chemicals <sup>a</sup> ( $N = 412$ )	Mutagens ( $N = 176$ )	Nonmutagens ( $N = 126$ )
Liver	206 (39%)	84 (39%)	40 (32%)	231 (56%)	92 (52%)	90 (71%)
Lung	55 (10%)	31 (14%)	3 (2%)	116 (28%)	54 (31%)	23 (18%)
Mammary gland	102 (19%)	60 (28%)	13 (10%)	24 (6%)	11 (6%)	8 (6%)
Kidney	86 (16%)	31 (14%)	36 (29%)	26 (6%)	12 (7%)	10 (8%)
Stomach	85 (16%)	45 (21%)	10 (8%)	63 (15%)	34 (19%)	14 (11%)
Vascular system	32 (6%)	18 (8%)	2 (2%)	59 (14%)	34 (19%)	11 (9%)
Hematopoietic system	56 (11%)	29 (14%)	16 (13%)	53 (13%)	23 (13%)	17 (13%)
Urinary bladder	49 (9%)	25 (12%)	14 (11%)	12 (3%)	8 (5%)	1
Nasal cavity/turbinates	43 (8%)	19 (9%)	6 (5%)	6 (1%)	6 (3%)	
Ear/Zymbal's gland	41 (8%)	31 (14%)	1	3	1	2 (2%)
Esophagus	36 (7%)	14 (7%)	1	8 (2%)	5 (3%)	1
Skin	33 (6%)	23 (11%)	3 (2%)	5 (1%)	4 (2%)	
Thyroid gland	33 (6%)	14 (7%)	12 (10%)	18 (4%)	9 (5%)	9 (7%)
Oral cavity	32 (6%)	18 (8%)	6 (5%)	3	2 (1%)	1
Large intestine	32 (6%)	22 (10%)	1	1		
Small intestine	29 (6%)	20 (9%)	2 (2%)	6 (1%)	4 (2%)	1
Uterus	26 (5%)	11 (5%)	6 (5%)	12 (3%)	8 (5%)	3 (2%)
Peritoneal cavity	22 (4%)	13 (6%)	5 (4%)	8 (2%)	2 (1%)	1
Pancreas	22 (4%)	8 (4%)	7 (6%)			
Central nervous system	21 (4%)	14 (7%)	2 (2%)	3	2 (1%)	1
Harderian gland				19 (5%)	9 (5%)	7 (6%)
Clitoral/preputial gland	21 (4%)	16 (7%)	4 (3%)	11 (3%)	3 (2%)	2 (2%)
Testis	18 (3%)	7 (3%)	4 (3%)	4		2 (2%)
Adrenal gland	16 (3%)	7 (3%)	6 (5%)	8 (2%)	3 (2%)	5 (4%)
Subcutaneous tissue	13 (2%)	11 (5%)	1	4	3 (2%)	
Ovary				10 (2%)	4 (2%)	5 (4%)
Pituitary gland	7 (1%)	2	4 (3%)	8 (2%)	2 (1%)	3 (2%)
Spleen	7 (1%)	4 (2%)	2 (2%)			
Bone	5	2	1			
Prostate	4	1	1			
Gall bladder				4		
Vagina	2	2		1	1	
Myocardium				2		1
Mesovarium	2					

<sup>a</sup>In the CPDB, 722 chemicals are carcinogenic in rats and/or mice, but mutagenicity in *Salmonella* is known for only 459 of them. The column "All chemicals" reports results for all carcinogens in each species, whether mutagenicity results are available or not.

<sup>b</sup>Percentage of rat carcinogens or mouse carcinogens that induce tumors at the given site. Many chemicals induce tumors at more than 1 site, and these are counted at each relevant target site. Therefore, many chemicals are counted more than once, and percentages cannot be added. For example, of 206 chemicals that induce liver tumors in rats, 126 (61%) are positive in at least one other site in rats.

TABLE 3.—Target organs in humans for 82 agents evaluated as human carcinogens by the International Agency for Research on Cancer (10, 15, 16).

Target site	Agent, mixture or industrial process
Anogenital	Human papilloma virus 16
Bladder	Aluminum production; *4-Aminobiphenyl <sup>a</sup> ; Analgesic mixtures containing phenacetin <sup>d</sup> ; *Auramine manufacture <sup>d,e</sup> ; *Benzidine <sup>a</sup> ; <i>N,N</i> -Bis(2-chloroethyl)-2-naphthylamine (chlornaphazine); Coal gasification; *Coal-tar pitches; *Cyclophosphamide <sup>a</sup> ; *Magenta manufacture <sup>d,e</sup> ; *2-Naphthylamine <sup>a,b</sup> ; Rubber industry; <i>Schistosoma hematobium</i> (infection); *Tobacco smoke
Bone	*Plutonium-239 and its decay products (may contain plutonium-240 and other isotopes), as aerosols; *Radium-224 and its decay products; *Radium-226 and its decay products; Radium-228 and its decay products
Brain	*Vinyl chloride <sup>a</sup>
Breast	*Diethylstilbestrol <sup>a</sup> ; *Estrogens, nonsteroidal <sup>a,e</sup> ; *Estrogens, postmenopausal therapy <sup>d,e</sup> ; *X-rays and $\gamma$ -rays
Cervix	Human papilloma virus 16; Human papilloma virus 18
Cervix/vagina	*Diethylstilbestrol <sup>a</sup> ; *Estrogens, nonsteroidal <sup>a,e</sup>
Endometrium	*Estrogens, steroidal <sup>a,e</sup> ; *Estrogens, postmenopausal therapy <sup>d,e</sup> ; Oral contraceptives, sequential; *Tamoxifen <sup>a</sup>
Esophagus	Alcoholic beverages <sup>d</sup> ; *Tobacco smoke
Gastrointestinal tract	*Asbestos
Hematopoietic system	
Leukemia	*Benzene <sup>a</sup> ; Boot and shoe manufacture and repair; 1,4-Butanediol dimethanesulphonate (Myleran) <sup>c</sup> ; *Chlorambucil <sup>a</sup> ; 1-(2-(Chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea (methyl-CCNU); *Cyclophosphamide <sup>a</sup> ; Etoposide in combination with cisplatin and bleomycin; *Melphalan <sup>a</sup> ; MOPP and other combined chemotherapy including alkylating agents; *Phosphorus-32, as phosphate; Rubber industry; *Thio-tepa <sup>a</sup> ; *Thorium-232 and its decay products, administered intravenously as a colloidal dispersion of thorium-232 dioxide; Treosulfan; *X-rays and $\gamma$ -rays
Lymphoma	Azathioprine <sup>a</sup> ; Cyclosporin <sup>c</sup> ; Epstein-Barr virus; Human immunodeficiency virus type 1 (HIV-1); Human T-cell lymphotropic virus type I (HTLV-I); *Vinyl chloride <sup>a</sup>
Hodgkin's disease	Epstein-Barr virus
Kaposi's sarcoma	Human immunodeficiency virus type 1 (HIV-1)
Kidney	Coke production
Renal pelvis	Analgesic mixtures containing phenacetin (renal pelvis/ureter) <sup>d</sup> ; *Tobacco smoke
Liver	*Aflatoxins <sup>a,b</sup> ; Alcoholic beverages <sup>d</sup> ; Hepatitis B virus (chronic infection); Hepatitis C virus (chronic infection); <i>Opisthorchis viverrini</i> (infection); *Oral contraceptives, combined <sup>d,e</sup> ; *Plutonium-239 and its decay products (may contain plutonium-240 and other isotopes), as aerosols; *Vinyl chloride <sup>a</sup>
Cholangiocarcinoma	<i>Opisthorchis viverrini</i> (infection)
Hepatobiliary system	Azathioprine <sup>a</sup>
Lung	Aluminum production; Arsenic and arsenic compounds <sup>a</sup> ; *Asbestos; *Beryllium and beryllium compounds <sup>c</sup> ; *Bis(chloromethyl)ether <sup>a</sup> and technical chloromethyl methyl ether <sup>a</sup> ; *Cadmium and cadmium compounds <sup>a</sup> ; *Chromium (VI) compounds <sup>a</sup> ; Coal gasification; *Coal-tar pitches; *Coal-tars; Coke production; Mustard gas (sulphur mustard); Hematite mining (underground), with exposure to radon; Iron and steel founding; *Nickel compounds <sup>c</sup> ; Painter (occupational exposure); *Plutonium-239 and its decay products (may contain plutonium-240 and other isotopes), as aerosols; *Radon-222 and its decay products; *Silica, crystalline, in the form of quartz or cristobalite from occupational sources; Soots; Strong inorganic acid mists containing sulfuric acid (occupational exposure); Talc containing asbestiform fibers; *Thorium-232 and its decay products, administered intravenously as a colloidal dispersion of thorium-232 dioxide; *Tobacco smoke; *Vinyl chloride <sup>a</sup>
Mesenchymal tumors	Azathioprine <sup>a</sup>
Nasal sinus	Boot and shoe manufacture and repair; Furniture and cabinet making; Isopropanol manufacture (strong acid process); *Nickel compounds <sup>c</sup> ; Wood dust
Nasopharynx	Epstein-Barr virus; Salted fish, Chinese-style
Paranasal sinus	Wood dust
Oral cavity	Alcoholic beverage <sup>d</sup> ; Betel-quid with tobacco; Tobacco products, smokeless (chewing tobacco, oral snuff); *Tobacco smoke
Larynx	Alcoholic beverage <sup>d</sup> ; *Asbestos; Mustard gas (sulphur mustard); Strong inorganic acid mists containing sulfuric acid (occupational exposure); *Tobacco smoke
Pharynx	Alcoholic beverage <sup>d</sup> ; Mustard gas (sulphur mustard); *Tobacco smoke
Pancreas	*Tobacco smoke
Peritoneum	*Asbestos; *Erionite
Pleura	*Asbestos; *Erionite
Skin	Arsenic and arsenic compounds <sup>a</sup> ; Azathioprine <sup>a</sup> ; Coal gasification; *Coal-tar pitches; *Coal-tars; Coke production; *8-Methoxypsoralen (methoxsalen) <sup>d</sup> plus UV radiation; *Mineral oils, untreated and mildly treated; *Shale-oils; *Solar radiation; Soots
Melanoma	*Solar radiation
Stomach	<i>Helicobacter pylori</i> (infection)
Testis	*Diethylstilbestrol <sup>a</sup> ; *Estrogens, nonsteroidal <sup>a,e</sup>
Thyroid	Radioiodines, short-lived isotopes, including iodine-131, from atomic reactor accidents and nuclear weapons detonation (exposure during childhood); *X-rays and $\gamma$ -rays

IARC has evaluated an additional 5 agents as having an overall evaluation, "carcinogenic to humans" but all 5 lack an IARC evaluation of "sufficient evidence" of carcinogenicity to humans:  $\alpha$ -particle-emitting radionuclides, internally deposited;  $\beta$ -particle-emitting radionuclides, internally deposited; ethylene oxide; neutron radiation; and TCDD.

\* = IARC has evaluated the evidence of carcinogenicity in animals as "sufficient" for these 40 human carcinogens.

<sup>a</sup>Tissues are reported in Table 1 for rodent experiments in the CPDB.

<sup>b</sup>Tissues reported in Table 1 for monkey experiments in the CPDB.

<sup>c</sup>Experiments are reported in the CPDB, but none are positive.

<sup>d</sup>For 5 chemicals, there are positive tests with target sites in the CPDB; however, for the agent or exposure circumstance evaluated by IARC as "carcinogenic to humans" there are no tests in the CPDB: auramine-O, estradiol, ethyl alcohol, phenacetin, and rosaniline (Magenta I).

<sup>e</sup>For 6 human carcinogens IARC considers the evidence of carcinogenicity in experimental animals as "sufficient" for some chemical constituent, but the group or exposure circumstance is not evaluated as "sufficient" in animals: auramine manufacture; estrogens, steroidal and nonsteroidal; estrogens, postmenopausal therapy; magenta manufacture; and oral contraceptives, combined.

sites: liver, lung, mammary gland, stomach, vascular system, kidney, hematopoietic system, and urinary bladder (7). Overall, 92% (354/384) of mouse carcinogens and 82% (388/471) of rat carcinogens are positive in at least one of these 8 sites.

#### Mutagenicity and Target Site

Mutagens compared to nonmutagens are: (a) more likely to be carcinogenic; (b) more likely to induce tumors at multiple target sites; and (c) more likely to be carcinogenic in 2 species (4, 5, 8).

Since tissue distribution and pharmacokinetics would not be expected to differ systematically between mutagens and nonmutagens, one would not expect systematic differences in the particular organs in which tumors are induced (8). Results in Table 2 do not support the idea that mutagens and nonmutagens induce tumors in different target organs. Liver is the most common site for both mutagens and nonmutagens; most organs are target sites for both mutagens and nonmutagens, and both mutagens and nonmutagens induce tumors in a wide variety of sites. Moreover, the same sites tend to be the most common sites for both: at least 81% of either mutagens or nonmutagens are positive in each species in at least one of the 8 most frequent target sites. We earlier compared results for mutagens and nonmutagens in specific tissues (18).

#### Target Organs of Human Carcinogens

To complement the compendium of target organs in carcinogenesis bioassays (Table 1), Table 3 reports the target organs of carcinogenicity in humans for 82 agents that the International Agency for Research in Cancer (IARC) evaluates as human carcinogens at a particular target site (10, 15, 16), <http://www.iarc.fr/>. In addition to individual chemicals such as those reported in Table 1 for bioassays, the agents that IARC evaluates as human carcinogens include industrial processes, therapeutic combinations, infectious agents, ionizing radiation, and mixtures such as tobacco smoke.

In Table 3, footnotes indicate which chemicals are included in the CPDB among the 82 IARC human carcinogens with human target sites. The reader can compare positivity and target sites in humans, rodents and monkeys for human carcinogens by searching for a chemical name in our table "Results by Chemical" on the Web (<http://potency.berkeley.edu/chemicalsummary.html>) or in our plot of the CPDB (<http://potency.berkeley.edu/database.html>).

Among the 82 human carcinogens with target sites, IARC considers 52 to have been adequately tested in experimental animals. Agents that have not been tested adequately are mostly exposure circumstances like the workplace, or infectious agents. Of the 52 that have been tested in animals, IARC evaluates 12 as having "limited evidence" in animals and 40 as "sufficient evidence." (The 40 include 6 agents for which a chemical constituent has "sufficient evidence" even though the group or exposure circumstance that is a human carcinogen, does not, e.g., auramine-O for auramine manufacture.) The 40 agents with "sufficient evidence" in animals are indicated in Table 3 by a "\*". Thus, evidence of carcinogenicity is "sufficient" in experimental animals for only 40/82 (49%) of human carcinogens.

Ultimately, for purposes of investigating interspecies extrapolation or the practice of risk assessment to humans from

bioassay data, one wants to know whether the large number (many hundreds) of chemicals that have been shown to be carcinogenic in experimental animals would also be carcinogenic in humans. This question cannot be answered by reversing the question, that is, by asking whether the small number of chemicals that are carcinogenic to humans are also carcinogenic in rodent bioassays. The reason for this is that even if most human carcinogens were carcinogenic to experimental animals, the converse does not necessarily follow, as can be demonstrated by a simple probabilistic argument (1).

#### ACKNOWLEDGMENTS

We thank the hundreds of scientists who have assisted us in developing the CPDB over the past 20 years by providing us with additional information on their experiments. We also thank Bruce N Ames and Jerry M Rice for their helpful advice. This work was supported by the National Institute of Environmental Health Sciences through the University of California, Berkeley (UCB) Center Grant ESO1896 and through the E.O. Lawrence Berkeley National Laboratory (LBNL) by an Interagency Agreement (YIES101901) with the U.S. Department of Energy (DOE) DE-AC-03-76SFO0098. Work was also supported by DOE DE-AC-03-76SFO0098 and by the Dean's Office of the College of Letters and Science at UCB for research in disease prevention.

#### REFERENCES

1. Freedman DA, Zeisel H (1988). From mouse to man: the quantitative assessment of cancer risks. *Stat Sci* 3: 3-56.
2. Gold LS, Manley NB, Slone TH, Rohrbach L (1999). Supplement to the Carcinogenic Potency Database (CPDB): Results of animal bioassays published in the general literature in 1993 to 1994 and by the National Toxicology Program in 1995 to 1996. *Environ Health Perspect* 107(Suppl. 4): 527-600.
3. Gold LS, Manley NB, Slone TH, Rohrbach L (in preparation). Supplement to the Carcinogenic Potency Database (CPDB): Results of animal bioassays published in the general literature in 1995 to 1996 and by the National Toxicology Program in 1997 to 1998.
4. Gold LS, Slone TH, Ames BN (1997). Overview of analyses of the carcinogenic potency database. In: *Handbook of Carcinogenic Potency and Genotoxicity Databases* (Gold LS, Zeiger E, eds). CRC Press, Boca Raton, FL, pp 661-685.
5. Gold LS, Slone TH, Ames BN (1998). What do animal cancer tests tell us about human cancer risk? Overview of analyses of the carcinogenic potency database. *Drug Metab Rev* 30: 359-404.
6. Gold LS, Slone TH, Ames BN, Manley NB, Garfinkel GB, Rohrbach L (1997). Carcinogenic Potency Database. In: *Handbook of Carcinogenic Potency and Genotoxicity Databases* (Gold LS, Zeiger E, eds). CRC Press, Boca Raton, FL, pp 1-605.
7. Gold LS, Slone TH, Manley NB, Bernstein L (1991). Target organs in chronic bioassays of 533 chemical carcinogens. *Environ Health Perspect* 93: 233-246.
8. Gold LS, Slone TH, Stern BR, Bernstein L (1993). Comparison of target organs of carcinogenicity for mutagenic and non-mutagenic chemicals. *Mutat Res* 286: 75-100.
9. Haseman JK, Huff JE, Zeiger E, McConnell EE (1987). Comparative results of 327 chemical carcinogenicity studies. *Environ Health Perspect* 74: 229-235.
10. International Agency for Research on Cancer (1971-2001). *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans*, vol 1-78, Suppl. 7. Lyon, France: IARC.
11. Kier LE, Brusick DJ, Auletta AE, Von Halle ES, Brown MM, Simmon VF, Dunkel V, McCann J, Mortelmans K, Prival M, Rao TK, Ray V (1986). The *Salmonella typhimurium*/mammalian microsomal assay: a report of the

- U.S. Environmental Protection Agency Gene-Tox Program. *Mutat Res* 168: 69–240.
12. National Cancer Institute (1976–1980). *Reports of NCI Bioassays of Chemical for Possible Carcinogenicity*. Bethesda, MD: National Cancer Institute.
  13. National Toxicology Program (1980–1998). *Reports of NTP Toxicology and Carcinogenesis Studies of Chemicals in F344/N Rats and B6C3F<sub>1</sub> Mice*. Research Triangle Park, NC: National Toxicology Program.
  14. U.S. National Library of Medicine (2001). Gene-Tox Database; <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?GENETOX>.
  15. Vainio H, Wilbourn J (1993). Cancer etiology: agents causally associated with human cancer. *Pharmacol Toxicol* 72 (Suppl. 1): 4–11.
  16. Vainio H, Wilbourn JD, Sasco AJ, Partensky C, Gaudin N, Heseltine E, Eragne I (1995). Identification des facteurs cancérigènes pour l'homme dans les Monographies du CIRC. *Bull Cancer* 82: 339–348.
  17. Zeiger E (1997). Genotoxicity database. In: *Handbook of Carcinogenic Potency and Genotoxicity Databases* (Gold LS, Zeiger E, eds). CRC Press, Boca Raton, FL, pp 687–729.