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Comparison of target organs of carcinogenicity for mutagenic and non-mutagenic chemicals

Lois Swirsky Gold [a,b], Thomas H. Slone [a,b], Bonnie R. Stern [a] and Leslie Bernstein [c]

[a] *Life Sciences Division, Lawrence Berkeley Laboratory, Berkeley, CA 94720, USA,* [b] *Division of Biochemistry and Molecular Biology, Barker Hall, University of California, Berkeley, CA 94720, USA and* [c] *Department of Preventive Medicine, University of Southern California School of Medicine, Los Angeles, CA 90033, USA*

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Summary

A comparison of target organs for mutagens and non-mutagens is presented for 351 rodent carcinogens in the Carcinogenic Potency Database (CPDB) with mutagenicity evaluations in Salmonella. Results are consistent with the hypotheses that in high-dose rodent tests mitogenesis is important in the carcinogenic response for mutagens and non-mutagens alike, and that mutagens have a multiplicative interaction for carcinogenicity because they can both damage DNA directly and cause cell division at high doses. These hypotheses would lead one to expect several results that are found in the analysis: *First*, a high proportion of both mutagens and non-mutagens induce tumors in rodent bioassays at the MTD. *Second*, mutagens compared to non-mutagens 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 two species. Among carcinogens that induce tumors at multiple sites in both rats and mice, 81% are mutagens; in comparison, among carcinogens that are positive at only a single target site in one species and are negative in the other, 42% are mutagens.

Since tissue distribution and pharmacokinetics would not be expected to differ systematically between mutagens and non-mutagens, one would not expect systematic differences in the particular organs in which tumors are induced. Results do not support the idea that mutagens and non-mutagens induce tumors in different target organs. Both mutagens and non-mutagens induce tumors in a wide variety of sites, and most organs are target sites for both. Moreover, the same sites tend to be the most common sites for both: 79% or more of both mutagenic and non-mutagenic carcinogens are positive in each species in at least one of the 8 most frequent target sites: liver, lung, mammary gland, stomach, vascular system, kidney, hematopoietic system and urinary bladder. Species differences are discussed as well as results for particular target organs: liver, Zymbal's gland and kidney.

Correspondence: Dr. Lois Swirsky Gold, Life Sciences Division, Lawrence Berkeley Laboratory, Berkeley, CA 94720, USA.

A compendium is presented of bioassay results organized by target organ for mutagens and non-mutagens, indicating the name of each chemical that is positive at each site. The compendium can be used to identify chemicals that induce tumors at particular sites, and to determine whether target sites are the same in rats and mice for chemicals positive in both species.

Introduction

In a recent paper we investigated target organs of carcinogenicity in rodent bioassays, and compared the patterns of target organ response in rats and mice (Gold et al., 1991). The analysis was based on our Carcinogenic Potency Database (CPDB), which includes results of long-term carcinogenesis bioassays published in the general literature and Technical Reports of the National Cancer Institute/National Toxicology Program (NCI/NTP) (Gold et al., 1984, 1986, 1987, 1990, in press). In this paper we expand that analysis to investigate whether the target organs of carcinogenicity in each species for chemical carcinogens that are mutagenic differ from those that are non-mutagenic. This analysis is based on the smaller group of rodent carcinogens for which data are available on mutagenicity in the Salmonella assay. Results that have been added to the CPDB since the publication of the previous paper are also included.

A scientific consensus developed in the 1970s that chemical carcinogenesis would be explained by the mutagenic potential of chemicals; however, recent analyses have shown that approximately 45% of the chemicals that are carcinogenic in rodent bioassays are not mutagenic in Salmonella (Gold et al., 1989, in press; Zeiger, 1987). A high proportion of both non-mutagens and mutagens are carcinogenic in rodent bioassays conducted at the maximum tolerated dose (MTD). We have postulated a mechanism for this result: In rodent bioassays, administration of near toxic doses can stimulate cell division (mitogenesis) e.g. by chronic cell killing and consequent cell replacement or by suppression of intercellular communication. Mitogenesis increases rates of mutagenesis and thus carcinogenesis (Ames and Gold, 1990a, b). Three key factors in mutagenesis and carcinogenesis are DNA lesions, cell division, and DNA-repair defense systems. Endogenous rates of DNA damage are enormous (Saul and Ames, 1986). Endogenous mutagens cause extensive DNA damage (oxidative and other lesions) some of which are converted to mutations when the cell divides; an unrepaired DNA lesion has a certain probability of giving rise to a mutation. An important factor in the mutagenic effect of an exogenous agent (whether it is genotoxic or non-genotoxic) is, therefore, the increment it causes over the background cell division rate (mitogenesis) in the stem cells, i.e. in cells which are not on their way to being discarded. Increasing their cell division rate increases mutation and therefore cancer. The effectiveness of a particular DNA lesion depends on whether it is excised by a DNA-repair system, and the probability that it gives rise to a mutation when the cell divides. Thus, cell division rates are important determinants of mutagenesis and carcinogenesis (Ames, Shigenaga and Gold, in press). To the extent that increases in tumor incidence in rodent studies are due to the secondary effects of administering high doses, then *any* chemical that increases mitogenesis, whether mutagenic or not, may be a rodent carcinogen; thus, one would expect that a high proportion of chemicals tested at the MTD would be positive and this is what is found.

Non-mutagenic carcinogens are likely to be acting by this mechanism in high dose rodent tests, since mitogenesis itself indirectly increases mutation (Ames and Gold, 1990a; Ames, Shigenaga and Gold, in press). For mutagens, mitogenesis at the MTD is also important and may be the dominant factor in carcinogenesis. Mutagenic chemicals, because they directly damage DNA, are expected to be more effective than non-mutagens at killing cells at high doses (with consequent cell replacement) and thus more effective at causing mitogenesis. Mutagens, unlike non-mutagens, can damage DNA as well as increase

mitogenesis at high doses, giving a multiplicative interaction for carcinogenesis. This would lead one to expect that the proportion of chemicals that are carcinogenic in rodent studies conducted at the MTD will be high for both mutagens and non-mutagens, and will be even higher for mutagens, as has been found (Ashby and Tennant, 1988; Gold et al., 1989; Zeiger, 1987). Moreover, the multiplicative interaction for mutagens would lead one to expect that mutagens would be more likely to be positive in both rats and mice and more likely to induce tumors in multiple target organs than non-mutagens, as has also been documented (Ashby and Tennant, 1988; Gold et al., 1989; Zeiger, 1987).

The focus of this paper is to describe and evaluate specific target organs of carcinogenicity for mutagens compared to non-mutagens. Tissue distribution and pharmacokinetics of a chemical are crucial factors in determining the particular organ(s) in which tumors are induced. Since one would not expect these factors to differ systematically on the basis of whether chemicals are mutagenic, a priori, target organs would not be expected to differ systematically between mutagens and non-mutagens. Additionally, if mitogenesis is a dominant mechanism for both mutagens and non-mutagens, then one would not expect systematic differences in target organs on the basis of mutagenicity of the chemical. Thus, with respect to the particular sites at which tumors are induced, there do not seem to be any strong theoretical reasons to anticipate systematic differences between mutagenic and non-mutagenic rodent carcinogens.

Ashby and Tennant (1988) concluded that carcinogens that were mutagenic in Salmonella and structurally alerted, induced tumors at 16 target sites that were never target sites for non-genotoxins (i.e. carcinogens that were neither mutagenic nor structurally alerted, with the exception of benzene). Their 1988 analysis was based on 99 carcinogens in NCI/NTP bioassays that were concordant in mutagenicity and structure activity; carcinogens for which structure activity and mutagenicity were not in agreement were deleted from the analysis. In 1991, using an expanded dataset of 142 NCI/NTP carcinogens, Ashby and Tennant reached a different conclusion: only 2 organs were exclusively target sites for structurally active mutagens. In this paper we use a larger dataset to investigate this issue further.

We present a compendium of bioassay results organized by target organ for mutagens and non-mutagens, indicating the name of each chemical that is positive at each site and whether it is positive in both rats and mice when tested in both species. In addition, we compare results for mutagens and non-mutagens with respect to:

(1) The proportion of test agents that are carcinogenic; (2) the proportion of carcinogens that induce tumors at more than one target site within a species; (3) the strength of evidence of carcinogenicity when mutagens and non-mutagens are tested in both rats and mice; (4) the frequency distribution of target organs for mutagens and non-mutagens; and (5) the variety of target-organ responses by species. Finally, we compare our results to those of Ashby and Tennant (Ashby and Tennant, 1988, 1991; Ashby et al., 1989; Tennant and Ashby, 1991).

Methods

In this analysis experimental results are used for 351 chemicals that are positive in rats or mice in the Carcinogenic Potency Database and that have mutagenicity evaluations in Salmonella. The CPDB includes results of chronic exposure animal bioassays that were published either in the general literature through 1988 or in Technical Reports of the National Cancer Institute/National Toxicology Program (NCI/NTP) through June 1989 (Gold et al., 1984, 1986, 1987, 1990, in press). 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, i.v. injection or i.p. injection, and if the length of the experiment in rodents was at least one year with dosing for at least 6 months. For the CPDB, evidence of 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. (See Gold et al., 1984 for further details.)

Mutagenicity. Mutagenicity data were obtained from two sources: the National Institute of Environmental Health Sciences Experimental Carcinogenesis and Mutagenesis Branch (Haworth et al., 1983; Mortelmans et al., 1986; Zeiger, 1987, 1990; Zeiger et al., 1987, 1988, 1992; E. Zeiger, personal communication) and the Environmental Protection Agency Gene-Tox Program (Kier et al., 1986; A.E. Auletta, personal communication). A chemical was classified as mutagenic in the Salmonella assay if it was evaluated as either "mutagenic" or "weakly mutagenic" by NIEHS or as "positive", with or without activation, by the Gene-Tox Program.

Carcinogenicity. A chemical is classified as a rodent carcinogen if it is positive in at least one target organ in one experiment of either rats or mice. A target organ is classified 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 Technical Reports the evidence for carcinogenicity at a site was considered only "associated" with compound administration or in NTP Technical Reports as "equivocal"; 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 (DHHS, Public Health Service, National Institutes of Health et al., 1989). 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 2 target sites in a species, the results may represent 2 different experiments, although this occurs infrequently. We repeat our analyses below using only results in a single experiment to define a target site, and indicate those results as well.

Datasets. Results from 2 datasets are presented below. The majority of analyses presented are based on the 351 rodent chemical carcinogens in the CPDB with results reported for target organs and with mutagenicity evaluations in Salmonella. In the CPDB, 378 chemicals (carcinogens and non-carcinogens) have been tested in both rats and mice and Salmonella. We also present results for this dataset.

More chemicals are included in these analyses than in previous comparisons of mutagenicity and target organ. Of the 351 carcinogens, only 45% were tested by NCI/NTP and thus could have been included in the previous analyses of Ashby and Tennant (Ashby and Tennant, 1988, 1991; Tennant and Ashby, 1991).

Mutagenicity, carcinogenicity and multiple target sites

Among all CPDB chemicals tested for mutagenicity, a high proportion of both mutagens and non-mutagens are carcinogenic, and the proportion is higher for mutagens (75%) than non-mutagens (45%). By species, in the dataset of 351 rodent carcinogens used in this paper 66% (172/259) of rat carcinogens are mutagenic and 60% (130/218) of mouse carcinogens are mutagenic. Table 1 compares the number of target sites per chemical for mutagens and non-mutagens. In both rats and mice, mutagens are more likely to induce tumors in multiple organs than non-mutagens. This effect is stronger in the rat than in the mouse. Although we have defined multiple-site carcinogenesis in this analysis as target sites in any of the experiments on a chemical (multiple site across experiments), the results are similar if multiple-site is defined as 2 or more target organs *within* a single experiment (i.e. if at least one experiment of the chemical has 2 or more target sites).

These two findings (1) the higher proportion of mutagens than non-mutagens among carcinogens in the analysis, and (2) the greater frequency of multiple target sites for mutagens compared to

TABLE 1

COMPARISON OF THE NUMBER OF POSITIVE TARGET ORGANS FOR MUTAGENS AND NON-MUTAGENS BY SPECIES

	Chemicals evaluated as carcinogenic in:							
	Rats				Mice			
	Mutagens		Non-mutagens		Mutagens		Non-mutagens	
No. of Target Organs	N	(%)	N	(%)	N	(%)	N	(%)
1	70	(43)	48	(60)	63	(50)	56	(64)
2	35	(21)	23	(28)	35	(28)	20	(23)
≥3	60	(36)	10	(12)	28	(22)	11	(13)
Total No. of Chemicals	165	(100)	81	(100)	126	(100)	87	(100)

The total number of carcinogens in this table, 246 for rats and 213 for mice, differs from that in Table 3, which has 259 and 218 respectively. This difference is due to the fact that multiple-site carcinogenesis cannot be measured for experiments that restrict histopathological examination or report data for only a few selected tissues. The exclusion of such experiments results in a smaller number of chemicals in this table.

non-mutagens, have important implications for the comparison of target organs for mutagens and non-mutagens. Based on these 2 facts, one would expect that at any given target site more of the carcinogens would be mutagens than non-mutagens.

Strength of evidence of carcinogenicity

Among chemicals that are tested in both rats and mice and positive in at least one species, mutagens are more likely than non-mutagens to be positive in both species (Ashby and Tennant, 1988; Gold et al., 1989, 1991). Thus, we find that the strength of evidence of carcinogenicity is greater for mutagens in 3 ways: a higher proportion of mutagens than non-mutagens are carcinogenic, mutagens more often induce tumors at multiple sites within a species, and mutagens are more often positive in both rats and mice.

Table 2 summarizes the proportion of chemicals that are mutagenic among chemicals with different weights of evidence of carcinogenicity among the 378 chemicals tested for carcinogenicity in both rats and mice and for mutagenicity in Salmonella. Whereas 46% of all chemicals tested are mutagens, the proportion is much greater among chemicals with the strongest evidence of carcinogenicity: 81% of carcinogens that induce tumors at multiple sites in both rats and mice are mutagens; 65% are mutagens among chemicals that are positive in both species but induce tumors at multiple sites in just one species. 42% are mutagenic among chemicals that are positive in only one species and at only a single site; 26% of

[text continues on p. 90]

TABLE 2

PROPORTION OF CHEMICALS THAT ARE MUTAGENIC BY STRENGTH OF EVIDENCE OF CARCINOGENICITY AMONG 378 CHEMICALS TESTED IN BOTH RATS AND MICE

Strength of Evidence	Proportion Mutagenic[a]	
All chemicals	172/378	(46%)
Multiple site in both rats and mice	34/42	(81%)
Multiple site in 1 species, single in other	32/49	(65%)
Single site in both species	18/30	(60%)
Multiple site in 1 species, negative in other	18/36	(50%)
Single site in 1 species, negative in other	31/73	(42%)
Negative in both species	39/148	(26%)

[a]Overall, 230/378 chemicals are carcinogens; among the 230, 133 (58%) are mutagenic.

TABLE 3

CARCINOGENIC RESPONSE BY TARGET ORGAN FOR MUTAGENS AND NON-MUTAGENS TESTED IN RATS OR MICE AND CLASSIFIED AS POSITIVE BY AUTHOR'S OPINION

A chemical is listed under each organ 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, symbols follow 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 five published plots of the Carcinogenic Potency Database (2-6). N = the number of mutagens or non-mutagens with at least one positive test at that site in that species.

Tissue	Species	Mutagenicity	N	Chemical names
Adrenal gland	Mouse	+	2	4,4′-methylenedianiline.2*HCl*‡; *p*-rosaniline.*HCl*‡
		–	4	carbon tetrachloride‡; 2,3,4,5,6-pentachlorophenol (Dowicide EC-7); 2,3,4,5,6-pentachlorophenol, technical grade; 1,1,2-trichloroethane†
	Rat	+	4	bromoethane‡; 4-chloro-*m*-phenylenediamine‡; 1,2-dibromo-3-chloropropane‡,[a]; 1,2-propylene oxide‡
		–	5	acrylamide; diethylstilbestrol‡,[a]; ethyl alcohol; 2-mercaptobenzothiazole†; reserpine‡
Bone	Rat	+	2	1-(2-hydroxyethyl)-1-nitrosourea; *o*-toluidine.*HCl*‡
		–	1	*N,N*-dimethylaniline†
Central nervous system	Mouse	+	1	*N*-nitrosodimethylamine‡
		–	1	procarbazine.*HCl*‡
	Rat	+	10	acrylonitrile; bromoethane‡; chlorambucil‡; cyclophosphamide‡; 1-ethyl-1-nitrosourea; ethylene oxide‡; *N*-nitrosodiethanolamine; 1-phenyl-3,3-dimethyltriazene; propane sultone; vinyl chloride‡
		–	2	acrylamide; procarbazine.*HCl*‡
Clitoral gland	Mouse	–	1	acetaldehyde methylformylhydrazone
	Rat	+	4	2,4-diaminoanisole sulfate‡; 1,5-naphthalenediamine‡; 5-nitro-*o*-anisidine‡; 5-nitroacenaphthene‡
		–	1	nalidixic acid†
Ear/Zymbal's gland	Mouse	+	1	cupferron‡
		–	1	benzene‡
	Rat	+	19	acrylonitrile; 3-amino-9-ethylcarbazole mixture‡; azoxymethane; *N-N*-butyl-*N*-nitrosourea; chlorambucil‡; cupferron‡; 2,4-diaminoanisole sulfate‡; 3,3′-dichlorobenzidine; formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl]hydrazide‡; hydrazobenzene‡; 8-methoxypsoralen; 4,4′-methylene-bis(2-chloroaniline); 5-nitro-*o*-anisidine‡; 5-nitroacenaphthene‡; phenacetin‡; *p*-rosaniline.*HCl*‡; thio-TEPA‡; 4,4′-thiodianiline‡; vinyl chloride‡
		–	1	benzene‡
Esophagus	Mouse	+	5	benzo(*a*)pyrene‡; 1,2-dibromoethane‡; *N*-hydroxy-2-acetylaminofluorene‡; nitrosodibutylamine‡; *N*-nitrosohexamethyleneimine
	Rat	+	11	*N-N*-butyl-*N*-nitrosourea; dimethylvinyl chloride‡; dinitrosohomopiperazine; *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine; nitroso-1,2,3,6-tetrahydropyridine; *N*-nitrosodiethanolamine; *N*-nitrosodiethylamine; *N*-nitrosodipropylamine; nitrosoheptamethyleneimine; 2-nitrosomethylaminopyridine; *N*-nitrosothiomorpholine
		-	1	dihydrosafrole‡

TABLE 3 (continued)

Tissue	Species	Mutagenicity	N	Chemical names
Harderian gland	Mouse	+	4	benzidine.2*HCl*; cupferron[‡]; ethylene oxide[‡]; 4,4′-oxydianiline[‡]
		–	3	benzene[‡]; gentian violet; *N*-methylolacrylamide[†]
Hematopoietic system	Mouse	+	18	2-aminoanthraquinone[‡]; 5-azacytidine[‡]; 1,3-butadiene[‡]; chlorambucil[‡]; cyclophosphamide[‡]; dacarbazine[‡]; dibromodulcitol[‡]; dibromomannitol[‡]; ethylene oxide[‡]; formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl]hydrazide[‡]; isophosphamide[‡]; melphalan[‡]; methyl methanesulfonate; 4,4′-methylenedianiline.2*HCl*[‡]; metronidazole[‡]; *N*-[4-(5-nitro-2-furyl)-2-thiazolyl] formamide[‡]; thio-TEPA[‡]; urethane
		–	11	acetamide[‡]; allyl isovalerate[‡]; benzene[‡]; chlorinated paraffins (*C*23, 43% chlorine)[†]; DDT[‡]; gentian violet; hexanamide[†]; phenesterin[‡]; procarbazine.*HCl*[‡]; *p*-tolylurea[†]; C.I. Vat Yellow 4[†]
	Rat	+	19	benzidine; *N*-*N*-butyl-*N*-nitrosourea; chlorambucil[‡]; cyclophosphamide[‡]; dacarbazine[‡]; 3,3′-dichlorobenzidine; dichlorvos[‡]; 3,3′-dimethoxybenzidine-4,4′-diisocyanate[†]; 2-(2,2-dimethylhydrazino)-4-(5-nitro-2-furyl)thiazole; ethylene oxide[‡]; formaldehyde[‡]; formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl]hydrazide[‡]; 1-(2-hydroxyethyl)-1-nitrosourea; lasiocarpine; nitrite, sodium[†]; *N*-[5-(5-nitro-2-furyl)-1,3,4-thiadiazol-2-yl]acetamide[‡]; *N*-nitrosodiethanolamine; propane sultone; thio-TEPA[‡]
		–	11	allyl isovalerate[‡]; dimethyl morpholinophosphoramidate[†]; FD & C Green No. 2[†]; hematoxylin; hydroquinone[‡]; 2-mercaptobenzothiazole[†]; procarbazine.*HCl*[‡]; FD & C Red No. 2; FD & C Red No. 4[†]; tetrachloroethylene[‡]; 2,4,6-trichlorophenol[‡]
Kidney/ureter	Mouse	+	6	bromodichloromethane[‡]; *N*-hydroxy-2-acetylaminofluorene[‡]; phenacetin[‡]; streptozotocin[‡]; tris(2,3-dibromopropyl)phosphate[‡]; vinylidene chloride[†]
		–	4	chloroform[‡]; daminozide[‡]; nitrilotriacetic acid[‡]; ochratoxin A[‡]
	Rat	+	20	aflatoxin B_1[†]; 1-amino-2-methylanthraquinone[‡]; 2-amino-4-nitrophenol[†]; 2-amino-5-nitrothiazole[†]; *o*-anisidine.*HCl*[‡]; azoxymethane; bromate, potassium[†]; bromodichloromethane[‡]; formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl]hydrazide[‡]; 8-methoxypsoralen; *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-[(5-nitrofurfurylidene)amino]hydantoin[‡]; *N*-nitrosodiethanolamine; *N*-nitrosodimethylamine[‡]; C.I. Acid Orange 3[†]; phenacetin[‡]; streptozotocin[‡]; tris(2,3-dibromopropyl) phosphate[‡]; vinyl chloride[‡]
		–	20	benzofuran[‡]; chlorinated paraffins (*C*12, 60% chlorine)[‡]; chloroform[‡]; 3-(*p*-chlorophenyl)-1,1-dimethylurea[†]; chlorothalonil[†]; cinnamyl anthranilate[‡]; citrinin; 1,4-dichlorobenzene[‡]; dimethyl methylphosphonate[†]; hexachlorobutadiene; hexachloroethane[‡]; hydroquinone[‡]; isophorone[†]; lead acetate[†]; nitrilotriacetic acid[‡]; nitrilotriacetic acid, trisodium salt, monohydrate[†]; ochratoxin A[‡]; phenazone; *o*-phenylphenate, sodium[†]; tetrachloroethylene[‡]
Large intestine	Rat	+	8	aflatoxin B_1[†]; azoxymethane; bromodichloromethane[‡]; formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl]hydrazide[‡]; 1-(2-hydroxyethyl)-1-nitrosourea; 4,4′-thiodianiline[‡]; tribromomethane[†]; tris(2,3-dibromopropyl)phosphate[‡]
		–	1	phenazopyridine.*HCl*[‡]

TABLE 3 (*continued*)

Tissue	Species	Mutagenicity	N	Chemical names
Liver	Mouse	+	70	2-acetylaminofluorene‡; 3-amino-9-ethylcarbazole mixture‡; 3-amino-1-methyl-5*H*-pyrido [4,3-*b*]indole acetate‡; 1-amino-2-methylanthraquinone‡; 2-aminoanthraquinone‡; 4-aminodiphenyl; 4-aminodiphenyl.*HCl*‡; auramine-*O*‡; benzidine.2*HCl*; bis(2-chloro-1-methylethyl)ether†; bis-2-chloroethylether; HC Blue No. 1‡; bromodichloromethane‡; 1,3-butadiene‡; chloramben†; chlordane†; 1-chloro-2-nitrobenzene‡; 1-chloro-4-nitrobenzene†; 4-chloro-*m*-phenylenediamine‡; 4-chloro-*o*-phenylenediamine‡; *p*-cresidine‡; cupferron‡; diallate; 2,4-diaminotoluene‡; 2,6-dichloro-*p*-phenylenediamine†; 1,2-dichloropropane†; 1,1-dimethylhydrazine; ethylene imine; ethylene thiourea‡; hydrazine sulfate‡; hydrazobenzene‡; *N*-hydroxy-2-acetylaminofluorene‡; 2-hydroxyethylhydrazine; isoniazid‡; 3-methoxy-4-aminoazobenzene; methylene chloride‡; 4,4′-methylenebis(*N*,*N*-dimethyl)benzenamine‡; 4,4′-methylenedianiline.2*HCl*‡; methylhydrazine; Michler's ketone‡; 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†; 4,4′-oxydianiline‡; phenobarbital†; D & C Red No. 5‡; *p*-rosaniline.*HCl*‡; selenium sulfide‡; 4,4′-thiodianiline‡; toluene diisocyanate, commercial grade (2,4 (80%)- and 2,6 (20%)-)‡; *o*-toluidine.*HCl*‡; *p*-toluidine.*HCl*†; toxaphene†; trifluralin, technical grade†; 2,4,5-trimethylaniline‡; tris(2,3-dibromopropyl)phosphate‡; urethane; C.I. Disperse Yellow 3‡
		–	67	acetaminophen‡; aldrin†; 3-aminotriazole‡; aroclor 1254†; benzofuran‡; benzyl acetate†; butylated hydroxytoluene†; captafol; carbazole; carbon tetrachloride‡; chlorendic acid‡; chlorinated paraffins (*C*12, 60% chlorine)‡; 5-chloro-*o*-toluidine†; chlorobenzilate†; chlorodibromomethane†; chloroform‡; cinnamyl anthranilate‡; *p,p′*-DDD†; *p,p′*-DDE†; DDT‡; 1,4-dichlorobenzene‡; dicofol†; dieldrin†; dihydrosafrole‡; 1,4-dioxane‡; estragole; dl-ethionine‡; di(2-ethylhexyl)adipate†; di(2-ethylhexyl)phthalate‡; gentian violet; griseofulvin; heptachlor†; hexachlorobenzene‡; β-1,2,3,4,5,6-hexachlorocyclohexane; γ-1,2,3,4,5,6-hexachlorocyclohexane†; hexachloroethane‡; hydroquinone‡; 1′-hydroxyestragole; 1′-hydroxysafrole‡; kepone‡; luteoskyrin; malonaldehyde, sodium salt‡; *N*-methylolacrylamide†; mirex†; ochratoxin A‡; pentachloroethane†; pentachloronitrobenzene†; 2,3,4,5,6-pentachlorophenol (Dowicide EC-7); 2,3,4,5,6-pentachlorophenol, technical grade; phenazopyridine.*HCl*‡; phenobarbital, sodium‡; piperonyl sulfoxide†; safrole‡; 2,3,7,8-tetrachlorodibenzo-*p*-dioxin†; 1,1,1,2-tetrachloroethane†; 1,1,2,2-tetrachloroethane†; tetrachloroethylene‡; tetrachlorvinphos†; thioacetamide‡; *m*-toluidine.*HCl*†; 2,4,6-trichloroaniline†; 1,1,2-trichloroethane†; trichloroethylene‡; trichloroethylene (without epichlorohydrin)†; 2,4,6-trichlorophenol‡; tris(2-ethylhexyl)phosphate†; zearalenone†
	Rat	+	61	2-acetylaminofluorene‡; aflatoxicol; aflatoxin B_1†; 3-amino-9-ethylcarbazole mixture‡; 3-amino-1-methyl-5*H*-pyrido[4,3-*b*]indole acetate‡; 1-amino-2-methylanthraquinone‡; 2-aminoanthraquinone‡; *o*-aminoazotoluene†; auramine-*O*‡; azoxymethane; benzidine; bromodichloromethane‡; *p*-cresidine‡; cupferron‡; 2,4-diaminotoluene‡; 1,2-dibromoethane‡; *N*,*N*-dimethyl-4-aminoazobenzene; dinitrosohomopiperazine; dinitrotoluene, technical grade (2,4 (77%)- and 2,6 (19%)-); ethylene thiourea‡; formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl]hydrazide‡; hydrazine sulfate‡; hydrazobenzene‡; *N*-hydroxy-2-acetylaminofluorene‡; isoniazid‡; lasiocarpine; 3′-methyl-4-dimethylaminoazobenzene; 2-methyl-1-nitroanthraquinone‡; 4,4′-methylene-bis(2-chloroaniline); 4,4′-methylene-bis(2-methylaniline); 4,4′-methylenedianiline.2*HCl*‡; metronidazole‡; Michler's ketone‡; nitrite, sodium†; 1-nitroso-5,6-dihydrouracil; *N*-nitroso-*N*-methyl-*N*-dodecylamine; nitroso-1,2,3,6-tetrahydropyridine; nitrosodibutylamine‡; *N*-nitrosodiethanolamine; *N*-nitrosodiethylamine; *N*-nitrosodimethylamine‡; *p*-nitrosodiphenylamine‡; *N*-nitrosodipropylamine; nitrosododecamethyleneimine; nitrosoethylmethylamine; nitrosoheptamethyleneimine; *N*-nitrosomorpholine; *N*-nitrosopyrrolidine; 4,4′-oxydianiline‡; 1-phenylazo-2-naphthol†; D & C Red No. 5‡; D & C Red No. 9†; *p*-rosaniline.*HCl*‡; selenium sulfide‡; sterigmatocystin‡; Telone II‡; 4,4′-thiodianiline‡; toluene diisocyanate, commercial grade (2,4 (80%)- and 2,6 (20%)-)‡; 2,4,5-trimethylaniline‡; vinyl chloride‡; C.I. Disperse Yellow 3‡

TABLE 3 (continued)

Tissue	Species	Mutagenicity	N	Chemical names
		–	28	acetamide‡; acetaminophen‡; 11-aminoundecanoic acid†; carbon tetrachloride‡; chlorendic acid‡; chlorinated paraffins (*C*12, 60% chlorine)‡; chlorobenzene†; chloroform‡; 3-(*p*-chlorophenyl)-1,1-dimethylurea†; DDT‡; decabromodiphenyl oxide†; 1,4-dioxane‡; ethionine; dl-ethionine‡; ethyl alcohol; di(2-ethylhexyl)phthalate‡; hexachlorobenzene‡; 1′-hydroxysafrole‡; kepone‡; methapyrilene.*HCl*; methyl carbamate†; monocrotaline; phenobarbital, sodium‡; FD & C Red No. 1; safrole‡; 2,3,7,8-tetrachlorodibenzo-*p*-dioxin‡; thioacetamide‡; vinyl acetate
Lung	Mouse	+	39	5-azacytidine‡; bis(2-chloro-1-methylethyl)ether†; 1,3-butadiene‡; chlorambucil‡; cyclophosphamide‡; dacarbazine‡; dibenz(*a,h*)anthracene; 1,2-dibromo-3-chloropropane‡; dibromodulcitol‡; 1,2-dibromoethane‡; dibromomannitol‡; 1,2-dichloroethane‡; 1,1-dimethylhydrazine; 1,2-dimethylhydrazine.2*HCl*; ethylene imine; ethylene oxide‡; hydrazine†; hydrazine sulfate‡; isoniazid‡; melphalan‡; methyl methanesulfonate; methylene chloride‡; methylhydrazine; metronidazole‡; 1,5-naphthalenediamine‡; *N*-[4-(5-nitro-2-furyl)-2-thiazolyl] formamide‡; nitrosodibutylamine‡; *N*-nitrosodimethylamine‡; *N*-nitrosopiperidine†; phenylethylhydrazine sulfate; selenium sulfide‡; streptozotocin‡; sulfallate‡; Telone II‡; trifluralin, technical grade†; tris(2,3-dibromopropyl)phosphate‡; urethane; vinyl chloride‡; vinylidene chloride†
		–	13	acetaldehyde methylformylhydrazone; benzene‡; benzofuran‡; butylated hydroxytoluene†; carbamyl hydrazine.*HCl*; daminozide‡; *p,p′*-DDD†; dihydrosafrole‡; γ-1,2,3,4,5,6-hexachlorocyclohexane†; *N*-methylolacrylamide†; phenesterin‡; procarbazine.*HCl*‡; trichloroethylene‡
	Rat	+	21	2-amino-5-nitrothiazole†; HC Blue No. 1‡; bromoethane‡; 1,2-dibromoethane‡; dimethyl hydrogen phosphite†; trans-2-[(dimethylamino)methylimino]-5-[2-(5-nitro-2-furyl)vinyl]-1,3,4-oxadiazole; 1,2-epoxybutane†; 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‡; 5-nitroacenaphthene‡; *N*-nitroso-*N*-methyl-*N*-dodecylamine; nitrosodibutylamine‡; *N*-nitrosodimethylamine‡; nitrosoethylmethylamine; 2,4,5-trimethylaniline‡; vinyl chloride‡
		–	2	cadmium chloride; 2,3,7,8-tetrachlorodibenzo-*p*-dioxin‡
Mammary gland	Mouse	+	9	5-azacytidine‡; 1,3-butadiene‡; 1,2-dibromoethane‡; 1,2-dichloroethane‡; ethylene oxide‡; isoniazid‡; sulfallate‡; vinyl chloride‡; vinylidene chloride†
		–	5	benzene‡; diethylstilbestrol‡; estradiol; furosemide†; reserpine‡
	Rat	+	48	2-acetylaminofluorene‡; acrylonitrile; AF-2‡; 2-amino-5-nitrothiazole†; 4-aminodiphenyl.*HCl*‡; benzidine; 1,3-butadiene‡; chlorambucil‡; cytembena†; dacarbazine‡; 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‡; 3,3′-dichlorobenzidine; 1,2-dichloroethane‡; 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; formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl]hydrazide‡; hydrazobenzene‡; 1-(2-hydroxyethyl)-3-[(5-nitrofurfurylidene) amino]-2-imidazolidinone; 1-(2-hydroxyethyl)-1-nitrosourea; isoniazid‡; 4-methyl-1-[(5-nitrofurfurylidene)amino]-2- imidazolidinone; 3-methylcholanthrene; 4,4′-methylene-bis(2-chloroaniline); 4,4′-methylene-bis(2-methylaniline); methylene chloride‡; metronidazole‡; nithiazide‡; 5-nitro-2-furaldehyde semicarbazone‡; 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‡; phenacetin‡; propane sultone; 1,2-propylene oxide‡; styrene†; sulfallate‡; 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†
		–	6	acrylamide; carbon tetrachloride‡; carboxymethylnitrosourea; ochratoxin A‡; phenesterin‡; procarbazine.*HCl*‡
Myocardium	Mouse	–	1	phenesterin‡
Nasal cavity[b]	Mouse	+	4	1,2-dibromo-3-chloropropane‡; 1,2-dibromoethane‡; formaldehyde‡; 1,2-propylene oxide‡

TABLE 3 (continued)

Tissue	Species	Mutagenicity	N	Chemical names
	Rat	+	17	acrylonitrile; *p*-cresidine[‡]; 1,2-dibromo-3-chloropropane[‡]; 1,2-dibromoethane[‡]; dimethylvinyl chloride[‡]; dinitrosohomopiperazine; 1,2-epoxybutane[†]; ethylnitrosocyanamide; formaldehyde[‡]; hydrazine[‡]; *N*-nitrosodiethanolamine; *N*-nitrosodipropylamine; nitrosoethylmethylamine; phenacetin[‡]; phenylglycidyl ether; 1,2-propylene oxide[‡]; vinyl chloride[‡]
		–	3	acetaldehyde; benzene[‡]; 1,4-dioxane[‡]
Oral cavity[c]	Mouse	+	1	*N*-nitrosohexamethyleneimine
	Rat	+	8	acrylonitrile; 1,2-dibromo-3-chloropropane[‡]; dimethylvinyl chloride[‡]; dinitrosohomopiperazine; *N*-nitrosodiethylamine; nitrosoheptamethyleneimine; 1-nitrosohydantoin; *N*-nitrosothiomorpholine
		–	3	acrylamide; benzene[‡]; 2,3,7,8-tetrachlorodibenzo-*p*-dioxin[‡]
Ovary	Mouse	+	4	1,3-butadiene[‡]; 5-nitro-2-furaldehyde semicarbazone[‡]; 5-nitroacenaphthene[‡]; 1-[(5-nitrofurfurylidene)amino]hydantoin[‡]
		–	3	benzene[‡]; *N*-methylolacrylamide[†]; 4-vinylcyclohexene
Pancreas	Rat	+	5	2-amino-5-nitrophenol[†]; azaserine; dichlorvos[‡]; nitrofen[‡]; toluene diisocyanate, commercial grade (2,4 (80%)- and 2,6 (20%)-)[‡,d]
		–	5	chlorendic acid[‡]; cinnamyl anthranilate[‡]; ethyl alcohol; malonaldehyde, sodium salt[‡,d]; 2-mercaptobenzothiazole[†]
Peritoneal cavity[c]	Mouse	+	2	dimethylcarbamyl chloride; phenoxybenzamine.*HCl*[‡]
	Rat	+	10	bromate, potassium[†]; chlorozotocin; cytembena[†]; 1,2-dibromoethane[‡]; dibromomannitol[‡]; ethylene oxide[‡]; melphalan[‡]; mitomycin-C; phenoxybenzamine.*HCl*[‡]; *o*-toluidine.*HCl*[‡]
		–	4	acrylamide; actinomycin D; aniline.*HCl*[†]; dapsone[†]
Pituitary gland	Mouse	–	1	zearalenone[†]
	Rat	+	2	1,2-dibromoethane[‡]; metronidazole[‡]
		–	5	acrylamide; 3-aminotriazole[‡]; diethylstilbestrol[‡]; ethyl alcohol; 2-mercaptobenzothiazole[†]
Preputial gland	Mouse	+	2	dimethylvinyl chloride[‡]; thio-TEPA[‡]
		–	2	acetaldehyde methylformylhydrazone; benzene[‡]
	Rat	+	1	2,4-diaminoanisole sulfate[‡]
		–	3	isophorone[†]; 2-mercaptobenzothiazole[†]; nalidixic acid[†]
Skin	Mouse	+	2	5-azacytidine[‡]; thio-TEPA[‡]
	Rat	+	13	2-acetylaminofluorene[‡]; 3-amino-9-ethylcarbazole mixture[‡]; 2,4-diaminoanisole sulfate[‡]; dibromodulcitol[‡]; dibromomannitol[‡]; 3,3'-dimethoxybenzidine-4,4'-diisocyanate[†]; dimethylvinyl chloride[‡]; lasiocarpine; 5-nitro-*o*-anisidine[‡]; *p*-rosaniline.*HCl*[‡]; thio-TEPA[‡]; vinyl chloride[‡]; FD & C Violet No. 1[†]
		–	3	benzene[‡]; carboxymethylnitrosourea; thiourea[†]
Small intestine	Mouse	+	1	hydrogen peroxide
		–	1	captafol
	Rat	+	11	acrylonitrile; 3-amino-1-methyl-5*H*-pyrido[4,3-*b*]indole acetate[‡]; trans-2-[(dimethylamino) methylimino]-5-[2-(5-nitro-2-furyl)vinyl]-1,3,4-oxadiazole; 1-ethyl-1-nitrosourea; formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl] hydrazide[‡]; lasiocarpine; *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine; *N*-[5-(5-nitro-2-furyl)-1,3,4-thiadiazol-2-yl] acetamide[‡]; nitrosoethylurethan; propane sultone; quercetin[†]
		–	1	carboxymethylnitrosourea

TABLE 3 (continued)

Tissue	Species	Mutagenicity	N	Chemical names
Spleen	Rat	+	3	azobenzene†; D & C Red No. 9†; *o*-toluidine.*HCl*‡
		–	2	aniline.*HCl*†; dapsone†
Stomach	Mouse	+	25	AF-2‡; 2-amino-4-(5-nitro-2-furyl)thiazole‡; benzyl chloride†; 1,3-butadiene‡; 3-chloro-2-methylpropene, technical grade (containing 5% dimethylvinyl chloride)‡; 3-(chloromethyl)pyridine.*HCl*‡; 1,2-dibromo-3-chloropropane‡; 1,2-dibromoethane‡; dichlorvos‡; diglycidyl resorcinol ether, technical grade‡; dimethylvinyl chloride‡; dinitrosopiperazine; formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl]hydrazide‡; *N*-hydroxy-2-acetylaminofluorene‡; *N*-[5-(5-nitro-2-furyl)-1,3,4-thiadiazol-2-yl]acetamide‡; *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide‡; nitrosodibutylamine‡; *N*-nitrosohexamethyleneimine; *N*-nitrosopiperidine†; β-propiolactone‡; styrene oxide‡; Telone II‡; 2,2,2-trifluoro-*N*-[4-(5-nitro-2-furyl)-2-thiazolyl]acetamide‡; trifluralin, technical grade†; tris(2,3-dibromopropyl) phosphate‡
		–	6	acetaldehyde methylformylhydrazone; benzofuran‡; benzyl acetate†; captafol; carbazole; ethyl acrylate‡
	Rat	+	39	1′-acetoxysafrole†; acrylonitrile; 2-amino-4-(5-nitro-2-furyl)thiazole‡; benzo(*a*)pyrene‡; *N*-*N*-butyl-*N*-nitrosourea; 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‡; dimethyl hydrogen phosphite†; trans-2-[(dimethylamino)methylimino]-5-[2-(5-nitro-2-furyl)vinyl]-1,3,4-oxadiazole; dimethylvinyl chloride‡; epichlorohydrin†; ethylene oxide‡; 1-(2-hydroxyethyl)-1-nitrosourea; *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine; *N*-methyl-*N*-nitrosobenzamide; methylnitrosocyanamide; *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-*N*-methyl-*N*-dodecylamine; nitroso-1,2,3,6-tetrahydropyridine; nitrosodibutylamine‡; *N*-nitrosodiethylamine; nitrosoethylurethan; phenacetin‡; pivalolactone†; β-propiolactone‡; *N*-propyl-*N*′-nitro-*N*-nitrosoguanidine; 1,2-propylene oxide‡; styrene oxide‡; sulfallate‡; Telone II‡
		–	6	benzene‡; butylated hydroxyanisole; catechol; ethyl acrylate‡; 1′-hydroxysafrole‡; 1-nitroso-3,5-dimethyl-4-benzoylpiperazine
Subcutaneous tissue	Mouse	+	1	1,2-dibromoethane‡
	Rat	+	5	1,2-dichloroethane‡; 4,4′-methylene-bis(2-methylaniline); *p*-rosaniline.*HCl*‡; toluene diisocyanate, commercial grade (2,4 (80%)- and 2,6 (20%)-)‡; *o*-toluidine.*HCl*‡
Testes	Mouse	–	1	reserpine‡
	Rat	+	6	5-azacytidine‡; 1,3-butadiene‡; *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine; metronidazole‡; *N*-nitrosodimethylamine‡; vinyl chloride‡
		–	2	2-chloro-1,1,1-trifluoroethane; trichloroethylene‡
Thyroid gland	Mouse	+	7	3-amino-4-ethoxyacetanilide†; HC Blue No. 1‡; 2,4-diaminoanisole sulfate‡; 4,4′-methylenedianiline.2*HCl*‡; 1,5-naphthalenediamine‡; 4,4′-oxydianiline‡; 4,4′-thiodianiline‡
		–	3	chlorinated paraffins (*C*12, 60% chlorine)‡; ethionamide†; 2,3,7,8-tetrachlorodibenzo-*p*-dioxin‡
	Rat	+	10	*o*-anisidine.*HCl*‡; 2,4-diaminoanisole sulfate‡; 1-ethyl-1-nitrosourea; ethylene thiourea‡; 4,4′-methylenebis(*N*,*N*-dimethyl)benzenamine‡; 4,4′-methylenedianiline.2*HCl*‡; 4,4′-oxydianiline‡; *p*-rosaniline.*HCl*‡; 4,4′-thiodianiline‡; zinc dimethyldithiocarbamate†
		–	8	3-aminotriazole‡; chlorinated paraffins (*C*12, 60% chlorine)‡; *N*,*N*′-diethylthiourea†; malonaldehyde, sodium salt‡; methimazole; 2,3,7,8-tetrachlorodibenzo-*p*-dioxin‡; trimethylthiourea†; vinyl acetate
Urinary bladder/ urethra	Mouse	+	9	2-acetylaminofluorene‡; 4-aminodiphenyl; 4-aminodiphenyl.*HCl*‡; *o*-anisidine.*HCl*‡; *p*-cresidine‡; *N*-hydroxy-2-acetylaminofluorene‡; *N*-[4-(5-nitro-2-furyl)-2-thiazolyl] formamide‡; phenacetin‡; Telone II‡

TABLE 3 (continued)

Tissue	Species	Mutagenicity	N	Chemical names
	Rat	+	21	allyl isothiocyanate†; 2-amino-4-(5-nitro-2-furyl)thiazole‡; 4-amino-2-nitrophenol†; *o*-anisidine.*HCl*‡; C.I. Disperse Blue 1†; *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine; 4-chloro-*o*-phenylenediamine‡; *m*-cresidine†; *p*-cresidine‡; cyclophosphamide‡; 2-naphthylamine‡; *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide‡; *N*-nitroso-*N*-methyl-*N*-dodecylamine; nitrosodibutylamine‡; *N*-nitrosodiethylamine; *N*-nitrosopyrrolidine; phenacetin‡; *o*-phenylphenol†; quercetin†; *p*-quinone dioxime†; *o*-toluidine.*HCl*‡
		–	11	acetaminophen‡; 11-aminoundecanoic acid†; diethylene glycol; melamine†; nitrilotriacetic acid‡; nitrilotriacetic acid, trisodium salt, monohydrate†; *N*-nitrosodiphenylamine†; phenazone; *o*-phenylphenate, sodium†; saccharin, sodium†; *o*-toluenesulfonamide
Uterus	Mouse	+	6	bromoethane‡; chloroethane†; dacarbazine‡; 1,2-dichloroethane‡; ethylene oxide‡; trimethylphosphate†
		–	1	procarbazine.*HCl*‡
	Rat	+	6	3-amino-9-ethylcarbazole mixture‡; dacarbazine‡; 3,3′-dimethoxybenzidine-4,4′-diisocyanate†; isophosphamide‡; 1,5-naphthalenediamine‡; 4,4′-thiodianiline‡
		–	3	2-chloro-1,1,1-trifluoroethane; daminozide‡: vinyl acetate
Vagina	Rat	+	1	*N*-*N*-butyl-*N*-nitrosourea
Vascular system	Mouse	+	23	1-acetyl-2-phenylhydrazine; 4-aminodiphenyl.*HCl*‡; benzidine.2*HCl*; 2-biphenylamine.*HCl*‡; 1,3-butadiene‡; 1-chloro-4-nitrobenzene†; cupferron‡; dacarbazine‡; 1,2-dibromoethane‡; 7,12-dimethylbenz(*a*)anthracene; 1,1-dimethylhydrazine; 1,2-dimethylhydrazine.2*HCl*; 2-methyl-1-nitroanthraquinone‡; Michler's ketone‡; 5-nitro-*o*-toluidine†; nitrofen‡; phenylethylhydrazine sulfate; phenylhydrazine.*HCl*; sterigmatocystin‡; toluene diisocyanate, commercial grade (2,4 (80%)- and 2,6 (20%))-‡; *o*-toluidine.*HCl*‡; vinyl chloride‡; vinylidene chloride†,[f]
		–	9	captafol; carbamyl hydrazine.*HCl*; 5-chloro-*o*-toluidine†; 4-chloro-*o*-toluidine.*HCl*‡; daminozide‡; 1′-hydroxysafrole‡; 2,3,4,5,6-pentachlorophenol (Dowicide EC-7); 2,3,4,5,6-pentachlorophenol, technical grade; 2,4,6-trichloroaniline†
	Rat	+	15	3-amino-1-methyl-5*H*-pyrido[4,3-*b*]indole acetate‡; azobenzene†; cupferron‡; 1,2-dibromoethane‡; 1,2-dichloroethane‡; lasiocarpine; 4,4′-methylene-bis(2-chloroaniline); *N*-[5-(5-nitro-2-furyl)-1,3,4-thiadiazol-2-yl]acetamide‡; nitroso-1,2,3,6-tetrahydropyridine; *N*-nitrosodimethylamine‡; *N*-nitrosomorpholine[f]; *N*-nitrosopyrrolidine; sterigmatocystin‡; *o*-toluidine.*HCl*‡; vinyl chloride‡
		–	2	aniline.*HCl*†; benzene‡,[f]

†Adequately tested in both mice and rats, but positive in only one of them.
‡Positive in both rats and mice.
[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 by these chemicals.
[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.

APPENDIX TABLE 3

LIST OF 351 CHEMICALS IN TABLE 3

Chemical name	CAS number	Mutagenicity
Acetaldehyde	75-07-0	–
Acetaldehyde methylformylhydrazone	16568-02-8	–
Acetamide	60-35-5	–
Acetaminophen	103-90-2	–
1′-Acetoxysafrole	34627-78-6	+
1-Acetyl-2-phenylhydrazine	114-83-0	+
2-Acetylaminofluorene	53-96-3	+
Acrylamide	79-06-1	–
Acrylonitrile	107-13-1	+
Actinomycin D	50-76-0	–
AF-2	3688-53-7	+
Aflatoxicol	29611-03-8	+
Aflatoxin B_1	1162-65-8	+
Aldrin	309-00-2	–
Allyl isothiocyanate	57-06-7	+
Allyl isovalerate	2835-39-4	–
3-Amino-4-ethoxyacetanilide	17026-81-2	+
3-Amino-9-ethylcarbazole mixture	mixture	+
3-Amino-1-methyl-5h-pyrido[4,3-*b*] indole acetate	72254-58-1	+
1-Amino-2-methylanthraquinone	82-28-0	+
2-Amino-4-(5-nitro-2-furyl)thiazole	38514-71-5	+
2-Amino-4-nitrophenol	99-57-0	+
2-Amino-5-nitrophenol	121-88-0	+
4-Amino-2-nitrophenol	119-34-6	+
2-Amino-5-nitrothiazole	121-66-4	+
2-Aminoanthraquinone	117-79-3	+
o-Aminoazotoluene	97-56-3	+
4-Aminodiphenyl	92-67-1	+
4-Aminodiphenyl.*HCl*	2113-61-3	+
3-Aminotriazole	61-82-5	–
11-Aminoundecanoic acid	2432-99-7	–
Aniline.*HCl*	142-04-1	–
o-Anisidine.*HCl*	134-29-2	+
Aroclor 1254	27323-18-8	–
Auramine-*O*	2465-27-2	+
5-Azacytidine	320-67-2	+
Azaserine	115-02-6	+
Azobenzene	103-33-3	+
Azoxymethane	25843-45-2	+
Benzene	71-43-2	–
Benzidine	92-87-5	+
Benzidine.2*HCl*	531-85-1	+
Benzo(*a*)pyrene	50-32-8	+
Benzofuran	271-89-6	–
Benzyl acetate	140-11-4	–
Benzyl chloride	100-44-7	+
2-Biphenylamine.*HCl*	2185-92-4	+
Bis(2-chloro-1-methylethyl)ether	108-60-1	+
Bis-2-chloroethylether	111-44-4	+
C.I. Disperse Blue 1	2475-45-8	+
HC Blue No. 1	2784-94-3	+
Bromate, potassium	7758-01-2	+
Bromodichloromethane	75-27-4	+
Bromoethane	74-96-4	+
1,3-Butadiene	106-99-0	+
N-Butyl-*N*-(4-hydroxybutyl) nitrosamine	3817-11-6	+
N-*N*-butyl-*N*-nitrosourea	869-01-2	+
Butylated hydroxyanisole	25013-16-5	–
Butylated hydroxytoluene	128-37-0	–
Cadmium chloride	10108-64-2	–
Captafol	2425-06-1	–
Carbamyl hydrazine.*HCl*	563-41-7	–
Carbazole	86-74-8	–
Carbon tetrachloride	56-23-5	–
Carboxymethylnitrosourea	60391-92-6	–
Catechol	120-80-9	–
Chloramben	133-90-4	+
Chlorambucil	305-03-3	+
Chlordane	57-74-9	+
Chlorendic acid	115-28-6	–
Chlorinated paraffins (*C*12, 60% chlorine)	63449-39-8	–
Chlorinated paraffins (*C*23, 43% chlorine)	63449-39-8	–
3-Chloro-2-methylpropene, technical grade (containing 5% dimethylvinyl chloride)	563-47-3	+
1-Chloro-2-nitrobenzene	88-73-3	+
1-Chloro-4-nitrobenzene	100-00-5	+
4-Chloro-m-phenylenediamine	5131-60-2	+
4-Chloro-o-phenylenediamine	95-83-0	+
5-Chloro-o-toluidine	95-79-4	–
4-Chloro-o-toluidine.*HCl*	3165-93-3	–
2-Chloro-1,1,1-trifluoroethane	75-88-7	–
Chlorobenzene	108-90-7	–
Chlorobenzilate	510-15-6	–
Chlorodibromomethane	124-48-1	–
Chloroethane	75-00-3	+
Chloroform	67-66-3	–
3-(Chloromethyl)pyridine.*HCl*	6959-48-4	+
3-(*p*-Chlorophenyl)-1,1-dimethylurea	150-68-5	–
Chlorothalonil	1897-45-6	–
Chlorozotocin	54749-90-5	+
Cinnamyl anthranilate	87-29-6	–
Citrinin	518-75-2	–
m-Cresidine	102-50-1	+
p-Cresidine	120-71-8	+
Cupferron	135-20-6	+
Cyclophosphamide	50-18-0	+
Cytembena	16170-75-5	+
Dacarbazine	4342-03-4	+
Daminozide	1596-84-5	–
Dapsone	80-08-0	–
p,p′-DDD	72-54-8	–
p,p′-DDE	72-55-9	–
DDT	50-29-3	–
Decabromodiphenyl oxide	1163-19-5	–
Diallate	2303-16-4	+
4,6-Diamino-2-(5-nitro-2-furyl)-*S*-triazine	720-69-4	+
2,4-Diaminoanisole sulfate	39156-41-7	+
2,4-Diaminotoluene	95-80-7	+
Dibenz(*a,h*)anthracene	53-70-3	+
1,2-Dibromo-3-chloropropane	96-12-8	+
Dibromodulcitol	10318-26-0	+
1,2-Dibromoethane	106-93-4	+
Dibromomannitol	488-41-5	+
2,6-Dichloro-*p*-phenylenediamine	609-20-1	+
1,4-Dichlorobenzene	106-46-7	–

APPENDIX TABLE 3 (continued)

Chemical name	CAS number	Mutagenicity
3,3'-Dichlorobenzidine	91-94-1	+
1,2-Dichloroethane	107-06-2	+
1,2-Dichloropropane	78-87-5	+
Dichlorvos	62-73-7	+
Dicofol	115-32-2	–
Dieldrin	60-57-1	–
Diethylene glycol	111-46-6	–
Diethylstilbestrol	56-53-1	–
N,N'-diethylthiourea	105-55-5	–
Diglycidyl resorcinol ether, technical grade	101-90-6	+
Dihydrosafrole	94-58-6	–
3,3'-Dimethoxybenzidine-4,4'-diisocyanate	91-93-0	+
N,N-dimethyl-4-aminoazobenzene	60-11-7	+
Dimethyl hydrogen phosphite	868-85-9	+
Dimethyl methylphosphonate	756-79-6	–
Dimethyl morpholinophosphoramidate	597-25-1	–
1,2-Dimethyl-5-nitroimidazole	551-92-8	+
trans-2-[(Dimethylamino) methylimino]-5-[2-(5-nitro-2-furyl)vinyl]-1,3,4-oxadiazole	55738-54-0	+
N,N-Dimethylaniline	121-69-7	–
7,12-Dimethylbenz(*a*)anthracene	57-97-6	+
Dimethylcarbamyl chloride	79-44-7	+
1,1-Dimethylhydrazine	57-14-7	+
1,2-Dimethylhydrazine.2*HCl*	306-37-6	+
2-(2,2-Dimethylhydrazino)-4-(5-nitro-2-furyl)thiazole	26049-69-4	+
Dimethylvinyl chloride	513-37-1	+
Dinitrosohomopiperazine	55557-00-1	+
Dinitrosopiperazine	140-79-4	+
Dinitrotoluene, technical grade (2,4 (77%)- and 2,6 (19%)-)	---	+
1,4-Dioxane	123-91-1	–
Epichlorohydrin	106-89-8	+
1,2-Eppxybutane	106-88-7	+
Estradiol	50-28-2	–
Estragole	140-67-0	–
Ethionamide	536-33-4	–
Ethionine	13073-35-3	–
dl-Ethionine	67-21-0	–
Ethyl acrylate	140-88-5	–
Ethyl alcohol	64-17-5	–
1-Ethyl-1-nitrosourea	759-73-9	+
Ethylene imine	151-56-4	+
Ethylene oxide	75-21-8	+
Ethylene thiourea	96-45-7	+
di(2-Ethylhexyl)adipate	103-23-1	–
di(2-Ethylhexyl)phthalate	117-81-7	–
Ethylnitrosocyanamide	38434-77-4	+
Formaldehyde	50-00-0	+
Formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl]hydrazide	3570-75-0	+
Furosemide	54-31-9	–
Gentian violet	548-62-9	–
FD & C Green No. 2	5141-20-8	–
Griseofulvin	126-07-8	–
Hematoxylin	517-28-2	–
Heptachlor	76-44-8	–
Hexachlorobenzene	118-74-1	–
Hexachlorobutadiene	87-68-3	–
β-1,2,3,4,5,6-Hexachlorocyclohexane	319-85-7	–
γ-1,2,3,4,5,6-Hexachlorocyclohexane	58-89-9	–
Hexachloroethane	67-72-1	–
Hexanamide	628-02-4	–
Hydrazine	302-01-2	+
Hydrazine sulfate	10034-93-2	+
Hydrazobenzene	122-66-7	+
Hydrogen peroxide	7722-84-1	+
Hydroquinone	123-31-9	–
N-Hydroxy-2-acetylaminofluorene	53-95-2	+
1'-Hydroxyestragole	51410-44-7	–
1-(2-Hydroxyethyl)-3-[(5-nitrofurfurylidene)amino]-2-imidazolidinone	5036-03-3	+
1-(2-Hydroxyethyl)-1-nitrosourea	13743-07-2	+
2-Hydroxyethylhydrazine	109-84-2	+
1'-Hydroxysafrole	5208-87-7	–
Isoniazid	54-85-3	+
Isophorone	78-59-1	–
Isophosphamide	3778-73-2	+
Kepone	143-50-0	–
Lasiocarpine	303-34-4	+
Lead acetate	301-04-2	–
Luteoskyrin	21884-44-6	–
Malonaldehyde, sodium salt	24382-04-5	–
Melamine	108-78-1	–
Melphalan	148-82-3	+
2-Mercaptobenzothiazole	149-30-4	–
Methapyrilene.*HCl*	135-23-9	–
Methimazole	60-56-0	–
3-Methoxy-4-aminoazobenzene	3544-23-8	+
8-Methoxypsoralen	298-81-7	+
Methyl carbamate	598-55-0	–
3'-Methyl-4-dimethylaminoazobenzene	55-80-1	+
Methyl methanesulfonate	66-27-3	+
N-Methyl-*N*-nitro-*N*-nitrosoguanidine	70-25-7	+
2-Methyl-1-nitroanthraquinone	129-15-7	+
4-Methyl-1-[(5-nitrofurfurylidene) amino]-2-imidazolidinone	21638-36-8	+
N-Methyl-*N*-nitrosobenzamide	63412-06-6	+
3-Methylcholanthrene	56-49-5	+
4,4'-Methylene-bis(2-chloroaniline)	101-14-4	+
4,4'-Methylene-bis(2-methylaniline)	838-88-0	+
Methylene chloride	75-09-2	+
4,4'-Methylenebis(*N,N*-dimethyl) benzenamine	101-61-1	+
4,4'-Methylenedianiline.2*HCl*	13552-44-8	+
Methylhydrazine	60-34-4	+
Methylnitrosocyanamide	33868-17-6	+
N-Methylolacrylamide	924-42-5	–
Metronidazole	443-48-1	+
Michler's ketone	90-94-8	+
Mirex	2385-85-5	–
Mitomycin-C	50-07-7	+
Monocrotaline	315-22-0	–
Nalidixic acid	389-08-2	–
1,5-Naphthalenediamine	2243-62-1	+
2-Naphthylamine	91-59-8	+
Nithiazide	139-94-6	+
Nitrilotriacetic acid	139-13-9	–
Nitrilotriacetic acid, trisodium salt,		

APPENDIX TABLE 3 (continued)

Chemical name	CAS number	Mutagenicity
monohydrate	18662-53-8	–
Nitrite, sodium	7632-00-0	+
3-Nitro-*p*-acetophenetide	1777-84-0	+
5-Nitro-*o*-anisidine	99-59-2	+
5-Nitro-2-furaldehyde semicarbazone	59-87-0	+
N-{[3-(5-Nitro-2-furyl)-1,2,4-oxadiazole-5-yl]-methyl}acetamide	36133-88-7	+
N-[5-(5-Nitro-2-furyl)-1,3,4-thiadiazol-2-yl]acetamide	2578-75-8	+
4-(5-Nitro-2-furyl)thiazole	53757-28-1	+
N-[4-(5-Nitro-2-furyl)-2-thiazolyl] acetamide	531-82-8	+
N-[4-(5-Nitro-2-furyl)-2-thiazolyl] formamide	24554-26-5	+
N,N'-[6-(5-Nitro-2-furyl)-*S*-triazine-2,4-diyl]bisacetamide	51325-35-0	+
2-Nitro-*p*-phenylenediamine	5307-14-2	+
5-Nitro-*o*-toluidine	99-55-8	+
5-Nitroacenaphthene	602-87-9	+
6-Nitrobenzimidazole	94-52-0	+
Nitrofen	1836-75-5	+
1-[(5-Nitrofurfurylidene)amino] hydantoin	67-20-9	+
8-Nitroquinoline	607-35-2	+
Nitroso-Baygon	38777-13-8	+
1-Nitroso-5,6-dihydrouracil	16813-36-8	+
1-Nitroso-3,5-dimethyl-4-benzoyl piperazine	61034-40-0	–
N-Nitroso-*N*-methyl-*N*-dodecylamine	55090-44-3	+
Nitroso-1,2,3,6-tetrahydropyridine	55556-92-8	+
Nitrosodibutylamine	924-16-3	+
N-Nitrosodiethanolamine	1116-54-7	+
N-Nitrosodiethylamine	55-18-5	+
N-Nitrosodimethylamine	62-75-9	+
N-Nitrosodiphenylamine	86-30-6	–
p-Nitrosodiphenylamine	156-10-5	+
N-Nitrosodipropylamine	621-64-7	+
Nitrosododecamethyleneimine	40580-89-0	+
Nitrosoethylmethylamine	10595-95-6	+
Nitrosoethylurethan	614-95-9	+
Nitrosoheptamethyleneimine	20917-49-1	+
N-Nitrosohexamethyleneimine	932-83-2	+
1-Nitrosohydantoin	42579-28-2	+
2-Nitrosomethylaminopyridine	16219-98-0	+
N-Nitrosomorpholine	59-89-2	+
N-Nitrosopiperidine	100-75-4	+
N-Nitrosopyrrolidine	930-55-2	+
N-Nitrosothiomorpholine	26541-51-5	+
Ochratoxin A	303-47-9	–
C.I. Acid Orange 3	6373-74-6	+
4,4'-Oxydianiline	101-80-4	+
Pentachloroethane	76-01-7	–
Pentachloronitrobenzene	82-68-8	–
2,3,4,5,6-Pentachlorophenol (Dowicide EC-7)	87-86-5	–
2,3,4,5,6-Pentachlorophenol, technical grade	87-86-5	–
Phenacetin	62-44-2	+
Phenazone	60-80-0	–
Phenazopyridine.*HCl*	136-40-3	–
Phenesterin	3546-10-9	–
Phenobarbital	50-06-6	+
Phenobarbital, sodium	57-30-7	–
Phenoxybenzamine.*HCl*	63-92-3	+
1-Phenyl-3,3-dimethyltriazene	7227-91-0	+
1-Phenylazo-2-naphthol	842-07-9	+
Phenylethylhydrazine sulfate	156-51-4	+
Phenylglycidyl ether	122-60-1	+
Phenylhydrazine.*HCl*	59-88-1	+
o-Phenylphenate, sodium	132-27-4	–
o-Phenylphenol	90-43-7	+
Piperonyl sulfoxide	120-62-7	–
Pivalolactone	1955-45-9	+
Procarbazine.*HCl*	366-70-1	–
Propane sultone	1120-71-4	+
β-Propiolactone	57-57-8	+
N-Propyl-*N'*-nitro-*N*-nitrosoguanidine	13010-07-6	+
1,2-Propylene oxide	75-56-9	+
Quercetin	117-39-5	+
p-Quinone dioxime	105-11-3	+
D & C Red No. 5	3761-53-3	+
D & C Red No. 9	5160-02-1	+
FD & C Red No. 1	3564-09-8	–
FD & C Red No. 2	915-67-3	–
FD & C Red No. 4	4548-53-2	–
Reserpine	50-55-5	–
p-Rosaniline.*HCl*	569-61-9	+
Saccharin, sodium	128-44-9	–
Safrole	94-59-7	–
Selenium sulfide	7446-34-6	+
Sterigmatocystin	10048-13-2	+
Streptozotocin	18883-66-4	+
Styrene	100-42-5	+
Styrene oxide	96-09-3	+
Sulfallate	95-06-7	+
Telone II	542-75-6	+
2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	1746-01-6	–
1,1,1,2-Tetrachloroethane	630-20-6	–
1,1,2,2-Tetrachloroethane	79-34-5	–
Tetrachloroethylene	127-18-4	–
Tetrachlorvinphos	961-11-5	–
Thio-TEPA	52-24-4	+
Thioacetamide	62-55-5	–
4,4'-Thiodianiline	139-65-1	+
Thiourea	62-56-6	–
Toluene diisocyanate, commercial grade (2,4 (80%)- and 2,6 (20%)-)	26471-62-5	+
o-Toluenesulfonamide	88-19-7	–
m-Toluidine.*HCl*	638-03-9	–
o-Toluidine.*HCl*	636-21-5	+
p-Toluidine.*HCl*	540-23-8	+
p-Tolylurea	622-51-5	–
Toxaphene	8001-35-2	+
Tribromomethane	75-25-2	+
2,4,6-Trichloroaniline	634-93-5	–
1,1,2-Trichloroethane	79-00-5	–
Trichloroethylene	79-01-6	–
Trichloroethylene (without epichlorohydrin)	79-01-6	–
2,4,6-Trichlorophenol	88-06-2	–
2,2,2-Trifluoro-*N*-[4-(5-nitro-2-furyl)-2-thiazolyl]acetamide	42011-48-3	+
Trifluralin, technical grade	1582-09-8	+
2,4,5-Trimethylaniline	137-17-7	+
Trimethylphosphate	512-56-1	+

APPENDIX TABLE 3 (continued)

Chemical name	CAS number	Mutagenicity
Trimethylthiourea	2489-77-2	–
Tris(2,3-dibromopropyl)phosphate	126-72-7	+
Tris(2-ethylhexyl)phosphate	78-42-2	–
Urethane	51-79-6	+
Vinyl acetate	108-05-4	–
Vinyl chloride	75-01-4	+
4-vinylcyclohexene	100-40-3	–
Vinylidene chloride	75-35-4	+
FD & C Violet No. 1	1694-09-3	+
C.I. Disperse Yellow 3	2832-40-8	+
C.I. Vat Yellow 4	128-66-5	–
Zearalenone	17924-92-4	–
Zinc dimethyldithiocarbamate	137-30-4	+

the negatives in both species are mutagenic. It is important to note that these findings do not indicate that single-site, single-species carcinogens are non-mutagens or that 2-species carcinogens are mutagens. Indeed, of the single-site, single-species carcinogens 42% are mutagens and of the 2-species carcinogens 31% are non-mutagens.

A compendium of carcinogenic response by target organ for mutagens and non-mutagens

Table 3 is a compendium of the 351 chemicals in the CPDB (i.e. chemicals that induce tumors) at one or more sites in either rats or mice, and for which mutagenicity results are available in Salmonella. Every chemical that induced tumors at each of 32 target sites is listed, and the table is organized alphabetically by site, species, mutagenicity status, and chemical. This compendium permits comparisons between mutagens and non-mutagens at each site, as well as between species. For example, Table 3 indicates that the lung is a target for 39 mutagens in the mouse and 13 non-mutagens. In rats, 21 mutagens and 2 non-mutagens are positive in the lung. In each species the carcinogens are ordered alphabetically within mutagens and non-mutagens. We have also indicated with superscripts those chemicals that have been tested in both rats and mice and whether they are positive in both species or only in one. This makes it possible to determine whether the lung is a target organ in both species for a given chemical. For example, under lung in the mouse, vinyl chloride is listed under mutagens with the symbol ‡, indicating that it has been tested in both rats and mice and is positive in both species at *some* target site. Since vinyl chloride is also listed under lung for mutagens in the rat, it induces tumors in both species. In contrast, whereas 5-azacytidine is listed under lung for mouse mutagens with the same symbol ‡, indicating that it is positive in the rat and mouse, it is not listed under lung mutagens in the rat; therefore, lung is not a target in the rat for 5-azacytidine, but it is positive in the rat at a different site. Another example under mouse lung for non-mutagens, is *p,p'*-DDD 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 mouse. Acetaldehyde methylformylhydrazone under lung for mouse non-mutagens has no superscript, since it has not been tested in the rat. When a chemical is listed with superscripts, the information applies only to rats and mice, and not to other species in the CPDB such as hamsters. In Table 3, chemicals not listed for either rats or mice under a given organ, did not induce such tumors in either rats or mice. An appendix to Table 3 lists alphabetically the 351 chemicals in the analysis and reports the Chemical Abstracts Service Registry Number (CAS) and mutagenicity status for each one.

While Table 3 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 experimental work, results of negative tests, and route of administration, sex, and strain. The 5 plots of the CPDB analyze published papers chronologically, and appear in *Environmental Health Perspectives* (Gold et al., 1984, 1986, 1987, 1990, in press). 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 Gold et al. (in press). This appendix lists all 1136 chemicals that appear in any of the 5 plots of the CPDB, indicating which plot(s) contains results on each chemical. Thus, for any target organ of interest, using Table 3 in conjunction with the published plots of

the CPDB will provide detailed information on each experiment. A combined plot of the entire CPDB, that merges results from all 5 plots and is organized by chemical can be obtained from the first author. A computer readable (SAS) database is also available.

Comparison of target organs of mutagens and non-mutagens

The frequency of carcinogenic response by target site in rats and mice is tabulated in Table 4 and shown in Figs. 1a and 1b. Both mutagens and non-mutagens induce tumors at a wide variety of target sites in both rats and mice: in the rat there are 29 different target organs for mutagens and 27 for non-mutagens; in the mouse there are 23 and 20 respectively. In both species, the liver is the most common target site for mutagens as well as non-mutagens, and in the mouse it is the predominant site for both mutagens and non-mutagens. In rats, 35% of mutagens induce liver tumors compared to 32% of non-mutagens; in mice, 54% of mutagens and 76% of non-mutagens induce liver tumors. In rats compared to

TABLE 4

FREQUENCY OF TARGET ORGANS FOR MUTAGENS AND NON-MUTAGENS BY SPECIES

	Chemicals evaluated as carcinogenic in:							
	Rats				Mice			
	Mutagens (N=172)		Non-mutagens (N=87)		Mutagens (N=130)		Non-mutagens (N=88)	
Target Organ	N	%	N	%	N	%	N	%
Liver	61	35%	28	32%	70	54%	67	76%
•Lung	21	12%	2	2%	39	30%	13	15%
Mammary gland	48	28%	6	7%	9	7%	5	6%
•Stomach	39	23%	6	7%	25	19%	6	7%
•Vascular system	15	9%	2	2%	23	18%	9	10%
Kidney/ureter	20	12%	20	23%	6	5%	4	5%
Hematopoietic system	19	11%	11	13%	18	14%	11	13%
Urinary bladder/urethra	21	12%	11	13%	9	7%		
Nasal cavity/turbinates	17	10%	3	3%	4	3%		
•Ear/Zymbal's gland	19	11%	1	1%	1		1	1%
Esophagus	11	6%	1	1%	5	4%		
•Skin	13	8%	3	3%	2	2%		
•Small intestine	11	6%	1	1%	1		1	1%
Thyroid gland	10	6%	8	9%	7	5%	3	3%
Peritoneal cavity	10	6%	4	5%	2	2%		
Oral cavity	8	5%	3	3%	1			
•Large intestine	8	5%	1	1%				
Central nervous system	10	6%	2	2%	1		1	1%
•Uterus	6	3%	3	3%	6	5%	1	1%
Pancreas	5	3%	5	6%				
•Subcutaneous tissue	5	3%			1			
Adrenal gland	4	2%	5	6%	2	2%	4	5%
Pituitary gland	2	1%	5	6%			1	1%
•Clitoral gland	4	2%	1	1%			1	1%
•Preputial gland	1		3	3%	2	2%	2	2%
Testes	6	3%	2	2%			1	1%
•Harderian gland					4	3%	3	3%
•Spleen	3	2%	2	2%				
•Ovary					4	3%	3	3%
Bone	2	1%	1	1%				
Myocardium							1	1%
Vagina	1							

Sites marked by • are Ashby and Tennant (1988) 100% genotoxic sites (i.e. both mutagenic in *Salmonella* and structurally alerted).

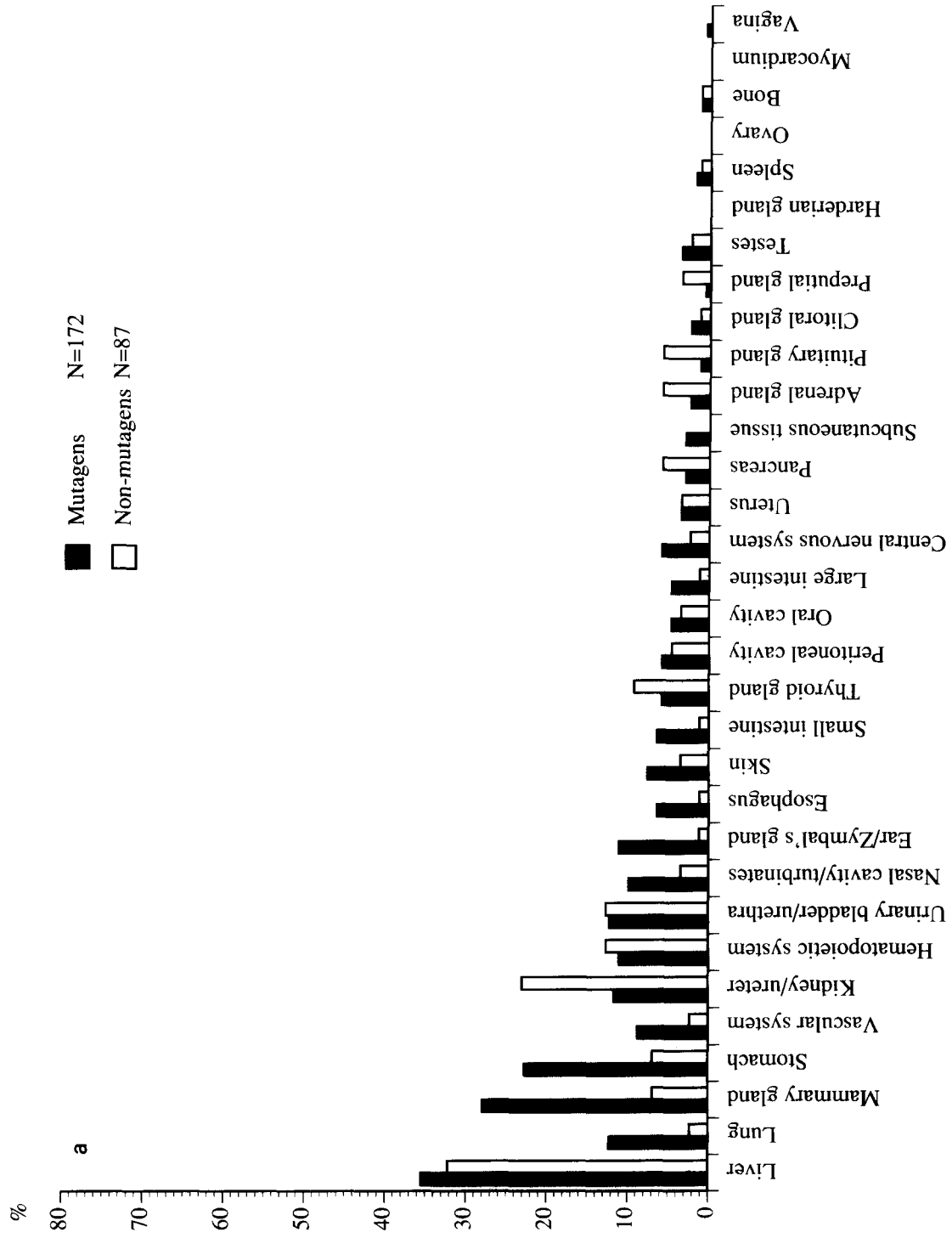

Fig. 1a. Rats: percentage of mutagens and non-mutagens that induce tumors at each target site.

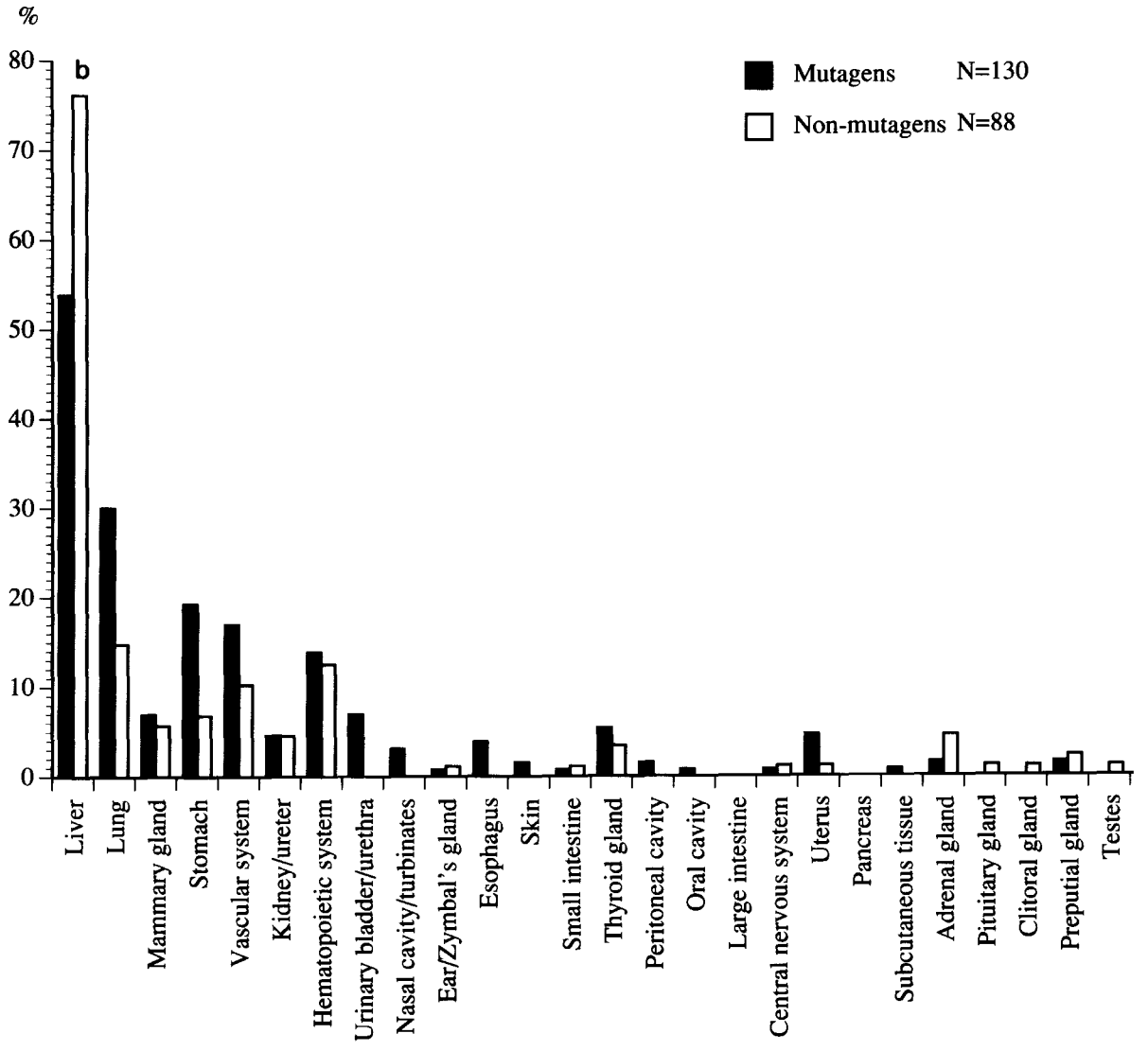

Fig. 1b. Mice: percentage of mutagens and non-mutagens that induce tumors at each target site.

mice, more organs are target sites for a greater percentage of the carcinogens, as shown in Figs. 1a and 1b, and as we reported earlier (Gold et al., 1991). Many sites in both rats and mice are targets for only a small number of carcinogens.

Another similarity between mutagens and non-mutagens is that the same target sites tend to be the most common sites for both. In our earlier paper on target organs (Gold et al., 1991) we reported that each of 8 sites was a target for at least 10% of the chemicals in the overall CPDB, and that more than 80% of carcinogens in rats and in mice were positive in at least one of these sites: liver, lung, mammary gland, stomach, vascular system, kidney, hematopoietic system and urinary bladder. The same 8 sites are most frequent in the dataset of chemicals with mutagenicity results. A similar analysis for this mutagenicity dataset indicates that, despite the wide variety of target organs in each group, due to the frequency of multiple-site carcinogens and the fact that the liver is such a frequent site, a high proportion of mutagens and of non-mutagens can be identified by these 8 most common sites. In the rat, 87% of mutagens are positive in at least one of the 8 sites compared to 79% of non-mutagens; in the mouse, 90% of mutagens are positive in at least one of these sites compared to 98% of non-mutagens.

The results shown in Table 1, i.e. that it is common for chemicals to induce tumors in more than one site, are reflected in Table 4 and Figs. 1a and 1b where the summation of the percentages of chemicals that are positive in the various organs for each of the 4 groups is far greater than 100% due to the induction of tumors at more than one site by a chemical. Among rat carcinogens, mutagens are positive at, on average, 2.4 target sites per chemical compared to 1.6 target sites per chemical for non-mutagens; among mouse carcinogens, the average number of positive target sites are 1.9 for mutagens and 1.6 for non-mutagens (Table 4). Therefore one cannot simply compare the percentage of chemicals positive at each target site for mutagens and non-mutagens. In spite of the relatively greater frequency of target sites for mutagens, some sites are targets for a higher proportion of non-mutagens than mutagens, e.g. rat kidney, rat thyroid and mouse liver (Table 4 and Figs. 1a, 1b).

Some sites are much more common for mutagens than non-mutagens, e.g. Zymbal's gland in the rat. Sometimes there is a lack of consistency between species, for example, the lung is a target organ for only 2% of rat non-mutagens compared to 12% of mutagens; however, in the mouse it is the second most common site for non-mutagens: 15% of the non-mutagens induce lung tumors compared to 30% of mutagens. A lack of consistency between species is also evident for urinary bladder: in the mouse 7% of mutagens but no non-mutagens induce bladder tumors; however, in the rat it is a target for 12% of mutagens and 13% of non-mutagens.

Comparison of results to Ashby and Tennant

Ashby and Tennant in 1988 investigated the interrelationships among mutagenicity, carcinogenicity and structure–activity for a subset of chemicals tested by NCI/NTP. Among carcinogens, they found an 89% concordance between mutagenicity in Salmonella and structure–activity status, and they proceeded to examine target organs for 99 carcinogens that were either mutagenic and structurally-alerted (genotoxic) or non-mutagenic and not structurally-alerted (non-genotoxic). Chemicals that were discordant between mutagenicity and structure activity were deleted from their analysis. The authors concluded that many organs were the "exclusive preserve" of genotoxins. In 1991, they re-evaluated this issue using a larger dataset of 142 NCI/NTP carcinogens, and concluded that only 2 organs were exclusively target sites for genotoxins: Zymbal's gland and lung (Ashby and Tennant, 1991). Although genotoxins induced tumors in a much wider range of sites than non-genotoxins in the dataset of 99 carcinogens, a wide range of target sites was found for both groups in the dataset of 142 carcinogens. It is important to note that the analyses of Ashby and Tennant present only the *number* of genotoxins and non-genotoxins at each target site and thus do not take into account the fact that a higher proportion of the carcinogens in their analysis were genotoxins than non-genotoxins. Moreover, because they reported the number of chemicals positive at each site rather than the percentage of chemicals, there is a

greater likelihood of finding sites that are predominantly genotoxic because mutagens are more frequently positive at multiple sites.

Table 4 indicates that there are similarities in target organ responses of mutagens and nonmutagens, as discussed above (without taking structure activity into account). Thus our results are more consistent with the second, larger analysis of Ashby and Tennant. The sites that Ashby and Tennant concluded in 1988 were the exclusive preserve of genotoxins are marked with a "•" in Table 4. Many of these sites are uncommon for both species, with only a few carcinogens inducing tumors at each one. Thus, as Ashby and Tennant pointed out in 1991, there are too few chemicals positive at each of these less common sites to be considered statistically reliable. The more common sites considered as exclusively

TABLE 5

TARGET SITES IDENTIFIED BY ASHBY AND TENNANT AS POSITIVE ONLY FOR GENOTOXIC CHEMICALS AS DEFINED BY POSITIVITY IN *SALMONELLA* AND STRUCTURAL ALERT

Target Organ	Ashby and Tennant chemicals: rats or mice — proportion structurally alert and *Salmonella* positive 1988	1991	Discordant results in the CPDB (negative in *Salmonella* and no structural alert)[a]
Lung[b]	14/15	21/23	**benzene** (FM,MM), **benzofuran** (FM,MM), cadmium chloride (MR), *p,p'*-DDD (FM,MM), dihyrosafrole (FM), TCDD (FR), TCE (FM,MM)
Stomach[b]	12/13	18/22	**benzaldehyde** (FM,MM)[c], **benzene** (FM,MM), **benzofuran** (FM,MM), **benzyl acetate** (FM,MM), BHA (FR,MR), captafol (FM, MM), carbazole (FM,MM), catechol (MR), 1'-hydroxysafrole (MR)
Vascular system	10/10	12/13	captafol (FM, MM), 1'-hydroxysafrole (MM), **pentachlorophenol** (FM)
Ear/Zymbal's gland[b]	6/7	10/11	**benzene** (FM,MM,FR,MR)
Skin[b]	4/5	9/10	**benzene** (MR), thiourea (MR)
Intestine/colon	2/2	6/6	
Uterus	5/5	9/9	vinyl acetate (FR)
Subcutaneous tissue	6/6	8/8	
Clitoral gland	4/4	7/8	**nalidixic acid** (FR)
Preputial gland[b]	0/1	4/7	**benzene** (MM), **2-mercaptobenzothiazole** (MR), **nalidixic acid** (MR)
Harderian gland[b]	1/2	4/5	**benzene** (FM,MM)
Spleen	2/2	3/3	
Ovary[b]	1/2	6/7	**benzene** (FM)
Multiple organ sites	2/2	3/3	
Tunica vaginalis	1/1	2/2	
Bile duct	1/1	1/2	**furfural** (MR)[c]
100% Sites	39/39	62/62	
All Sites	62/99	90/142	

[a]Chemicals in **boldface** are also included in Ashby and Tennant's analyses.

[b]Benzene is neither mutagenic in *Salmonella* nor structurally alerted and is therefore non-genotoxic according to the classification scheme of Ashby and Tennant; however, Ashby and Tennant (1988) reported that benzene was carcinogenic to these sites but deleted it from their target site analysis because it is clastogenic. If benzene had been included as a non-genotoxin, then these sites would not have been exclusively positive for genotoxins in their 1988 analysis. In this table benzene is classified as non-mutagenic to *Salmonella* and not structurally alerted; benzene induced tumors at these sites.

[c]Benzaldehyde and furfural were reported by Ashby and Tennant. These NTP studies are not in the first 5 plots of the CPDB and are therefore not in other analyses in this paper.

genotoxic sites by Ashby and Tennant in 1988, are targets for both mutagens and non-mutagens in our larger dataset.

Table 5 presents target sites identified by Ashby and Tennant as positive only for genotoxic chemicals as defined by positivity in Salmonella and structural alert. We have taken structure–activity into account in this table for CPDB chemicals, and list the carcinogens that are discordant with Ashby and Tennant's 1988 analysis, i.e. chemicals that are negative in Salmonella and are not structurally alerted, but induce tumors at each of those sites (J. Ashby, personal communication). Table 5 indicates that there are discordant results in our dataset for most of their "exclusively genotoxic sites", particularly for the most common target sites: lung, stomach, and vascular system. For Zymbal's gland, the only exception is benzene, a non-alerted non-mutagen, which Ashby and Tennant excluded from their analysis because it is clastogenic (Dean, 1985). Using the definition of Ashby and Tennant, we found no "non-genotoxic" carcinogens that induce tumors in the intestine/colon, subcutaneous tissue, spleen, or tunica vaginalis; however, the small number of "genotoxins" that induce tumors in these sites does not permit one to draw any conclusions. Additionally in the CPDB, at least one carcinogen that is not mutagenic in Salmonella but is structurally alerted, induces tumors at each of these uncommon sites, with the exception of subcutaneous tissue.

Discussion

Single-site, single-species carcinogens. The results in this paper on target-organ specificity emphasize the similarities between mutagens and non-mutagens with respect to the wide range of tissues at which tumors are induced and the particular organs that are most common in rats and mice. It is of interest to determine whether target organs differ for mutagens and non-mutagens among the group of carcinogens that induce tumors in only one site of one species. In the CPDB, 230 rodent carcinogens with mutagenicity evaluations have been tested in both rats and mice, and 73 of these (32%) induce tumors in only one target site of one species (Table 2). 31 of these are mutagens. Investigation of the specific target sites for these 73 chemicals does not suggest differences in the responses of mutagens and non-mutagens. The mouse liver is the most common single-site, single-species target organ for both mutagens (10 chemicals) and non-mutagens (19 chemicals). Many of the non-mutagens in this group are chlorinated compounds (composed solely of chlorine, carbon, hydrogen and optionally oxygen). Excluding chlorinated compounds, 7 mutagens and 7 non-mutagens are single-species carcinogens positive only in the mouse liver. Among the single-site, single-species carcinogens that do not induce mouse liver tumors, mutagens and non-mutagens are similar: several different sites are target organs and only a few chemicals are uniquely positive at each site.

Liver. Results for a few target organs are unusual, and we have investigated these further. The liver is the most common target site in rats and mice for both mutagens and non-mutagens, and there is a species difference in the predominance of the liver in mice compared to rats. In the mouse 54% (70/130) of mutagens compared to 76% (67/88) of non-mutagens induce liver tumors, while the proportions in the rat are 35% (61/172) and 32% (28/87). Thus, while the proportion of rat carcinogens that are positive in the liver is similar for mutagens and non-mutagens, in mice a higher proportion of non-mutagens than mutagens are liver carcinogens. This finding in mice reflects the fact that chlorinated compounds are frequently positive in the mouse liver and not mutagenic in Salmonella. Excluding the chlorinated compounds, results in mice are more similar for mutagens and non-mutagens: 55% (65/118) of mutagens and 65% (37/57) of non-mutagens are mouse-liver carcinogens.

Zymbal's gland. The Zymbal's gland and the lung are the 2 target sites that Ashby and Tennant evaluated in 1991 as exclusively positive for "genotoxins".

We have identified several lung carcinogens in the CPDB that are discordant with that conclusion because they are negative in Salmonella and are not structurally alerted (Table 5). For the Zymbal's gland, our findings are similar to those

of Ashby and Tennant: the only discordant chemical is benzene; all other chemicals that induce Zymbal's gland tumors are mutagenic and structurally alerted. Because Zymbal's gland is an unusual target site, we investigated it further. Of the 351 carcinogens in rats or mice, 2 chemicals induce Zymbal's gland tumors in mice, compared to 20 chemicals in rats, including the same 2 chemicals positive in mice (Table 3). Compounds that induce Zymbal's gland tumors in the rat are all positive at multiple sites. When tested in both species, all rat Zymbal's gland carcinogens are also positive at some site in the mouse. There is additional support for strong evidence of carcinogenicity for those chemicals that induce Zymbal's gland tumors. In the CPDB overall, only 18% (42/230) of carcinogens tested in both rats and mice are positive at multiple sites in both species (Table 2); however, among the chemicals tested in both species that induce Zymbal's gland tumors, 71% (10/14) induce tumors at more than one site in both species.

Kidney. The kidney is a common site in the rat, and is unusual because the proportion of carcinogens that are positive in the kidney is greater for non-mutagens than mutagens (Table 4, Fig. 1b), despite the fact that rat mutagens more frequently induce tumors at multiple sites. Mutagenic and non-mutagenic rat kidney carcinogens are similar in that both are frequently positive at an additional target site. In the CPDB, 57% (95/165) of mutagenic rat carcinogens are multiple-sited (Table 1) compared to 80% (16/20) of mutagens that induce rat kidney tumors; similarly, among non-mutagens in the CPDB 40% overall are multiple-sited compared to 63% of rat kidney carcinogens.

Recent observations in the study of renal carcinogenesis suggest that for some chemicals the mechanism of action in the kidney of male F344 rats may be the accumulation of the male rat-specific urinary protein, α-2u-globulin, which causes cytotoxicity and carcinogenicity (Goldsworthy et al., 1988; Short and Swenberg, 1991; Ward et al., 1991). In the CPDB, 17 chemicals induce tumors in the kidney tubules of male F344 rats: 6 mutagens and 11 non-mutagens. All of these chemicals induce other tumors as well, either in the female rat, other tumors in the male rat, or in the mouse. The rarity of carcinogens that are uniquely positive in male F344 rat kidney tubules was noted previously (Barrett and Huff, 1991).

Spontaneous tumor rates. It has been suggested that organs with a high rate of spontaneously-occurring tumors are more likely than other organs to be the targets for non-mutagenic carcinogens, since the tissue is already susceptible to tumorigenesis (Clayson, 1987, 1989). We investigated this issue by comparing target sites with high spontaneous rates to those that are most frequently the sites of tumorigenesis in F344 rats and $B6C3F_1$ mice, strains for which spontaneous tumor data are available from the NCI/NTP (Haseman et al., 1985; Tarone, Chu and Ward, 1981; Ward, 1983). In the F344 rat, the sites with highest spontaneous rates are the testis, pituitary gland, hematopoietic system, mammary gland, adrenal gland and uterus. For non-mutagenic carcinogens in F344 rats in the CPDB, the most common sites, liver and kidney, are not those with the highest background rates. Hematopoietic system is a common target site for non-mutagens that does have a high background rate, but it is also a common site for mutagens.

In the $B6C3F_1$ mouse, the highest spontaneous rates are for liver, hematopoietic system and lung, and these are the most common sites of tumorigenesis for non-mutagens. However, if non-mutagenic carcinogens are acting by enhancing a process for which spontaneous tumors are an indicator, then results in the CPDB suggest that mutagens are likely to be acting similarly: liver and lung are also the most common sites for mutagens in the $B6C3F_1$ mouse.

Species differences. Several results in this paper have indicated a difference in the target organ responses of rats and mice. (1) In rats compared to mice, more organs are target sites for a greater percentage of the carcinogens (Table 4) (see also Gold et al., 1991). (2) Mutagens are more often multiple-site carcinogens than non-mutagens in both species; however, mutagens more often induce tumors at multiple sites in rats than in mice: on average, mutagens induce

tumors in rats at 2.4 sites per chemical compared to 1.9 sites in mice. (3) Some target organs are common in one species and not in the other; for example, in rats but not in mice, mammary gland and Zymbal's gland are among the common sites. Lung is a common site in mice but not in rats. (4) Among non-mutagenic carcinogens, a higher proportion in mice than rats are positive in one of the 8 most common sites (98% for mice compared to 79% for rats). (5) While the liver is the most common site in both species, it is a more frequent site in the mouse. In the rat, similar proportions of mutagens and non-mutagens induce liver tumors, whereas in the mouse the proportion of non-mutagens is higher than mutagens. This is due in part to chlorinated compounds, as discussed above. (6) Finally, we note that our analysis in F344 rats and $B6C3F_1$ mice has shown that in mice the organs that have the highest spontaneous tumor rates are common sites of carcinogenicity for non-mutagens (liver, hematopoietic system and lung). However, in rats the sites with the highest spontaneous rates are not the most common. We have also compared target organ responses in rats and mice for the subset of chemicals that have been tested in both species, and have found these 6 differences in that subset as well.

Conclusions. The results presented in this paper are consistent with our theoretical arguments for taking mitogenesis into account in animal cancer tests. The induction of tumors in high-dose rodent bioassays is not dependent on the direct mutagenicity of the test agent, since a high proportion of rodent carcinogens are not mutagenic. Chemicals that are not mutagenic in short-term tests can be indirectly mutagenic in high-dose rodent tests by increasing cell division. For mutagens, mitogenesis may also be the dominant factor in carcinogenesis at high doses; since mutagens can also damage DNA, they can have a multiplicative interaction for carcinogenicity (Ames and Gold, 1990a; Ames, Shigenaga and Gold, in press). These hypotheses would lead one to expect that the evidence for carcinogenicity will be stronger for mutagens than non-mutagens, as our results indicate. Mutagens compared to non-mutagens 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 two species. We have shown that among carcinogens that induce tumors at multiple sites in both rats and mice, 81% are mutagens; in comparison, among carcinogens that are positive at only a single target site in one species and negative in the other, 42% are mutagens (Table 2).

One would not always expect the mutagenicity of a chemical in Salmonella to indicate the mechanism in a rodent. Our results indicate that among 378 chemicals tested for carcinogenicity in both rats and mice, 26% of the non-carcinogens are mutagens in Salmonella; these presumably are not acting as significant mutagens in the rodents. Additionally, some non-mutagens in Salmonella may be mutagenic in higher organisms. Even those mutagens that are carcinogens may not all be acting as genotoxins in animals because of detoxification and other processes.

Analyses of dose–response in animal tests are consistent with the idea that mitogenesis from cell-killing and cell replacement is important at the high doses tested, for both mutagens and non-mutagens. In the usual experimental design of dosing at the MTD and 1/2 MTD, both dose levels are usually high and may result in mitogenesis. Even at these two high doses, we have found that 44% of the positive sites in NTP bioassays are statistically significant at the MTD but not at 1/2 the MTD. Moreover, the proportion positive only at the high dose is similar for mutagens and non-mutagens (Ames and Gold, 1991).

Our results do not support the idea that mutagens and non-mutagens induce tumors in different target organs. Theoretically one would not expect target sites to differ by mutagenicity of the compound since tissue distribution and pharmacokinetics are not expected to differ systematically between mutagens and non-mutagens. Our results indicate that tumors are induced in a wide variety of target organs by mutagens and non-mutagens. Moreover, the same sites are most frequent for both: 79% or more of mutagenic and non-mutagenic carcinogens are positive in each species in at least one of the 8 most common target sites: liver, lung, mammary gland, stomach,

vascular system, kidney, hematopoietic system and urinary bladder.

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