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Chemicals Associated with Site-Specific Neoplasia in 1394 Long-Term Carcinogenesis Experiments in Laboratory Rodents

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The carcinogenicity data base used for this paper originated in the late 1960s by the National Cancer Institute and since 1978 has been continued and made more comprehensive by the National Toxicology Program. The extensive files contain among other sets of information detailed pathology data on more than 400 long-term (most often 24 month) chemical carcinogenesis studies, comprised of nearly 1600 individual experiments having at least 10 million tissue sections that have been evaluated for toxicity and carcinogenicity. Using the current data set of 379 studies made up of 1394 experiments, we have compiled listings of chemicals having like carcinogenic target sites for each of the 34 organs or systems for which histopathology diagnoses have been recorded routinely. The most common tumor site is the liver (15% of all experiments), followed in rank order by: lung, hematopoietic system and kidneys, mammary glands, forestomach, thyroid glands, Zymbal glands, urinary bladder, skin and uterus/cervix, and circulatory system and adrenal glands. These compilations are most useful for maintaining a historic perspective when evaluating the carcinogenicity of contemporary experiments. Equally important, the chemical-tumor-organ connection permits an evaluation of how well chemically induced cancers in a particular organ in one sex or species will predict or correlate with the other sex or species. Using liver cancers as an example, the overall interspecies concordance is 80%. Likewise target site predictions can be made for chemicals selected for study that may be similar to those already evaluated; thereby experimental protocols could be adjusted to allow, for example, more extensive pathology on preselected target organs (i.e., serial sections of the kidney). Further from these observations, one could decide to use two strains of mice to evaluate a short-chain chlorinated aliphatic compound or to study a human carcinogen in a sex-species known to develop chemically induced tumors in the same site observed in humans. Structural classes of chemicals having a propensity for certain organs can be easily identified from these data. Sex-species responders to particular induced cancers become clearly evident, such as in the ovary of female mice or in the kidney of male rats.

Introduction

Evaluating chemicals in laboratory rodents remains the cornerstone for identifying those chemicals most likely to cause cancer in humans (*1–6*). In the absence of adequate data from human experience and epidemiological investigations, long-term studies in laboratory animals are the best method currently available for evaluating and identifying potential carcinogenic hazards to public health (for example *1,2,4–12*).

Since 1918 when Yamagiwa and Ichikawa (*13*) first exposed laboratory animals to chemicals for the purpose of detecting chemical carcinogens, and the era of experimental carcinogenesis can be said to have had its beginning (*14*), much has been learned about the relevance of these findings for possible effects in humans (*1,2,4,15,16*). Likewise, an enormous amount of knowledge has been gained over the years concerning the design, conduct, evaluation, and interpretation of the data collected from these carcinogenesis studies (*17–23*). The major public health value of these long-term chemical carcinogenesis experiments is to allow better risk assessment (*24*) and risk management decisions (*25,26*) to be made for reducing, preventing, or eliminating exposures to those chemicals identified as constituting real risks to humans (*27–29*).

A valuable characteristic of our program and the extensive collection of experimental chemical carcinogenesis information is that the data we evaluate come from our own experiments; that is, we design the protocols,

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oversee conduct of these studies, validate the experimental results, evaluate the data, present the findings and conclusions before nongovernmental panels of experts; print the collections of "raw" data together with detailed literature reviews, evaluations, interpretations, and conclusions in a series of technical reports; and publish the essence in scientific journals (*3,30*). Another program uniqueness stems from our decision not to make overall or combinational evaluations for a chemical; that is, we separately evaluate and report levels of evidence for each experimental grouping or cohort: male rats, female rats, male mice, and female mice are the usual makeup of the experimental cells for each long-term chemical carcinogenesis study (*31–34*).

This paper provides the site-specific neoplastic results from 1394 individual experiments in rodents exposed separately in 379 chemical carcinogenesis studies. The carcinogenicity evaluations given in this paper are based on established criteria (*33,34*) with the primary emphasis for interpreting long-term experiments in laboratory animals being centered on site-specific tumor analyses and comparisons (*35*).

The carcinogenicity data base used for this paper originated in the late 1960s by the National Cancer Institute (NCI) and since 1978 has been continued and made more comprehensive by the National Toxicology Program (NTP). The extensive files contain among other sets of information detailed pathology diagnoses on at least 10 million tissue sections that have been evaluated for nonneoplastic and neoplastic lesions (*16*); these are stored in the NTP Archives and are available on-location for independent study. Using the current and collective data set, we have compiled listings of chemicals having like carcinogenic target sites for each of the 34 organs or systems for which histopathology diagnoses have been recorded routinely. These data form the basis of this paper.

Materials and Methods

The chemical carcinogenesis data given in this paper come from the *NCI and NTP Technical Reports Series* (*3,15,23,30*), and include those data, results, and conclusions that have been peer reviewed in public meetings through June 1991. In total, the data base used for this paper comes from 379 long-term chemical carcinogenesis studies involving 1394 sex-species experiments. These toxicology studies are typically carried out using both sexes of two species of rodents divided randomly into sets of 50 to 60 animals per control and exposure groups; two or three exposure concentrations are graduated down from a top level, a level of exposure selected to show some minimal yet obvious chemical-associated toxicity that should not compromise unduly the animals normal well-being or growth and survival (*3,11,17–20,23,36,37*).

The species most often used by the NCI and NTP are the inbred Fischer 344 rat and the hybrid B6C3F1 (C3H × C57B16) mouse. Duration of exposure is generally 2 years (or about ⅔ the life span of these rodent species); animals are assessed for visible lesions during necropsy, and prescribed tissues and organs are evaluated microscopically. These diagnoses are substantiated and peer reviewed (*38,39*). The data are tabulated with appropriate tumor combinations (*40–42*), and statistical comparisons are made which adjust for possible differences in survival between groups (*43*). The collated findings are evaluated, subjected to extensive audits (*44,45*), interpreted, and presented in public meetings to a nongovernment peer review panel of experts in chemical carcinogenesis (*3,23*).

Each experimental grouping (that is, male rats, female rats, male mice, and female mice) is given an overall level of evidence of carcinogenicity (or "carcinogenic activity") selected from five categories: two positive levels (clear evidence and some evidence), one uncertain (equivocal evidence), one for no observed response (no evidence), and one for seriously flawed experiments (inadequate experiment) (*34*).

For each experiment, the results given in this paper reflect the original evaluations given in the individual *Technical Reports* (*30,41*). The chemically associated neoplastic observations have been grouped according to the organs or systems affected. For completeness, a chemical has been included if the neoplastic response was positively caused by the exposure or if the neoplastic effect was equivocally related to exposure (sometimes referred to as "may have been related"). These differences are clearly indicated. Moreover, a "yes" or "no" indication is given to show whether a particular tumor response was the only neoplastic effect caused by that chemical. To allow comprehensiveness, chemicals have been listed that did not induce any increases in cancers.

Selected Experimental Results

The data selected for these analyses are divided into a series of tables. Table 1 contains the basic data-set, listing by organ or system the chemicals judged to cause tumors at that site. If evaluated by the NTP for mutagenesis in Salmonella, the results are given; no attempt has been made to supplement either the organ and tissue sites of carcinogenicity or mutagenicity data from the literature. Other information listed in Table 1 includes the *Technical Report* numbers (Tr No.), routes of exposure, the level of evidence for each experimental unit (male rats, female rats, male mice, and female mice) with the group in which an effect occurred at this site shown in parentheses, tumors that show marginal increases, and whether other sites are affected. To make the chemical data set complete, the end section of this table lists those chemicals that were evaluated as not causing any increases of tumors at any site (128 chemicals or 465 experiments).

The data given in Table 1 permit an evaluation of how well a target site in one sex mimics or predicts for the same response in the other sex of that species, or for the same sex in the other species. Using the liver as a specific example of organ-to-organ correspondence be-

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Table 1. Organs/systems and associated chemicals exhibiting induced neoplasia observed in 379 chemical carcinogenesis studies involving 1394 sex-species experiments (1976–1991).

TR No[d]	Chemical	SAL[e]	RUT[f]	Levels of evidence of carcinogenicity[a] MR[g]	FR	MM	FM	May have been related[b] (sex species)	Other[c] sites
	ADRENAL GLAND								
021	ALDRIN	-	F	E	(E)[h]	P	N		Y
318	AMPICILLIN TRIHYDRATE	-	G	(EE)	NE	NE	NE		Y
363	BROMOETHANE (ETHYL BROMIDE)	-,+	I	(SE)	EE	EE	CE		Y
305	CHLORINATED PARAFFINS: C23, 43% CHLORINE	-	G	NE	(EE)	CE	EE		Y
351	P-CHLOROANILINE HYDROCHLORIDE	-,+,+W	G	CE	(EE)	SE	NE	(MR)	Y
075	CHLOROBENZILATE	-,-,-	F	(E)	(E)	P	P		Y
085	4-CHLORO-M-PHENYLENEDIAMINE	+	F	(P)	N	N	P		Y
405	C.I. ACID RED 114	+	W	CE	CE			(MR) (FR)	Y
285	C.I. BASIC RED 9 MONOHYDROCHLORIDE	+	F	CE	CE	CE	(CE)		Y
206	1,2-DIBROMO-3-CHLOROPROPANE	+	I	P	(P)	P	P		Y
319	1,4-DICHLOROBENZENE (P-DICHLOROBENZENE)	-	G	CE	NE	CE	CE	(MM)	Y
402	FURAN	-	G	CE	CE	(CE)	(CE)		Y
361	HEXACHLOROETHANE	-,-	G	CE	NE			(MR)	Y
330	4-HEXYLRESORCINOL	-,-	G	NE	NE	(EE)	NE		Y
332	2-MERCAPTOBENZOTHIAZOLE	?,-	G	(SE)	(SE)	NE	EE		Y
248	4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE	+,+	W	P	P	(P)	P		Y
313	MIREX	-	F	(CE)	CE				Y
315	OXYTETRACYCLINE HYDROCHLORIDE	-	F	(EE)	EE	NE	NE		Y
070	PARATHION	+W,-	F	(E)	(E)	N	N		N
349	PENTACHLOROPHENOL, DOWICIDE EC-7	-	F			(CE)	(CE)		Y
349	PENTACHLOROPHENOL, TECHNICAL	-	F			(CE)	SE		Y
240	PROPYL GALLATE	-	F	(E)	N	E	N		Y
193	RESERPINE	-	F	(P)	N	P	P		Y
364	RHODAMINE 6G	-	F	EE	(EE)	NE	NE		Y
033	TETRACHLORVINPHOS	-	F	N	(P)	P	P		Y
074	1,1,2-TRICHLOROETHANE	-,-,-	G	N	N	(P)	(P)		Y
274	TRIS(2-ETHYLHEXYL)PHOSPHATE	-	G	(EE)	NE	NE	SE		Y
303	4-VINYLCYCLOHEXENE	-,-	G	IS	IS	IS	CE	(FM)	Y
	Number of Chemicals = 28		TOTALS[i]	14	10	7	5		
	BONE								
049	ACRONYCINE		J	(P)	P	IS	IS		Y
341	NITROFURANTOIN	+,+,+	S	SE	NE	NE	CE	(MR)	Y
393	SODIUM FLUORIDE	-	W	(EE)	NE	NE	NE		N
	Number of Chemicals = 3		TOTALS	3	0	0	0		
	BRAIN								
088	1,2,3-BENZOTRIAZOLE	+W	F	(E)	(E)	N	E		Y
363	BROMOETHANE (ETHYL BROMIDE)	-,+	I	SE	(EE)	EE	CE	(MR)	Y
288	1,3-BUTADIENE	+	I			CE	CE	(MM)	Y
346	CHLOROETHANE	+	I	EE	(EE)	IS	CE		Y
397	C.I. DIRECT BLUE 15	-	W	CE	CE			(MR)	Y
372	3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE	+,+,+	W	CE	CE			(MR)	Y
390	3,3'-DIMETHYLBENZIDINE DIHYDROCHLORIDE	+	W	CE	CE			(MR) (FR)	Y
355	DIPHENHYDRAMINE HYDROCHLORIDE	-	F	(EE)	EE	NE	NE		Y
356	FUROSEMIDE	-	F	(EE)	NE	NE	SE		Y
374	GLYCIDOL	+,+	G	(CE)	(CE)	CE	CE		Y
019	PROCARBAZINE HYDROCHLORIDE	-	J	(P)	(P)	(P)	(P)		Y
	Number of Chemicals = 11		TOTALS	9	6	2	1		

[a]Levels of evidence are (these designations reflect changes in classification scheme over time): P, positive evidence of carcinogenicity; CE, clear evidence; SE, some evidence; E or EE, equivocal evidence; N or NE, no evidence; IS, inadequate experiment. Blank space under an animal group indicates NO experiment was conducted for that chemical. [b]Sex-specific groups that show a marginal increase for this tumor site. [c]Indicates whether other site-specific cancers were induced; Y, yes; N, no. [d]NCI or *NTP Technical Report* number. [e]*Salmonella typhimurium* results: +, positive; +W, weakly positive; ?, inconclusive; −, negative. [f]Route of exposure: F, feed; G, gavage; I, inhalation; W, drinking water; J, injection; S, skin application. [g]Sex and species: MR, male rats; FR, female rats; MM, male mice; FM, female mice. [h]( ), the sex-species animal group in which a carcinogenic response was chemically induced in that particular organ or system. [i]Totals include positive and equivocal or may have been related responses; under each sex-species column = number of chemicals for that tumor.

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Table 1. (*continued*)

TR No[d]	Chemical	SAL[e]	RUT[f]	Levels of evidence of carcinogenicity[a] MR[g]	FR	MM	FM	May have been related[b] (sex species)	Other[c] sites
	CIRCULATORY SYSTEM (HEMANGIOMA/HEMANGIOSARCOMA)								
233	2-BIPHENYLAMINE HYDROCHLORIDE	+,+	F	N	N	(E)	(P)		N
288	1,3-BUTADIENE	+	I			(CE)	(CE)		Y
189	P-CHLOROANILINE	-,+,+W	F	E	N	(E)	(E)		Y
187	5-CHLORO-O-TOLUIDINE	-,-,-	F	N	N	(P)	(P)		Y
165	4-CHLORO-O-TOLUIDINE HYDROCHLORIDE	-,?	F	N	N	(P)	(P)		N
100	CUPFERRON	+	F	(P)	(P)	(P)	(P)		Y
086	1,2-DIBROMOETHANE	+	G	(P)	P	P	P		Y
210	1,2-DIBROMOETHANE	+	I	(P)	(P)	P	(P)		Y
123	2,7-DICHLORODIBENZO-P-DIOXIN	-	F	N	N	(E)	N		Y
066	1,1-DICHLOROETHANE	-	G	N	(E)	N	E		Y
055	1,2-DICHLOROETHANE	+	G	(P)	P	P	P		Y
029	2-METHYL-1-NITROANTHRAQUINONE	+	F	P	P	(P)	(P)		Y
181	MICHLER'S KETONE	+	F	P	P	(P)	P		Y
107	5-NITRO-O-TOLUIDINE	+	F	N	N	(P)	(P)		Y
251	2,4- & 2,6-TOLUENE DIISOCYANATE	+	G	P	P	N	(P)		Y
153	O-TOLUIDINE HYDROCHLORIDE	-,+	F	P	P	(P)	P		Y
	Number of Chemicals = 16		TOTALS	4	3	11	10		
	CLITORAL GLAND								
334	2-AMINO-5-NITROPHENOL	+	G	SE	NE	NE	NE	(FR)	Y
405	C.I. ACID RED 114	+	W	CE	(CE)				Y
397	C.I. DIRECT BLUE 15	-	W	CE	(CE)				Y
084	2,4-DIAMINOANISOLE SULFATE	+	F	P	(P)	P	P		Y
372	3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE	+,+,+	W	CE	(CE)				Y
390	3,3'-DIMETHYLBENZIDINE DIHYDROCHLORIDE	+	W	CE	(CE)				Y
374	GLYCIDOL	+,+	G	CE	(CE)	CE	CE		Y
368	NALIDIXIC ACID	-	F	CE	(CE)	EE	NE		Y
143	1,5-NAPHTHALENEDIAMINE	+	F	N	(P)	P	P		Y
118	5-NITROACENAPHTHENE	+	F	P	(P)	N	P		Y
127	5-NITRO-O-ANISIDINE	+	F	P	(P)	E	P		Y
	Number of Chemicals = 11		TOTALS	0	11	0	0		
	EPIDIDYMIS								
374	GLYCIDOL	+,+	G	CE	CE	(CE)	CE		Y
	Number of Chemicals = 1		TOTALS	0	0	1	0		
	ESOPHAGUS								
010	DICHLORVOS	+	F	N	N	N	N	(MM) (FM)	N
316	DIMETHYLVINYL CHLORIDE (DMVC)	-,+	G	(CE)	(CE)	CE	CE		Y
	Number of Chemicals = 2		TOTALS	1	1	1	1		
	FORESTOMACH								
073	ALLYL CHLORIDE	+	G	N	N	(E)	(E)		N
378	BENZALDEHYDE	-,-	G	NE	NE	(SE)	(SE)		N
370	BENZOFURAN	-	G	NE	SE	(CE)	(CE)		Y
250	BENZYL ACETATE	-	G	EE	NE	(SE)	(SE)		Y
239	BIS(2-CHLORO-1-METHYLETHYL) ETHER	+W,+,+	G			P	P	(FM)	Y
288	1,3-BUTADIENE	+	I			(CE)	(CE)		Y
300	3-CHLORO-2-METHYLPROPENE	+W,-,-	G	(CE)	(CE)	(CE)	(CE)		N
095	3-CHLOROMETHYLPYRIDINE HYDROCHLORIDE	+	G	(P)	(E)	(P)	(P)		N
063	4-CHLORO-O-PHENYLENEDIAMINE	+	F	(P)	(P)	P	P		Y
222	C.I. DISPERSE YELLOW 3	+	F	P	N	N	P	(MR)	Y
100	CUPFERRON	+	F	(P)	(P)	P	P		Y
242	DIALLYL PHTHALATE	-,-	G			(E)	(E)		Y
028	1,2-DIBROMO-3-CHLOROPROPANE	+	G	(P)	(P)	(P)	(P)		Y
086	1,2-DIBROMOETHANE	+	G	(P)	(P)	(P)	(P)		Y
055	1,2-DICHLOROETHANE	+	G	(P)	P	P	P		Y
269	1,3-DICHLOROPROPENE (TELONE II)	+	G	(CE)	(SE)	IS	(CE)		Y
342	DICHLORVOS	+	G	SE	EE	(SE)	(CE)		Y
257	DIGLYCIDYL RESORCINOL ETHER (DGRE)	+	G	(P)	(P)	(P)	(P)		N
354	DIMETHOXANE	+	G	NE	NE	(EE)	NE		N
360	N,N-DIMETHYLANILINE	-	G	SE	NE	NE	(EE)		Y
287	DIMETHYL HYDROGEN PHOSPHITE	+W,?	G	(CE)	(EE)	NE	NE		Y
316	DIMETHYLVINYL CHLORIDE (DMVC)	-,+	G	(CE)	(CE)	(CE)	(CE)		Y
059	ESTRADIOL MUSTARD		G	N	N	(P)	(P)		Y

Table 1. (*continued*)

TR No[d]	Chemical	SAL[e]	RUT[f]	Levels of evidence of carcinogenicity[a] MR[g]	FR	MM	FM	May have been related[b] (sex species)	Other[c] sites
259	ETHYL ACRYLATE	+W,-,-	G	(P)	(P)	(P)	(P)		N
382	FURFURAL	?,-	G	SE	NE	CE	SE		(FM) Y
374	GLYCIDOL	+,+	G	(CE)	(CE)	(CE)	CE		Y
340	IODINATED GLYCEROL	+	G	SE	NE	NE	SE		(FM) Y
140	PIVALOLACTONE		G	(P)	(P)	N	N		N
115	SULFALLATE	+	F	(P)	P	P	P		Y
399	TITANOCENE DICHLORIDE	+	G	(EE)	(EE)				N
034	TRIFLURALIN	+W	F	N	N	N	(P)		Y
076	TRIS(2,3-DIBROMOPROPYL) PHOSPHATE		F	P	P	(P)	(P)		Y
	Number of Chemicals FORESTOMACH = 32		TOTALS	17	14	18	22		
	GLANDULAR STOMACH								
091	CLONITRALID		F	N	(E)	IS	N		Y
374	GLYCIDOL	+,+	G	CE	(CE)	CE	CE		Y
	Number of Chemicals = 2		TOTALS	0	2	0	0		
	HARDERIAN GLAND								
289	BENZENE	-	G	CE	CE	(CE)	CE		Y
100	CUPFERRON	+	F	P	P	P	(P)		Y
326	ETHYLENE OXIDE		I			(CE)	(CE)		Y
152	ETHYL TELLURAC	-,-	F	E	N	(E)	(E)		Y
374	GLYCIDOL	+,+	G	CE	CE	(CE)	(CE)		Y
330	4-HEXYLRESORCINOL	-,-	G	NE	NE	(EE)	NE		Y
340	IODINATED GLYCEROL	+	G	SE	NE	NE	(SE)		Y
352	N-METHYLOLACRYLAMIDE	-	G	NE	NE	(CE)	(CE)		Y
205	4,4'-OXYDIANILINE	+	F	P	P	(P)	(P)		Y
391	TRIS(2-CHLOROETHYL) PHOSPHATE	-	G	CE	CE	EE	(EE)		Y
	Number of Chemicals = 10		TOTALS	0	0	7	8		
	HEART								
288	1,3-BUTADIENE	+	I			(CE)	(CE)		Y
059	ESTRADIOL MUSTARD		G	N	N	(P)	(P)		Y
060	PHENESTERIN	-,-	G	N	P	(P)	(P)		Y
	Number of Chemicals = 3		TOTALS	0	0	3	3		
	HEMATOPOIETIC SYSTEM (LEUKEMIA/LYMPHOMA)								
394	ACETAMINOPHEN (4-HYDROXYACETANILIDE)	-	F	NE	(EE)	NE	NE		N
253	ALLYL ISOVALERATE	-	G	(P)	N	N	(P)		N
144	2-AMINOANTHRAQUINONE	+	F	P	IS	P	(P)		Y
053	2-AMINO-5-NITROTHIAZOLE	+	F	(P)	N	N	N		N
216	11-AMINOUNDECANOIC ACID	-	F	P	N	(E)	N		Y
318	AMPICILLIN TRIHYDRATE	-	G	(EE)	NE	NE	NE		Y
042	5-AZACYTIDINE	+	J	IS	IS	IS	(P)		N
289	BENZENE	-	G	CE	CE	(CE)	(CE)		Y
215	BISPHENOL A	-,-,-	F	(E)	N	N	N		N
288	1,3-BUTADIENE	+	I			(CE)	(CE)		Y
213	BUTYL BENZYL PHTHALATE	-,-	F	IS	(P)	N	N		N
392	CHLORAMINATED WATER		W	NE	(EE)	NE	NE		N
308	CHLORINATED PARAFFINS: C12, 60% CHLORINE	-	G	CE	CE	CE	CE	(MR)	Y
305	CHLORINATED PARAFFINS: C23, 43% CHLORINE	-	G	NE	EE	(CE)	EE		Y
392	CHLORINATED WATER		W	NE	(EE)	NE	NE		N
405	C.I. ACID RED 114	+	W	CE	CE			(FR)	Y
285	C.I. BASIC RED 9 MONOHYDROCHLORIDE	+	F	CE	CE	CE	CE		(FM) Y
397	C.I. DIRECT BLUE 15	-	W	CE	CE			(MR) (FR)	Y
222	C.I. DISPERSE YELLOW 3	+	F	P	N	N	P		(FM) Y
134	C.I. VAT YELLOW 4	-,-	F	N	N	(P)	N		N
242	DIALLYL PHTHALATE	-,-	G			(E)	E		Y
284	DIALLYL PHTHALATE	-,-	G	NE	(EE)				N
162	2,4-DIAMINOTOLUENE	+	F	P	P	N	P		(FM) Y
123	2,7-DICHLORODIBENZO-P-DIOXIN	-	F	N	N	(E)	N		Y
342	DICHLORVOS	+	G	(SE)	EE	SE	CE		Y
128	3,3'-DIMETHOXYBENZIDINE-4,4'-DIISOCYANATE	+	F	(P)	(P)	N	N		Y
390	3,3'-DIMETHYLBENZIDINE DIHYDROCHLORIDE	+	W	CE	CE			(FR)	Y
323	DIMETHYL METHYLPHOSPHONATE	-	G	SE	NE	IS	NE	(MR)	Y
298	DIMETHYL MORPHOLINOPHOSPHORAMIDATE	-	G	(SE)	(SE)	NE	NE		N
059	ESTRADIOL MUSTARD		G	N	N	(P)	(P)		Y
326	ETHYLENE OXIDE		I			CE	(CE)		Y
402	FURAN	-	G	(CE)	(CE)	CE	CE		Y

(Continued on next page)

Table 1. (*continued*)

TR No[d]	Chemical	SAL[e]	RUT[f]	Levels of evidence of carcinogenicity[a] MR[g]	FR	MM	FM	May have been related[b] (sex species)	Other[c] sites
374	GLYCIDOL	+,+	G	CE	(CE)	CE	CE		Y
366	HYDROQUINONE	-	G	SE	(SE)	NE	SE		Y
078	ICRF-159		J	N	P	N	(P)		Y
018	IPD (3,3'-IMINOBIS-1-PROPANOL DIMETHANESULF		J	E	E	(E)	(E)		Y
340	IODINATED GLYCEROL	+	G	(SE)	NE	NE	SE		Y
291	ISOPHORONE	-	G	SE	NE	(EE)	NE		Y
032	ISOPHOSPHAMIDE		J	N	P	N	(P)		Y
039	LASIOCARPINE	+	F	P	(P)				Y
332	2-MERCAPTOBENZOTHIAZOLE	?,-	G	(SE)	SE	NE	EE		Y
248	4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE	+,+	W	P	P	P	(P)		Y
313	MIREX	-	F	CE	(CE)				Y
060	PHENESTERIN	-,-	G	N	P	(P)	(P)		Y
019	PROCARBAZINE HYDROCHLORIDE	-	J	(P)	(P)	(P)	(P)		Y
240	PROPYL GALLATE	-	F	E	N	(E)	N		Y
311	TETRACHLOROETHYLENE	-	I	(CE)	(SE)	CE	CE		Y
155	2,4,6-TRICHLOROPHENOL	-	F	(P)	N	P	P		Y
058	TRIS(AZIRIDINYL)-PHOSPHINE SULFIDE	+	J	(P)	P	(P)	(P)		Y
391	TRIS(2-CHLOROETHYL) PHOSPHATE	-	G	CE	CE	EE	EE	(MR) (FR)	Y
	Number of Chemicals = 50		TOTALS	18	18	14	17		
	INTESTINE								
038	AROCLOR 1254	-	F	(E)	(E)				Y
295	ASBESTOS, CHRYSOTILE(IR)		F	(SE)	NE				N
321	BROMODICHLOROMETHANE	-	G	(CE)	(CE)	CE	CE		Y
015	CAPTAN	+	F	N	N	(P)	(P)		N
405	C.I. ACID RED 114	+	W	CE	(CE)				Y
397	C.I. DIRECT BLUE 15	-	W	(CE)	(CE)				Y
372	3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE	+,+,+	W	(CE)	(CE)				Y
390	3,3'-DIMETHYLBENZIDINE DIHYDROCHLORIDE	+	W	(CE)	(CE)				Y
374	GLYCIDOL	+,+	G	(CE)	CE	CE	CE		Y
099	PHENAZOPYRIDINE HYDROCHLORIDE	?	F	(P)	(P)	N	P		Y
005	PROFLAVIN HYDROCHLORIDE		F	(E)	N	E	E		Y
047	4,4'-THIODIANILINE	+	F	(P)	P	P	P		Y
350	TRIBROMOMETHANE	?,-,?	G	(SE)	(CE)	NE	NE		N
	Number of Chemicals = 13		TOTALS	11	8	1	1		
	KIDNEY								
111	1-AMINO-2-METHYLANTHRAQUINONE	+	F	(P)	P	N	P		Y
339	2-AMINO-4-NITROPHENOL	+,+	G	(SE)	NE	NE	NE		N
089	O-ANISIDINE HYDROCHLORIDE	?,+,+	F	(P)	P	P	P		Y
067	ASPIRIN, PHENACETIN, AND CAFFEINE		F	N	(E)	N	N		Y
370	BENZOFURAN	-	G	NE	(SE)	CE	CE		Y
321	BROMODICHLOROMETHANE	-	G	(CE)	(CE)	(CE)	CE		Y
308	CHLORINATED PARAFFINS: C12, 60% CHLORINE	-	G	(CE)	CE	CE	CE		Y
041	CHLOROTHALONIL	-	F	(P)	(P)	N	N		N
335	C.I. ACID ORANGE 3	+	G	NE	(CE)	NE	NE		N
411	C.I. PIGMENT RED 23	+	F	(EE)	NE	NE	NE		N
196	CINNAMYL ANTHRANILATE	-	F	(P)	N	P	P		Y
401	2,4-DIAMINOPHENOL DIHYDROCHLORIDE	+	G	NE	NE	(SE)	NE		N
319	1,4-DICHLOROBENZENE (P-DICHLOROBENZENE)	-	G	(CE)	NE	CE	CE		Y
323	DIMETHYL METHYLPHOSPHONATE	-	G	(SE)	NE	IS	NE		Y
382	FURFURAL	?,-	G	SE	NE	CE	SE	(MM)	Y
356	FUROSEMIDE	-	F	(EE)	NE	NE	SE		Y
252	GERANYL ACETATE	-	G	N	N	N	N	(MR)	Y
361	HEXACHLOROETHANE	-,-	G	(CE)	NE				Y
366	HYDROQUINONE	-	G	(SE)	SE	NE	SE		Y
291	ISOPHORONE	-	G	(SE)	NE	EE	NE		Y
347	D-LIMONENE	-	G	(CE)	NE	NE	NE		N
359	8-METHOXYPSORALEN	+	G	(CE)	NE				Y
369	ALPHA-METHYLBENZYL ALCOHOL	-	G	(SE)	NE	NE	NE		N
348	METHYLDOPA SESQUIHYDRATE	-	F	NE	NE	(EE)	NE		N
313	MIREX	-	F	(CE)	CE				Y
266	MONURON	-	F	(CE)	NE	NE	NE		Y
006	NITRILOTRIACETIC ACID (NTA)	-	F	(P)	P	(P)	(P)		Y
006	NITRILOTRIACETIC ACID TRISODIUM MONOHYDRATE	-	F	(P)	(P)				Y
006	NITRILOTRIACETIC ACID TRISODIUM MONOHYDRATE	-	F	(E)	E	N	N		Y
341	NITROFURANTOIN	+,+,+	F	(SE)	NE	NE	CE		Y
358	OCHRATOXIN A	-	G	(CE)	(CE)				Y
367	PHENYLBUTAZONE	-	G	(EE)	(SE)	SE	NE	(FR)	Y
333	N-PHENYL-2-NAPHTHYLAMINE	-	F	NE	NE	NE	(EE)		N

Table 1. (*continued*)

TR No[d]	Chemical	SAL[e]	RUT[f]	Levels of evidence of carcinogenicity[a] MR[g]	FR	MM	FM	May have been related[b] (sex species)	Other[c] sites
409	QUERCETIN	+	F	(SE)	NE				N
311	TETRACHLOROETHYLENE	-	I	(CE)	SE	CE	CE		Y
391	TRIS(2-CHLOROETHYL) PHOSPHATE	-	G	(CE)	(CE)	(EE)	EE		Y
076	TRIS(2,3-DIBROMOPROPYL) PHOSPHATE	+	F	(P)	(P)	(P)	P		Y
	Number of Chemicals = 37		TOTALS	30	11	7	2		
	LIVER								
021	ALDRIN	-	F	E	E	(P)	N		Y
144	2-AMINOANTHRAQUINONE	+	F	(P)	IS	(P)	(P)		Y
093	3-AMINO-9-ETHYLCARBAZOLE HCL	+	F	(P)	(P)	(P)	(P)		Y
111	1-AMINO-2-METHYLANTHRAQUINONE	+	F	(P)	(P)	N	(P)		Y
216	11-AMINOUNDECANOIC ACID	-	F	(P)	N	E	N		Y
038	AROCLOR 1254	-	F	(E)	(E)				Y
370	BENZOFURAN	-	G	NE	SE	(CE)	(CE)		Y
250	BENZYL ACETATE	-	G	EE	NE	(SE)	(SE)		Y
239	BIS(2-CHLORO-1-METHYLETHYL) ETHER	+W,+,+	G			(P)	P		Y
321	BROMODICHLOROMETHANE	-	G	CE	CE	CE	(CE)		Y
288	1,3-BUTADIENE	+	I			CE	(CE)		Y
025	CHLORAMBEN	+	F	N	N	(E)	(P)		N
008	CHLORDANE (ANALYTICAL GRADE)	-	F	N	N	(P)	(P)		N
304	CHLORENDIC ACID	-	F	(CE)	(CE)	(CE)	NE		Y
308	CHLORINATED PARAFFINS: C12, 60% CHLORINE	-	G	(CE)	(CE)	(CE)	(CE)		Y
305	CHLORINATED PARAFFINS: C23, 43% CHLORINE	-	G	NE	EE	CE	(EE)		Y
351	P-CHLOROANILINE HYDROCHLORIDE	-,+,+W	G	CE	EE	(SE)	NE		Y
261	CHLOROBENZENE	-,-	G	(E)	N	N	N		N
075	CHLOROBENZILATE	-,-,-	F	E	E	(P)	(P)		Y
282	CHLORODIBROMOMETHANE	-	G	NE	NE	(EE)	(SE)		N
346	CHLOROETHANE	+	I	EE	EE	IS	CE	(FM)	Y
085	4-CHLORO-M-PHENYLENEDIAMINE	+	F	P	N	N	(P)		Y
063	4-CHLORO-O-PHENYLENEDIAMINE	+	F	P	P	(P)	(P)		Y
187	5-CHLORO-O-TOLUIDINE	-,-,-	F	N	N	(P)	(P)		Y
405	C.I. ACID RED 114	+	W	(CE)	(CE)				Y
285	C.I. BASIC RED 9 MONOHYDROCHLORIDE	+	F	(CE)	CE	(CE)	(CE)		Y
108	C.I. DIRECT BLACK 38	+,+	F	(P)	(P)				N
108	C.I. DIRECT BLUE 6	-,-	F	(P)	(P)				N
397	C.I. DIRECT BLUE 15	-	W	(CE)	(CE)				Y
108	C.I. DIRECT BROWN 95	+W,-	F	N	(P)				N
299	C.I. DISPERSE BLUE 1	+	F	CE	CE	(EE)	NE		Y
222	C.I. DISPERSE YELLOW 3	+	F	(P)	N	N	(P)		Y
226	C.I. SOLVENT YELLOW 14	+,+	F	(P)	(P)	N	N		N
196	CINNAMYL ANTHRANILATE	-	F	P	N	(P)	(P)		Y
142	P-CRESIDINE	+	F	(P)	P	P	(P)		Y
100	CUPFERRON	+	F	(P)	(P)	P	(P)		Y
083	DAMINOZIDE	-	F	N	P	(E)	N		Y
225	D & C RED NO. 9	+W	F	(P)	(E)	N	N		Y
309	DECABROMODIPHENYL OXIDE	-	F	(SE)	(SE)	(EE)	NE		Y
162	2,4-DIAMINOTOLUENE	+	F	(P)	(P)	N	(P)		Y
086	1,2-DIBROMOETHANE	+	G	P	(P)	P	P		Y
319	1,4-DICHLOROBENZENE (P-DICHLOROBENZENE)	-	G	CE	NE	(CE)	(CE)		Y
123	2,7-DICHLORODIBENZO-P-DIOXIN	-	F	N	N	(E)	N		Y
131	P,P'-DICHLORODIPHENOLDICHLOROETHYLENE	-,-	F	N	N	(P)	(P)		N
219	2,6-DICHLORO-P-PHENYLENEDIAMINE	+,+	F	N	N	(P)	(P)		N
263	1,2-DICHLOROPROPANE (PROPYLENE DICHLORIDE)	+W,+W	G	NE	EE	(SE)	(SE)		Y
269	1,3-DICHLOROPROPENE (TELONE II)	+	G	(CE)	SE	IS	CE		Y
090	DICOFOL	-	F	N	N	(P)	N		N
021	DIELDRIN	-	F	N	N	(E)	N		N
212	DI(2-ETHYLHEXYL)ADIPATE	-,-,-	F	N	N	(P)	(P)		N
217	DI(2-ETHYLHEXYL) PHTHALATE	-,-,-	F	(P)	(P)	(P)	(P)		N
156	DI(P-ETHYLPHENYL)DICHLOROETHANE	+	F	N	N	N	(E)		N
372	3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE	+,+,+	W	(CE)	(CE)				Y
390	3,3'-DIMETHYLBENZIDINE DIHYDROCHLORIDE	+	W	(CE)	(CE)				Y
080	1,4-DIOXANE	-,-,-	W	P	(P)	(P)	(P)		Y
132	2,5-DITHIOBIUREA	-	F	N	N	N	(E)		N
388	ETHYLENE THIOUREA (ETU)	-,+W	F	CE	CE	(CE)	(CE)		Y
223	EUGENOL	-	F	N	N	(E)	(E)		N
195	FLUOMETURON	-	F	N	N	(E)	N		N
402	FURAN	-	G	(CE)	(CE)	(CE)	(CE)		Y
382	FURFURAL	?,-	G	(SE)	NE	(CE)	(SE)		Y
374	GLYCIDOL	+,+	G	CE	CE	(CE)	CE		Y
271	HC BLUE 1	+	F	(EE)	SE	(CE)	(CE)		Y
281	HC RED 3	+	G	NE	NE	(EE)	IS		N

(Continued on next page)

Table 1. (*continued*)

TR No[d]	Chemical	SAL[e]	RUT[f]	Levels of evidence of carcinogenicity[a] MR[g]	FR	MM	FM	May have been related[b] (sex species)	Other[c] sites
009	HEPTACHLOR	-,-	F	N	E	(P)	(P)		Y
198	1,2,3,6,7,8-HEXACHLORODIBENZO-P-DIOXIN		G	(E)	(P)	(P)	(P)		N
068	HEXACHLOROETHANE	-,-	G	N	N	(P)	(P)		N
092	HYDRAZOBENZENE	+	F	(P)	(P)	N	(P)		Y
357	HYDROCHLOROTHIAZIDE	-	F	NE	NE	(EE)	NE		N
366	HYDROQUINONE	-	G	SE	SE	NE	(SE)		Y
291	ISOPHORONE	-	G	SE	NE	(EE)	NE		Y
039	LASIOCARPINE	+	F	(P)	(P)				Y
332	2-MERCAPTOBENZOTHIAZOLE	?,-	G	SE	SE	NE	(EE)		Y
328	METHYL CARBAMATE	-	G	(CE)	(CE)	NE	NE		N
186	4,4'-METHYLENEBIS(N,N-DIMETHYL)BENZENAMINE	+	F	P	P	(E)	(P)		Y
306	METHYLENE CHLORIDE	+,-	I	SE	CE	(CE)	(CE)		Y
248	4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE	+,+	W	(P)	P	(P)	(P)		Y
029	2-METHYL-1-NITROANTHRAQUINONE	+	F	(P)	(P)	P	P		Y
352	N-METHYLOLACRYLAMIDE	-	G	NE	NE	(CE)	(CE)		Y
181	MICHLER'S KETONE	+	F	(P)	(P)	P	(P)		Y
313	MIREX	-	F	(CE)	(CE)				Y
266	MONURON	-	F	(CE)	NE	NE	NE		Y
143	1,5-NAPHTHALENEDIAMINE	+	F	N	P	P	(P)		Y
146	NITHIAZIDE	+	F	N	P	(P)	(E)		Y
118	5-NITROACENAPHTHENE	+	F	P	P	N	(P)		Y
133	3-NITRO-P-ACETOPHENETIDE	+	F	N	N	(P)	N		N
127	5-NITRO-O-ANISIDINE	+	F	P	P	(E)	(P)		Y
117	6-NITROBENZIMIDAZOLE	+	F	N	N	(P)	(P)		N
184	NITROFEN		F	N	N	(P)	(P)		N
026	NITROFEN		F	IS	P	(P)	(P)		Y
169	2-NITRO-P-PHENYLENEDIAMINE	+	F	N	N	N	(P)		N
052	3-NITROPROPIONIC ACID	+	G	(E)	N	N	N		Y
190	P-NITROSODIPHENYLAMINE	+W	F	(P)	N	(P)	N		N
107	5-NITRO-O-TOLUIDINE	+	F	N	N	(P)	(P)		Y
205	4,4'-OXYDIANILINE	+	F	(P)	(P)	(P)	(P)		Y
349	PENTACHLOROPHENOL, DOWICIDE EC-7	-	F			(CE)	(CE)		Y
349	PENTACHLOROPHENOL, TECHNICAL	-	F			(CE)	(SE)		Y
099	PHENAZOPYRIDINE HYDROCHLORIDE	?	F	P	P	N	(P)		Y
367	PHENYLBUTAZONE	-	G	EE	SE	(SE)	NE		Y
023	PICLORAM	-	F	N	(E)	N	N		N
124	PIPERONYL SULFOXIDE	-,-	F	N	N	(P)	N		N
244	POLYBROMINATED BIPHENYL MIX (FF1)		G	(P)	(P)	(P)	(P)		N
395	PROBENECID	-	G	NE	NE	NE	(SE)		N
005	PROFLAVIN HYDROCHLORIDE		F	E	N	(E)	(E)		Y
194	SELENIUM SULFIDE	+	G	(P)	(P)	N	(P)		Y
209	2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN	-	G	P	(P)	(P)	(P)		Y
027	1,1,2,2-TETRACHLOROETHANE	-,-	G	(E)	N	(P)	(P)		N
013	TETRACHLOROETHYLENE	-	G	IS	IS	(P)	(P)		N
311	TETRACHLOROETHYLENE	-	I	CE	SE	(CE)	(CE)		Y
033	TETRACHLORVINPHOS	-	F	N	P	(P)	(P)		Y
047	4,4'-THIODIANILINE	+	F	(P)	P	(P)	(P)		Y
251	2,4- & 2,6-TOLUENE DIISOCYANATE	+	G	P	(P)	N	(P)		Y
153	O-TOLUIDINE HYDROCHLORIDE	-,+	F	P	P	P	(P)		Y
037	TOXAPHENE	+	F	E	E	(P)	(P)		Y
074	1,1,2-TRICHLOROETHANE	-,-,-	G	N	N	(P)	(P)		Y
002	TRICHLOROETHYLENE	-,-	G	N	N	(P)	(P)		N
243	TRICHLOROETHYLENE	-,-	G	IS	N	(P)	(P)		N
155	2,4,6-TRICHLOROPHENOL	-	F	P	N	(P)	(P)		Y
034	TRIFLURALIN	+W	F	N	N	N	(P)		Y
160	2,4,5-TRIMETHYLANILINE	+	F	(P)	(P)	(E)	(P)		Y
076	TRIS(2,3-DIBROMOPROPYL) PHOSPHATE		F	P	P	P	(P)		Y
274	TRIS(2-ETHYLHEXYL)PHOSPHATE	-	G	EE	NE	NE	(SE)		Y
278	2,6-XYLIDINE	-,+W,+W	F	P	P			(FR)	Y
235	ZEARALENONE	-	F	N	N	P	(P)		Y
	Number of Chemicals = 124		TOTALS	44	36	74	83		
	LUNG								
289	BENZENE	-	G	CE	CE	(CE)	(CE)		Y
370	BENZOFURAN	-	G	NE	SE	(CE)	(CE)		Y
088	1,2,3-BENZOTRIAZOLE	+W	F	E	E	N	(E)		Y
239	BIS(2-CHLORO-1-METHYLETHYL) ETHER	+W,+,+	G			(P)	(P)		Y
363	BROMOETHANE (ETHYL BROMIDE)	-,+	I	SE	(EE)	(EE)	CE	(MR)	Y
288	1,3-BUTADIENE	+	I			(CE)	(CE)		Y

Table 1. (*continued*)

TR No[d]	Chemical	SAL[e]	RUT[f]	Levels of evidence of carcinogenicity[a] MR[g]	FR	MM	FM	May have been related[b] (sex species)	Other[c] sites
304	CHLORENDIC ACID	-	F	CE	CE	CE	NE	(MR)	Y
405	C.I. ACID RED 114	+	W	CE	(CE)			(MR)	Y
299	C.I. DISPERSE BLUE 1	+	F	CE	CE	(EE)	NE		Y
206	1,2-DIBROMO-3-CHLOROPROPANE	+	I	P	P	(P)	(P)		Y
086	1,2-DIBROMOETHANE	+	G	P	P	(P)	(P)		Y
210	1,2-DIBROMOETHANE	+	I	P	(P)	(P)	(P)		Y
055	1,2-DICHLOROETHANE	+	G	P	P	(P)	(P)		Y
269	1,3-DICHLOROPROPENE (TELONE II)	+	G	CE	SE	IS	(CE)		Y
390	3,3'-DIMETHYLBENZIDINE DIHYDROCHLORIDE	+	W	(CE)	(CE)				Y
287	DIMETHYL HYDROGEN PHOSPHITE	+W,?	G	(CE)	(EE)	NE	NE		Y
121	DIMETHYL TEREPHTHALATE	-	F	N	N	(E)	N		N
355	DIPHENHYDRAMINE HYDROCHLORIDE	-	F	(EE)	EE	NE	NE		Y
329	1,2-EPOXYBUTANE	+	I	(CE)	EE	NE	NE		Y
059	ESTRADIOL MUSTARD		G	N	N	(P)	(P)		Y
326	ETHYLENE OXIDE		I			(CE)	(CE)		Y
374	GLYCIDOL	+,+	G	CE	CE	(CE)	CE		Y
271	HC BLUE 1	+	F	EE	(SE)	CE	CE		Y
359	8-METHOXYPSORALEN	+	G	CE	NE			(MR)	Y
306	METHYLENE CHLORIDE	+,-	I	SE	CE	(CE)	(CE)		Y
352	N-METHYLOLACRYLAMIDE	-	G	NE	NE	(CE)	(CE)		Y
410	NAPHTHALENE	-	I			NE	(SE)		N
143	1,5-NAPHTHALENEDIAMINE	+	F	N	P	P	(P)		Y
118	5-NITROACENAPHTHENE	+	F	(P)	(P)	N	P		Y
060	PHENESTERIN	-,-	G	N	P	(P)	(P)		Y
019	PROCARBAZINE HYDROCHLORIDE	-	J	P	P	(P)	(P)		Y
194	SELENIUM SULFIDE	+	G	P	P	N	(P)		Y
185	STYRENE	-	G	N	N	(E)	N		N
115	SULFALLATE	+	F	P	P	(P)	P		Y
386	TETRANITROMETHANE	+	I	(CE)	(CE)	(CE)	(CE)		N
034	TRIFLURALIN	+W	F	N	N	N	(P)		Y
160	2,4,5-TRIMETHYLANILINE	+	F	P	(P)	E	P		Y
076	TRIS(2,3-DIBROMOPROPYL) PHOSPHATE		F	P	P	(P)	(P)		Y
362	4-VINYL-1-CYCLOHEXENE DIEPOXIDE	+	S	CE	CE	CE	CE		(FM) Y
238	ZIRAM	+	F	P	N	N	(E)		Y
	Number of Chemicals = 40		TOTALS	10	9	22	24		
	MAMMARY GLAND								
049	ACRONYCINE		J	P	(P)	IS	IS		Y
289	BENZENE	-	G	CE	CE	CE	(CE)		Y
288	1,3-BUTADIENE	+	I			CE	(CE)		Y
379	2-CHLOROACETOPHENONE (CN)	-	I	NE	(EE)	NE	NE		N
405	C.I. ACID RED 114	+	W	CE	CE			(FR)	Y
285	C.I. BASIC RED 9 MONOHYDROCHLORIDE	+	F	CE	CE	CE	CE	(FR)	Y
091	CLONITRALID		F	N	(E)	IS	N		Y
207	CYTEMBENA	+	J	P	(P)	N	N		Y
162	2,4-DIAMINOTOLUENE	+	F	P	(P)	N	P		Y
028	1,2-DIBROMO-3-CHLOROPROPANE	+	G	P	(P)	P	P		Y
210	1,2-DIBROMOETHANE	+	I	P	(P)	P	(P)		Y
066	1,1-DICHLOROETHANE	-	G	N	(E)	N	E		Y
055	1,2-DICHLOROETHANE	+	G	P	(P)	P	(P)		Y
263	1,2-DICHLOROPROPANE (PROPYLENE DICHLORIDE)	+W,+W	G	NE	(EE)	SE	SE		Y
342	DICHLORVOS	+	G	SE	(EE)	SE	CE		Y
372	3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE	+,+,+	W	CE	(CE)				Y
390	3,3'-DIMETHYLBENZIDINE DIHYDROCHLORIDE	+	W	CE	(CE)				Y
054	2,4-DINITROTOLUENE	+	F	P	(P)	N	N		Y
326	ETHYLENE OXIDE		I			CE	(CE)		Y
356	FUROSEMIDE	-	F	EE	NE	NE	(SE)		Y
374	GLYCIDOL	+,+	G	(CE)	(CE)	CE	(CE)		Y
092	HYDRAZOBENZENE	+	F	P	(P)	N	P		Y
032	ISOPHOSPHAMIDE		J	N	(P)	N	P		Y
306	METHYLENE CHLORIDE	+,-	I	(SE)	(CE)	CE	CE		Y
146	NITHIAZIDE	+	F	N	(P)	P	E		Y
118	5-NITROACENAPHTHENE	+	F	P	(P)	N	P		Y
337	NITROFURAZONE	+	F	EE	(CE)	NE	CE		Y
358	OCHRATOXIN A	-	G	CE	(CE)				Y
060	PHENESTERIN	-,-	G	N	(P)	P	P		Y
019	PROCARBAZINE HYDROCHLORIDE	-	J	(P)	(P)	P	P		Y
193	RESERPINE	-	F	P	N	P	(P)		Y
115	SULFALLATE	+	F	P	(P)	P	(P)		Y
251	2,4- & 2,6-TOLUENE DIISOCYANATE	+	G	P	(P)	N	P		Y
153	O-TOLUIDINE HYDROCHLORIDE	-,+	F	P	(P)	P	P		Y
	Number of Chemicals = 34		TOTALS	3	29	0	9		

(Continued on next page)

Table 1. (*continued*)

TR No[d]	Chemical	SAL[e]	RUT[f]	Levels of evidence of carcinogenicity[a] MR[g]	FR	MM	FM	May have been related[b] (sex species)	Other[c] sites
	MESOTHELIUM (ABDOMINAL CAVITY/TUNICA VAGINALIS)								
049	ACRONYCINE		J	(P)	(P)	IS	IS		Y
207	CYTEMBENA	+	J	(P)	P	N	N		Y
210	1,2-DIBROMOETHANE	+	I	(P)	P	P	P		Y
372	3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE	+,+,+	W	(CE)	CE				Y
390	3,3'-DIMETHYLBENZIDINE DIHYDROCHLORIDE	+	W	(CE)	CE				Y
152	ETHYL TELLURAC	-,-	F	(E)	N	E	E		Y
374	GLYCIDOL	+,+	G	(CE)	CE	CE	CE		Y
018	IPD (3,3'-IMINOBIS-1-PROPANOL DIMETHANESULF		J	(E)	(E)	E	E		Y
337	NITROFURAZONE	+	F	(EE)	CE	NE	CE		Y
072	PHENOXYBENZAMINE HYDROCHLORIDE	+	J	(P)	(P)	(P)	(P)		N
153	O-TOLUIDINE HYDROCHLORIDE	-,+	F	(P)	P	P	P		Y
	Number of Chemicals = 11		TOTALS	11	3	1	1		
	NASAL CAVITY								
376	ALLYL GLYCIDYL ETHER	+	I	(EE)	NE	(SE)	(EE)		N
142	P-CRESIDINE	+	F	(P)	(P)	P	P		Y
206	1,2-DIBROMO-3-CHLOROPROPANE	+	I	(P)	(P)	(P)	(P)		Y
210	1,2-DIBROMOETHANE	+	I	(P)	(P)	P	(P)		Y
316	DIMETHYLVINYL CHLORIDE (DMVC)	-,+	G	(CE)	(CE)	CE	CE		Y
080	1,4-DIOXANE	-,-,-	W	(P)	(P)	P	P		Y
329	1,2-EPOXYBUTANE	+	I	(CE)	(EE)	NE	NE		Y
340	IODINATED GLYCEROL	+	G	SE	NE	NE	SE	(MR)	Y
267	1,2-PROPYLENE OXIDE	+,+,+	I	(SE)	(SE)	(CE)	(CE)		N
278	2,6-XYLIDINE	-,+W,+W	F	(P)	(P)				Y
	Number of Chemicals = 10		TOTALS	10	8	3	4		
	ORAL CAVITY								
289	BENZENE	-	G	(CE)	(CE)	CE	CE		Y
405	C.I. ACID RED 114	+	W	CE	(CE)			(MR)	Y
397	C.I. DIRECT BLUE 15	-	W	(CE)	(CE)				Y
206	1,2-DIBROMO-3-CHLOROPROPANE	+	I	(P)	(P)	P	P		Y
372	3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE	+,+,+	W	(CE)	(CE)				Y
390	3,3'-DIMETHYLBENZIDINE DIHYDROCHLORIDE	+	W	(CE)	(CE)				Y
316	DIMETHYLVINYL CHLORIDE (DMVC)	-,+	G	(CE)	(CE)	CE	CE		Y
374	GLYCIDOL	+,+	G	CE	(CE)	CE	CE		Y
	Number of Chemicals = 8		TOTALS	7	8	0	0		
	OVARY								
289	BENZENE	-	G	CE	CE	CE	(CE)		Y
288	1,3-BUTADIENE	+	I			CE	(CE)		Y
352	N-METHYLOLACRYLAMIDE	-	G	NE	NE	CE	(CE)		Y
118	5-NITROACENAPHTHENE	+	F	P	P	N	(P)		Y
341	NITROFURANTOIN	+,+,+	F	SE	NE	NE	(CE)		Y
337	NITROFURAZONE	+	F	EE	CE	NE	(CE)		Y
303	4-VINYLCYCLOHEXENE	-,-	G	IS	IS	IS	(CE)		Y
362	4-VINYL-1-CYCLOHEXENE DIEPOXIDE	+	S	CE	CE	CE	(CE)		Y
	Number of Chemicals = 8		TOTALS	0	0	0	8		
	PANCREAS								
334	2-AMINO-5-NITROPHENOL	+	G	(SE)	NE	NE	NE		Y
069	AZINPHOSMETHYL	+W,+	F	(E)	N	N	N		Y
250	BENZYL ACETATE	-	G	(EE)	NE	SE	SE		Y
304	CHLORENDIC ACID	-	F	(CE)	CE	CE	NE		Y
299	C.I. DISPERSE BLUE 1	+	F	(CE)	CE	EE	NE		Y
196	CINNAMYL ANTHRANILATE	-	F	(P)	N	P	P		Y
342	DICHLORVOS	+	G	(SE)	(EE)	SE	CE		Y
331	MALONALDEHYDE, SODIUM SALT	-	G	CE	CE	NE	NE	(MR)	Y
332	2-MERCAPTOBENZOTHIAZOLE	?,-	G	(SE)	SE	NE	EE		Y
026	NITROFEN		F	IS	(P)	P	P		Y
052	3-NITROPROPIONIC ACID	+	G	(E)	N	N	N		Y
240	PROPYL GALLATE	-	F	(E)	N	E	N		Y
345	ROXARSONE	-	F	(EE)	NE	NE	NE		N
251	2,4- & 2,6-TOLUENE DIISOCYANATE	+	G	(P)	(P)	N	P		Y
	Number of Chemicals = 14		TOTALS	13	3	0	0		

Table 1. (*continued*)

TR No[d]	Chemical	SAL[e]	RUT[f]	Levels of evidence of carcinogenicity[a] MR[g]	FR	MM	FM	May have been related[b] (sex species)	Other[c] sites
	PARATHYROID GLAND								
320	ROTENONE	-	F	(EE)	NE	NE	NE		N
	Number of Chemicals = 1		TOTALS	1	0	0	0		
	PITUITARY GLAND								
355	DIPHENHYDRAMINE HYDROCHLORIDE	-	F	EE	(EE)	NE	NE		Y
388	ETHYLENE THIOUREA (ETU)	-,+W	F	CE	CE	(CE)	(CE)		Y
340	IODINATED GLYCEROL	+	G	SE	NE	NE	(SE)		Y
332	2-MERCAPTOBENZOTHIAZOLE	?,-	G	SE	(SE)	NE	EE		Y
315	OXYTETRACYCLINE HYDROCHLORIDE	-	F	EE	(EE)	NE	NE		Y
235	ZEARALENONE	-	F	N	N	(P)	(P)		Y
	Number of Chemicals = 6		TOTALS	0	3	2	3		
	PREPUTIAL GLAND								
334	2-AMINO-5-NITROPHENOL	+	G	SE	NE	NE	NE	(MR)	Y
116	P-ANISIDINE HYDROCHLORIDE	-,+,+	F	(E)	N	N	N		N
289	BENZENE	-	G	CE	CE	(CE)	CE		Y
288	1,3-BUTADIENE	+	I			CE	CE	(MM)	Y
304	CHLORENDIC ACID	-	F	CE	CE	CE	NE	(MR)	Y
397	C.I. DIRECT BLUE 15	-	W	(CE)	CE				Y
084	2,4-DIAMINOANISOLE SULFATE	+	F	(P)	P	P	P		Y
372	3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE	+,+,+	W	(CE)	CE				Y
390	3,3'-DIMETHYLBENZIDINE DIHYDROCHLORIDE	+	W	(CE)	CE				Y
316	DIMETHYLVINYL CHLORIDE (DMVC)	-,+	G	CE	CE	(CE)	CE		Y
291	ISOPHORONE	-	G	(SE)	NE	EE	NE		Y
332	2-MERCAPTOBENZOTHIAZOLE	?,-	G	(SE)	SE	NE	EE		Y
368	NALIDIXIC ACID	-	F	(CE)	CE	EE	NE		Y
337	NITROFURAZONE	+	F	(EE)	CE	NE	CE		Y
240	PROPYL GALLATE	-	F	(E)	N	E	N		Y
058	TRIS(AZIRIDINYL)-PHOSPHINE SULFIDE	+	J	P	P	(P)	P		Y
	Number of Chemicals = 16		TOTALS	12	0	4	0		
	SEMINAL VESICLE								
193	RESERPINE	-	F	P	N	(P)	P		Y
	Number of Chemicals = 1		TOTALS	0	0	1	0		
	SKIN								
093	3-AMINO-9-ETHYLCARBAZOLE HCL	+	F	(P)	P	P	P		Y
289	BENZENE	-	G	(CE)	CE	CE	CE		Y
346	CHLOROETHANE	+	I	(EE)	EE	IS	CE		Y
405	C.I. ACID RED 114	+	W	(CE)	(CE)				Y
285	C.I. BASIC RED 9 MONOHYDROCHLORIDE	+	F	(CE)	CE	CE	CE		Y
397	C.I. DIRECT BLUE 15	-	W	(CE)	(CE)				Y
084	2,4-DIAMINOANISOLE SULFATE	+	F	(P)	P	P	P		Y
310	DIESEL FUEL MARINE	-	S			(EE)	(EE)		N
372	3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE	+,+,+	W	(CE)	(CE)				Y
128	3,3'-DIMETHOXYBENZIDINE-4,4'-DIISOCYANATE	+	F	(P)	P	N	N		Y
390	3,3'-DIMETHYLBENZIDINE DIHYDROCHLORIDE	+	W	(CE)	(CE)				Y
054	2,4-DINITROTOLUENE	+	F	(P)	P	N	N		Y
103	FENTHION	-,+W	F	N	N	(E)	N		N
252	GERANYL ACETATE	-	G	N	N	N	N	(MR)	Y
374	GLYCIDOL	+,+	G	(CE)	CE	(CE)	(CE)		Y
146	NITHIAZIDE	+	F	N	(P)	P	E		Y
127	5-NITRO-O-ANISIDINE	+	F	(P)	P	E	P		Y
337	NITROFURAZONE	+	F	(EE)	CE	NE	CE		Y
364	RHODAMINE 6G	-	F	(EE)	EE	NE	NE		Y
058	TRIS(AZIRIDINYL)-PHOSPHINE SULFIDE	+	J	(P)	(P)	(P)	P		Y
362	4-VINYL-1-CYCLOHEXENE DIEPOXIDE	+	S	(CE)	(CE)	(CE)	(CE)		Y
	Number of Chemicals = 21		TOTALS	18	7	5	3		
	SPLEEN								
130	ANILINE HYDROCHLORIDE		F	(P)	(P)	N	N		N
154	AZOBENZENE	+,+,+	F	(P)	(P)	N	N		N
189	P-CHLOROANILINE	-,+,+W	F	(E)	N	E	E		Y
351	P-CHLOROANILINE HYDROCHLORIDE	-,+,+W	G	(CE)	(EE)	(SE)	NE		Y
225	D & C RED NO. 9	+W	F	(P)	E	N	N		Y

(Continued on next page)

Table 1. (*continued*)

TR No[d]	Chemical	SAL[e]	RUT[f]	Levels of evidence of carcinogenicity[a] MR[g]	FR	MM	FM	May have been related[b] (sex species)	Other[c] sites
360	N,N-DIMETHYLANILINE	-	G	(SE)	NE	NE	EE		Y
349	PENTACHLOROPHENOL, DOWICIDE EC-7		F			CE	(CE)		Y
349	PENTACHLOROPHENOL, TECHNICAL	-	F			CE	(SE)		Y
016	PHOSPHAMIDON	+	F	(E)	E	N	N		Y
020	4,4'-SULFONYLDIANILINE (DAPSONE)	-	F	(P)	N	N	N		N
153	O-TOLUIDINE HYDROCHLORIDE	-,+	F	(P)	(P)	P	P		Y
	Number of Chemicals = 11		TOTALS	9	4	1	2		
	SUBCUTANEOUS TISSUE								
234	ALLYL ISOTHIOCYANATE	+W,-	G	P	(E)	N	N		Y
285	C.I. BASIC RED 9 MONOHYDROCHLORIDE	+	F	(CE)	(CE)	CE	CE		Y
210	1,2-DIBROMOETHANE	+	I	P	P	P	(P)		Y
055	1,2-DICHLOROETHANE	+	G	(P)	P	P	P		Y
374	GLYCIDOL	+,+	G	CE	CE	CE	(CE)		Y
018	IPD (3,3'-IMINOBIS-1-PROPANOL DIMETHANESULF		J	E	E	(E)	(E)		Y
291	ISOPHORONE	-	G	SE	NE	(EE)	NE		Y
359	8-METHOXYPSORALEN	+	G	CE	NE			(MR)	Y
029	2-METHYL-1-NITROANTHRAQUINONE	+	F	(P)	(P)	P	P		Y
368	NALIDIXIC ACID	-	F	CE	CE	(EE)	NE		Y
341	NITROFURANTOIN	+,+,+	F	SE	NE	NE	CE	(MR)	Y
201	2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN	-	S			(E)	(P)		N
251	2,4- & 2,6-TOLUENE DIISOCYANATE	+	G	(P)	(P)	N	P		Y
153	O-TOLUIDINE HYDROCHLORIDE	-,+	F	(P)	P	P	P		Y
081	TRIMETHYLPHOSPHATE	+	G	(P)	N	N	P		Y
278	2,6-XYLIDINE	-,+W,+W	F	P	P			(MR) (FR)	Y
	Number of Chemicals = 16		TOTALS	9	5	4	4		
	THYROID GLAND								
021	ALDRIN	-	F	(E)	(E)	P	N		Y
112	3-AMINO-4-ETHOXYACETANILIDE	+	F	N	N	(P)	N		N
089	O-ANISIDINE HYDROCHLORIDE	?,+,+	F	(P)	P	P	P		Y
069	AZINPHOSMETHYL	+W,+	F	(E)	N	N	N		Y
308	CHLORINATED PARAFFINS: C12, 60% CHLORINE	-	G	CE	(CE)	CE	(CE)		Y
285	C.I. BASIC RED 9 MONOHYDROCHLORIDE	+	F	(CE)	(CE)	CE	CE		Y
309	DECABROMODIPHENYL OXIDE	-	F	SE	SE	(EE)	NE		Y
084	2,4-DIAMINOANISOLE SULFATE	+	F	(P)	(P)	(P)	(P)		Y
149	N,N'-DIETHYLTHIOUREA	-	F	(P)	(P)	N	N		N
388	ETHYLENE THIOUREA (ETU)	-,+W	F	(CE)	(CE)	(CE)	(CE)		Y
374	GLYCIDOL	+,+	G	(CE)	(CE)	CE	CE		Y
271	HC BLUE 1	+	F	EE	SE	CE	CE	(MM)	Y
009	HEPTACHLOR	-,-	F	N	(E)	P	P		Y
340	IODINATED GLYCEROL	+	G	(SE)	NE	NE	SE		Y
331	MALONALDEHYDE, SODIUM SALT	-	G	(CE)	(CE)	NE	NE		Y
186	4,4'-METHYLENEBIS(N,N-DIMETHYL)BENZENAMINE	+	F	(P)	(P)	E	P		Y
248	4,4'-METHYLENEDIANILINE DIHYDROCHLORIDE	+,+	W	(P)	(P)	(P)	(P)		Y
143	1,5-NAPHTHALENEDIAMINE	+	F	N	P	(P)	(P)		Y
205	4,4'-OXYDIANILINE	+	F	(P)	(P)	P	(P)		Y
016	PHOSPHAMIDON	+	F	E	(E)	N	N		Y
231	STANNOUS CHLORIDE	-	F	(E)	N	N	N		N
209	2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN	-	G	(P)	P	P	(P)		Y
131	TETRACHLORODIPHENYLETHANE	-	F	(E)	N	N	N		N
033	TETRACHLORVINPHOS	-	F	N	(P)	P	P		Y
047	4,4'-THIODIANILINE	+	F	(P)	(P)	(P)	(P)		Y
037	TOXAPHENE	+	F	(E)	(E)	P	P		Y
129	TRIMETHYLTHIOUREA	-	F	N	(P)	N	N		N
391	TRIS(2-CHLOROETHYL) PHOSPHATE	-	G	CE	CE	EE	EE	(MR) (FR)	Y
238	ZIRAM	+	F	(P)	N	N	E		Y
	Number of Chemicals = 29		TOTALS	20	18	8	8		
	URETER								
006	NITRILOTRIACETIC ACID (NTA)	-	F	(P)	P	P	P		Y
006	NITRILOTRIACETIC ACID TRISODIUM MONOHYDRATE	-	F	(P)	(P)				Y
	Number of Chemicals = 2		TOTALS	2	1	0	0		
	URINARY BLADDER								
234	ALLYL ISOTHIOCYANATE	+W,-	G	(P)	E	N	N		Y
094	4-AMINO-2-NITROPHENOL	+	F	(P)	(E)	N	N		N

Table 1. (*continued*)

TR No[d]	Chemical	SAL[e]	RUT[f]	Levels of evidence of carcinogenicity[a] MR[g]	FR	MM	FM	May have been related[b] (sex species)	Other[c] sites
216	11-AMINOUNDECANOIC ACID	-	F	(P)	N	E	N		Y
089	O-ANISIDINE HYDROCHLORIDE	?,+,+	F	(P)	(P)	(P)	(P)		Y
067	ASPIRIN, PHENACETIN, AND CAFFEINE		F	N	(E)	N	N		Y
179	P-BENZOQUINONE DIOXIME	+,+	F	N	(P)	N	N		N
063	4-CHLORO-O-PHENYLENEDIAMINE	+	F	(P)	(P)	P	P		Y
299	C.I. DISPERSE BLUE 1	+	F	(CE)	(CE)	EE	NE		Y
105	M-CRESIDINE	+	G	(P)	(P)	IS	N		N
142	P-CRESIDINE	+	F	(P)	(P)	(P)	(P)		Y
269	1,3-DICHLOROPROPENE (TELONE II)	+	G	CE	SE	IS	(CE)		Y
374	GLYCIDOL	+,+	G	CE	CE	(CE)	CE		Y
245	MELAMINE	-	F	(P)	N	N	N		N
006	NITRILOTRIACETIC ACID (NTA)	-	F	P	(P)	P	P		Y
006	NITRILOTRIACETIC ACID TRISODIUM MONOHYDRATE	-	F	P	(P)				Y
006	NITRILOTRIACETIC ACID TRISODIUM MONOHYDRATE	-	F	E	(E)	N	N		Y
164	N-NITROSODIPHENYLAMINE	-	F	(P)	(P)	N	N		N
153	O-TOLUIDINE HYDROCHLORIDE	-,+	F	P	(P)	P	P		Y
	Number of Chemicals = 18		TOTALS	10	13	3	3		
	UTERUS/CERVIX								
093	3-AMINO-9-ETHYLCARBAZOLE HCL	+	F	P	(P)	P	P		Y
363	BROMOETHANE (ETHYL BROMIDE)	-,+	I	SE	EE	EE	(CE)		Y
346	CHLOROETHANE	+	I	EE	EE	IS	(CE)		Y
083	DAMINOZIDE	-	F	N	(P)	E	N		Y
066	1,1-DICHLOROETHANE	-	G	N	E	N	(E)		Y
055	1,2-DICHLOROETHANE	+	G	P	P	P	(P)		Y
372	3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE	+,+,+	W	CE	(CE)				Y
128	3,3'-DIMETHOXYBENZIDINE-4,4'-DIISOCYANATE	+	F	P	(P)	N	N		Y
326	ETHYLENE OXIDE		I			CE	(CE)		Y
374	GLYCIDOL	+,+	G	CE	CE	CE	(CE)		Y
078	ICRF-159		J	N	(P)	N	P		Y
032	ISOPHOSPHAMIDE		J	N	(P)	N	P		Y
143	1,5-NAPHTHALENEDIAMINE	+	F	N	(P)	P	P		Y
019	PROCARBAZINE HYDROCHLORIDE	-	J	P	P	P	(P)		Y
047	4,4'-THIODIANILINE	+	F	P	(P)	P	P		Y
081	TRIMETHYLPHOSPHATE	+	G	P	N	N	(P)		Y
	Number of Chemicals = 16		TOTALS	0	8	0	8		
	ZYMBAL GLAND								
093	3-AMINO-9-ETHYLCARBAZOLE HCL	+	F	(P)	(P)	P	P		Y
289	BENZENE	-	G	(CE)	(CE)	(CE)	(CE)		Y
288	1,3-BUTADIENE	+	I			CE	CE	(MM)	Y
405	C.I. ACID RED 114	+	W	(CE)	(CE)				Y
285	C.I. BASIC RED 9 MONOHYDROCHLORIDE	+	F	(CE)	(CE)	CE	CE		Y
397	C.I. DIRECT BLUE 15	-	W	(CE)	(CE)				Y
100	CUPFERRON	+	F	P	(P)	P	(P)		Y
084	2,4-DIAMINOANISOLE SULFATE	+	F	(P)	(P)	P	P		Y
372	3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE	+,+,+	W	(CE)	(CE)				Y
128	3,3'-DIMETHOXYBENZIDINE-4,4'-DIISOCYANATE	+	F	(P)	(P)	N	N		Y
390	3,3'-DIMETHYLBENZIDINE DIHYDROCHLORIDE	+	W	(CE)	(CE)				Y
374	GLYCIDOL	+,+	G	(CE)	CE	CE	CE		Y
092	HYDRAZOBENZENE	+	F	(P)	P	N	P		Y
359	8-METHOXYPSORALEN	+	G	(CE)	NE				Y
118	5-NITROACENAPHTHENE	+	F	(P)	(P)	N	P		Y
127	5-NITRO-O-ANISIDINE	+	F	(P)	(P)	E	P		Y
365	PENTAERYTHRITOL TETRANITRATE	-	F	(EE)	(EE)	NE	NE		N
047	4,4'-THIODIANILINE	+	F	(P)	(P)	P	P		Y
057	BETA-THIOGUANIDINE DEOXYRIBOSIDE		J	(E)	(P)	IS	IS		N
058	TRIS(AZIRIDINYL)-PHOSPHINE SULFIDE	+	J	(P)	(P)	P	P		Y
	Number of Chemicals = 20		TOTALS	18	16	2	2		
	NO SITE								
050	ACETOHEXAMIDE	-	F	N	N	N	N		N
230	AGAR		F	N	N	N	N		N
136	ALDICARB	-	F	N	N	N	N		N
387	DL-AMPHETAMINE SULFATE	?	F	NE	NE	NE	NE		N
104	ANILAZINE	-	F	N	N	N	N		N
036	O-ANTHRANILIC ACID	-	F	N	N	N	N		N
279	ASBESTOS, AMOSITE		F	N	N				N

(Continued on next page)

Table 1. (*continued*)

TR No[d]	Chemical	SAL[e]	RUT[f]	Levels of evidence of carcinogenicity[a] MR[g]	FR	MM	FM	May have been related[b] (sex species)	Other[c] sites
295	ASBESTOS, CHRYSOTILE(SR)		F	NE	NE				N
280	ASBESTOS, CROCIDOLITE		F	N	N				N
277	ASBESTOS, TREMOLITE		F	N	N				N
247	L-ASCORBIC ACID	+W,-	F	N	N	N	N		N
204	BENZOIN	-,-,+W	F	N	N	N	N		N
343	BENZYL ALCOHOL	-	G	NE	NE	NE	NE		N
191	BIS(2-CHLORO-1-METHYLETHYL) ETHER	+W,+,+	G	N	N				N
324	BORIC ACID	?,-	F			NE	NE		N
150	BUTYLATED HYDROXYTOLUENE	-	F	N	N	N	N		N
312	N-BUTYL CHLORIDE	-,-	G	NE	NE	NE	NE		N
163	CALCIUM CYANAMIDE	+W,?	F	N	N	N	N		N
214	CAPROLACTAM	-	F	N	N	N	N		N
173	CARBROMAL	-,-	F	N	N	N	N		N
381	D-CARVONE	-	G			NE	NE		N
294	CHLORINATED TRISODIUM PHOSPHATE	+W	G	IS	IS	NE	NE		N
177	4-(CHLOROACETYL)ACETANILIDE	+	F	N	N	N	N		N
377	O-CHLOROBENZALMALON NITRILE (CS)	?,?	I	NE	NE	NE	NE		N
275	2-CHLOROETHANOL (ETHYLENE CHLOROHYDRIN)	+,+,+	S	NE	NE	NE	NE		N
158	2-CHLOROETHYLTRIMETHYLAMMONIUM CHLORIDE	-,-	F	N	N	N	N		N
178	2-CHLOROMETHYLPYRIDINE HYDROCHLORIDE	+	G	N	N	N	N		N
113	2-CHLORO-P-PHENYLENEDIAMINE SULFATE	+	F	N	N	N	N		N
065	CHLOROPICRIN	+,+	G	IS	IS	N	N		N
145	3-CHLORO-P-TOLUIDINE	-,+W	F	N	N	N	N		N
317	CHLORPHENIRAMINE MALEATE	-	G	NE	NE	NE	NE		N
045	CHLORPROPAMIDE	-	F	N	N	N	N		N
211	C.I. ACID ORANGE 10	-	F	N	N	N	N		N
220	C.I. ACID RED 14	-	F	N	N	N	N		N
096	COUMAPHOS	-	F	N	N	N	N		N
030	DIARYLANILIDE YELLOW	-	F	N	N	N	N		N
137	DIAZINON	-	F	N	N	N	N		N
122	DIBENZO-P-DIOXIN		F	N	N	N	N		N
183	DIBUTYLTIN DIACETATE	-	F	N	IS	N	N		N
255	1,2-DICHLOROBENZENE (O-DICHLOROBENZENE)	-	G	N	N	N	N		N
131	DICHLORODIPHENYLTRICHLOROETHANE (DDT)	-	F	N	N	N	N		N
353	2,4-DICHLOROPHENOL	-	F	NE	NE	NE	NE		N
010	DICHLORVOS	-	F	N	N	N	N		N
056	N,N'-DICYCLOHEXYLTHIOUREA	-	F	N	N	N	N		N
022	DIELDRIN	-	F	N	N				N
004	DIMETHOATE	+,+	F	N	N	N	N		N
171	2,4-DIMETHOXYANILINE HYDROCHLORIDE	+	F	N	N	N	N		N
125	DIOXATHION	+	F	N	N	N	N		N
062	ENDOSULFAN	-	F	IS	N	IS	N		N
012	ENDRIN	-	F	N	N	N	N		N
307	EPHEDRINE SULFATE	-	F	NE	NE	NE	NE		N
338	ERYTHROMYCIN STEARATE	-	F	NE	NE	NE	NE		N
046	ETHIONAMIDE	-	F	N	N	N	N		N
208	FD & C YELLOW NO. 6	-	F	N	N	N	N		N
101	FORMULATED FENAMINOSULF	+	F	N	N	N	N		N
252	GERANYL ACETATE	-	G	N	N	N	N		N
229	GUAR GUM	-	F	N	N	N	N		N
227	GUM ARABIC	-	F	N	N	N	N		N
293	HC BLUE 2	+	F	NE	NE	NE	NE		N
202	1,2,3,6,7,8-HEXACHLORODIBENZO-P-DIOXIN		S			N	N		N
040	HEXACHLOROPHENE	-	F	N	N				N
276	8-HYDROXYQUINOLINE	+	F	NE	NE	NE	NE		N
110	IODOFORM	+,+	G	N	N	N	N		N
151	LEAD DIMETHYLDITHIOCARBAMATE	+	F	N	N	N	N		N
014	LINDANE	-	F	N	N	N	N		N
175	LITHOCHOLIC ACID	-	G	N	N	N	N		N
221	LOCUST BEAN GUM	-	F	N	N	N	N		N
135	MALAOXON	-	F	N	N	N	N		N
024	MALATHION	-	F	N	N	N	N		N
192	MALATHION	-	F	N	N				N
236	D-MANNITOL	-,-,-	F	N	N	N	N		N
098	DL-MENTHOL	-	F	N	N	N	N		N
035	METHOXYCHLOR	-,-	F	N	N	N	N		N
385	METHYL BROMIDE	+	I			NE	NE		N
314	METHYL METHACRYLATE	-,-	I	NE	NE	NE	NE		N
157	METHYL PARATHION	+	F	N	N	N	N		N
147	MEXACARBATE		F	N	N	N	N		N
396	MONOCHLOROACETIC ACID	-	G	NE	NE	NE	NE		N

Table 1. (*continued*)

TR No[d]	Chemical	SAL[e]	RUT[f]	Levels of evidence of carcinogenicity[a] MR[g]	FR	MM	FM	May have been related[b] (sex species)	Other[c] sites
168	N-(1-NAPHTHYL)ETHYLENEDIAMINE DIHYDROCHLORI	+	F	N	N	N	N		N
310	NAVY FUELS JP-5	-	S			NE	NE		N
109	4-NITROANTHRANILIC ACID	+,+	F	N	N	N	N		N
064	1-NITRONAPHTHALENE	+	F	N	N	N	N		N
180	4-NITRO-O-PHENYLENEDIAMINE	+,+,+	F	N	N	N	N		N
170	BETA-NITROSTYRENE	+W,-	G	N	N	N	N		N
336	PENICILLIN VK	-	G	NE	NE	NE	NE		N
061	PENTACHLORONITROBENZENE	-	F	N	N	N	N		N
325	PENTACHLORONITROPENZENE	-	F			NE	NE		N
007	PHENFORMIN HYDROCHLORIDE	-	F	N	N	N	N		N
203	PHENOL	-,-	W	N	N	N	N		N
174	P-PHENYLENEDIAMINE DIHYDROCHLORIDE	+	F	N	N	N	N		N
322	PHENYLEPHRINE HYDROCHLORIDE	-	F	NE	NE	NE	NE		N
141	1-PHENYL-3-METHYL-5-PYRAZOLONE	-	F	N	N	N	N		N
301	O-PHENYLPHENOL	+W,-	S			NE	NE		N
082	N-PHENYL-P-PHENYLENEDIAMINE	-	F	N	N	N	N		N
148	1-PHENYL-2-THIOUREA	-	F	N	N	N	N		N
017	PHOTODIELDRIN	+	F	N	N	N	N		N
161	PHTHALAMIDE	-	F	N	N	N	N		N
159	PHTHALIC ANHYDRIDE	-,-	F	N	N	N	N		N
120	PIPERONYL BUTOXIDE	-	F	N	N	N	N		N
272	PROPYLENE	+	I	NE	NE	NE	NE		N
048	PYRAZINAMIDE	-	F	N	N	N	IS		N
077	PYRIMETHAMINE	-	F	N	N	IS	N		N
403	RESORCINOL	-	G	NE	NE	NE	NE		N
197	SELENIUM SULFIDE	+	S			N	N		N
199	SELSUN	-	S			N	N		N
389	SODIUM AZIDE	+	G	NE	NE				N
172	SODIUM DIETHYLDITHIOCARBAMATE	-	F	N	N	N	N		N
373	SUCCINIC ANHYDRIDE	-,-	G	NE	NE	NE	NE		N
138	SULFISOXAZOLE	-	G	N	N	N	N		N
102	3-SULFOLENE	-	G	N	N	N	N		N
224	TARA GUM	-	F	N	N	N	N		N
114	2,3,5,6-TETRACHLORO-4-NITROANISOLE	-	F	N	N	N	N		N
344	TETRACYCLINE HYDROCHLORIDE	-	F	NE	NE	NE	NE		N
166	TETRAETHYLTHIURAM DISULFIDE	-	F	N	N	N	N		N
296	TETRAKIS(HYDROXYMETHYL)PHOSPHONIUM CHLORIDE	-	G	NE	NE	NE	NE		N
296	TETRAKIS(HYDROXYMETHYL)PHOSPHONIUM SULFATE	-	G	NE	NE	NE	NE		N
097	TITANIUM DIOXIDE	-	F	N	N	N	N		N
051	TOLAZAMIDE	?	F	N	N	N	N		N
031	TOLBUTAMIDE	-	F	N	N	N	N		N
371	TOLUENE	-	I	NE	NE	NE	NE		N
200	2,6-TOLUENEDIAMINE DIHYDROCHLORIDE	+	F	N	N	N	N		N
126	2,5-TOLUENEDIAMINE SULFATE	+	F	N	N	N	N		N
106	TRICHLOROFLUOROMETHANE	-	G	IS	IS	N	N		N
139	TRIPHENYLTIN HYDROXIDE	-	F	N	N	N	N		N
011	TRISODIUM ETHYLENEDIAMINETETRAACETATE TRIHYD	-	F	N	N	N	N		N
071	L-TRYPTOPHAN	-	F	N	N	N	N		N
375	VINYL TOLUENE	-	I	NE	NE	NE	NE		N
327	XYLENES (MIXED)	-	G	NE	NE	NE	NE		N
	Number of Chemicals = 128		TOTALS	115	115	117	118		

tween sexes and species, of the 104 chemicals inducing liver cancer, 87 were evaluated in studies that were considered to be adequate in all respects in each of the four sex-species experiments. From Table 1, 25 chemicals were carcinogenic to the liver in both rats and mice; 9 chemicals caused liver cancer only in rats; 53 caused liver cancer only in mice; and in 226/313 studies, no chemically related liver tumors were observed in either rats or mice (see Tables 5–8 as well). This clearly supports the evidence that in the majority of our carcinogenicity studies the liver does not show a carcinogenic response from chemical exposure (that is, only 28% [87/313] of these chemicals induced a carcinogenic response of the liver in at least one sex of one species).

These data show a strong but not perfect statistical correlation—among the chemicals causing liver cancer in rats, 74% (25/34) also induced liver tumors in mice. For chemicals not producing liver tumors in rats, the proportion causing liver tumors in mice is 19% (53/279). Thus, the overall interspecies concordance in liver carcinogenicity is 80% (251/313). Similar analyses have been conducted for other organ sites and reveal that the forestomach and the thyroid gland likewise show a high interspecies correlation.

Moreover, the organ-system site listing of chemicals can reveal other sex or species consistencies, as well as

any correlations or lack of correspondence among the chemicals in that particular grouping. For example, tumors of the skin were induced largely in animals that had been exposed to chemicals by other than the dermal route. As importantly, one can observe easily how well one species predicts or mimics the chemically induced response in the other species. For 1,2-dibromoethane three of the four experimental cells showed positive responses in the circulatory system from inhalation exposure while one of four showed the same response using the gavage route of chemical administration. Bromodichloromethane caused tumors in the kidney in all groups except for the female mice; obviously, most chemicals causing cancer in the kidney do not show cross-sex or cross-species correspondence (*46*).

Another important observation is the apparent lack of "sensitivity" of particular organ sites for showing chemical-associated carcinogenicity. For example, in only three instances has the heart responded to chemical carcinogens, all in both sexes of mice, and all induced other site-specific tumors as well. The parathyroid gland has not been considered as a carcinogenic site for any chemical, and rarely do tumors of this organ occur in control animals (*22*). For rotenone the association of adenomas of the parathyroid gland was decided to be "equivocal evidence," whereby one adenoma was observed in controls and four were found in the top exposure group (75 ppm); no other possible carcinogenic effects were detected in any of the eight sex-species exposed groups. Tumors of the seminal vesicle were found for only one chemical (reserpine) in male mice. Osteosarcomas of the bone have been induced by only one chemical (acronycine); two other chemicals showed a marginal increase in this tumor type, all in male rats.

Table 2 presents a summary of the levels of evidence: evaluations by chemical show that 198 of 379 chemicals (or 52%) were considered carcinogenic in at least one of the four experiments; an equally instructive view of the overall carcinogenicity of these chemicals is shown by the evaluations based on individual experiments, whereby of the 1394 cases, 459 (or 33%) showed carcinogenicity.

One qualitative way to categorize chemical carcinogens is to group them by the strength of the evidence based simply on the number of positive experimental cells across sexes and species. Consequently, we developed the data in Table 3 that qualitatively aggregate the chemicals by the number of positive experiments. In this way one begins to differentiate the 50% of chemicals causing cancer in experimental systems. These data show that 43 of the 313 chemicals caused cancer in each of the four experimental cells and 25 in the three of four grouping. These two classes of chemicals comprise 22% of the total number evaluated in long-term studies. The category of chemicals causing positive responses in two of the four experiments contains the largest number of chemicals—56—compared to the other three subsets with evidence of carcinogenicity. Chemicals that caused tumors in only one of the experiments equaled 38. For no evidence there were 151 chemicals.

Table 4 assesses the correlations between sexes and species, and the findings are consistent with those reported previously (*47*). The correlation of carcinogenic responses between rats and mice is a reasonable 74%, but certainly not perfect or as good as that between sexes within a species (85–87%).

Table 5 contains a composite listing by site in alphabetical order of the numbers of chemicals showing increases in tumors for both positive evidence and equivocal evidence categories. Table 6 lists in rank order those organs or systems most often associated with chemically induced tumors. These sites account for almost all the experiments showing a positive response, and represent a sizeable number of the chemicals showing positive effects.

The percentage of chemicals showing positive responses within each sex-species cell is approximately similar, with the male mouse being the "least responsive" of the four (Tables 5 and 6). Mice appear twice as likely as do rats to show a positive effect in the liver. The female rat responds more than the other sex-species for chemically associated mammary tumors, whereas the male leads with chemicals causing tumors of the kidney (*46*) and of the pancreas (*48*). The forestomach responses to chemical carcinogens is interesting in its consistency across sex-species. While the urinary bladder and Zymbal gland cancers occur overwhelmingly in the rat, the Harderian gland neoplasms have been limited to the mouse. The skin and subcutaneously associated tumors seemed to be reserved primarily for the rat, and more frequently the male rat. A carcinogenic response of the clitoral gland was observed for ten chemicals in female rats while none occurred in female mice; conversely, in female mice the ovary showed car-

Table 2. Summary results from 379 carcinogenicity studies in rodents.

	By experiment					By chemical		
	Rats		Mice					
Study result	Male	Female	Male	Female	Total	Rats	Mice	Overall
Positive	127	107	102	123	459	146	137	198
Equivocal	41	36	35	20	132	48	35	53
No evidence	183	211	204	205	803	162	178	128
Totals	351	354	341	348	1394	356	350	379

Table 3. Carcinogenicity results for 313 chemical studies in rodents.[a]

Proportion of positive studies	Rats		Mice		Number of studies with these results		%
	Male	Female	Male	Female			
4/4	+	+	+	+	43		
					Subtotals	43	13.7
3/4	+	+	+	–	1		
	+	+	–	+	11		
	+	–	+	+	7		
	–	+	+	+	6		
					Subtotals	25	8.0
2/4	+	+	–	–	19		
	+	–	+	–	2		
	+	–	–	+	7		
	–	+	+	–	2		
	–	+	–	+	3		
	–	–	+	+	23		
					Subtotals	56	17.9
1/4	+	–	–	–	17		
	–	+	–	–	4		
	–	–	+	–	9		
	–	–	–	+	8		
					Subtotals	38	12.1
0/4	–	–	–	–	151		
					Subtotals	151	48.2
Totals						313	100

[a] Includes only those long-term studies considered adequate in all four sex-species experiments.

Note: Equivocal evidence (or marginal) results are considered to be between a positive response and no evidence of a response; these results are placed into the no evidence category.

Table 4. Intra- and inter-species concordance in carcinogenic responses in 379 chemical carcinogenicity studies in rodents.[a]

Comparison	Observed response				% Concordant (+ + or – –) responses
	+ +	+ –	– +	– –	
Male rats vs. female rats	88	38	16	207	84.5 (295/349)
Male rats vs. male mice	54	54	40	169	70.3 (223/317)
Male rats vs. female mice	70	41	41	169	74.5 (239/321)
Female rats vs. male mice	53	38	42	185	74.8 (239/318)
Female rats vs. female mice	65	28	47	183	76.8 (248/323)
Male mice vs. female mice	88	14	31	206	86.7 (294/339)
Rats vs. mice	82	40	40	151	74.4 (233/313)

[a] Equivocal evidence (or marginal) results are considered to be between a positive response and no evidence of a response; these results were placed into the no evidence category.

cinogenic responses for eight chemicals whereas none were found for the female rat.

Table 7 lists the most frequently occurring organ and tissue sites for chemically induced cancers in rats, and Table 8 contains the top 10 for mice. Separating the species allows a better demonstration of the number of unique chemicals per target site as well as to show the consistency among the available target sites, especially if one removes gender-related tumor sites.

Discussion and Conclusions

These site-specific tumor-chemical carcinogen compilations (Table 1) are most useful for maintaining a historic perspective when evaluating the carcinogenicity of contemporary experiments. Equally important, the chemical-tumor-organ connection permits an evaluation of how well chemically induced cancers in a particular organ in one sex or species will predict or correlate with the other sex or species. Likewise, target site predictions can be made for chemicals selected for study that may be similar to those already evaluated; thereby experimental protocols could be adjusted to allow for more extensive pathology on preselected target organs (i.e., serial sections of the kidney). Further from these observations, one could decide to use two strains of mice to evaluate a short-chain chlorinated aliphatic compound or to study a human carcinogen in a sex-species known to develop chemically induced tumors in the same site observed in humans.

Table 5. Numbers of chemicals associated with site-specific neoplasia in rats and mice from 1394 long-term carcinogenesis experiments.

	Rats[a]				Mice[a]				Totals[b]		
	Male		Female		Male		Female				
Site	POS	EE	POS	EE	POS	EE	POS	EE	POS	EE	POS/EE
Adrenal gland	5	9	3	7	5	2	4	1	13	15	28
Bone	1	2	0	0	0	0	0	0	1	2	3
Brain	2	7	2	4	1	1	1	0	2	9	11
Circulatory system	4	0	2	1	8	3	9	1	13	4	16
Clitoral gland	0	0	10	1	0	0	0	0	10	1	11
Epididymis	0	0	0	0	1	0	0	0	1	0	1
Esophagus	1	0	1	0	0	1	0	1	1	1	2
Forestomach	15	2	11	3	15	3	16	6	23	11	32
Glandular stomach	0	0	1	1	0	0	0	0	1	1	2
Harderian gland	0	0	0	0	5	2	6	2	7	3	10
Heart	0	0	0	0	3	0	3	0	3	0	3
Hematopoietic system	12	6	10	8	8	6	13	4	29	21	50
Intestines	9	2	7	1	1	0	1	0	11	2	13
Kidney	25	5	9	2	4	3	1	1	29	10	37
Liver	38	6	32	4	58	16	75	8	104	31	124
Lung	5	5	7	2	18	4	21	3	30	12	40
Mammary gland	3	0	22	7	0	0	9	0	27	7	34
Mesothelium (abdomen)	8	3	2	1	1	0	1	0	8	3	11
Nasal cavity	8	2	7	1	3	0	3	1	9	3	10
Oral cavity	6	1	8	0	0	0	0	0	8	1	8
Ovary	0	0	0	0	0	0	8	0	8	0	8
Pancreas	7	6	2	1	0	0	0	0	8	7	14
Parathyroid gland	0	1	0	0	0	0	0	0	0	1	1
Pituitary gland	0	0	1	2	2	0	3	0	4	2	6
Preputial gland	7	5	0	0	3	1	0	0	10	6	16
Seminal vesicle	0	0	0	0	1	0	0	0	1	0	1
Skin	14	4	7	0	3	2	2	1	15	6	21
Spleen	7	2	3	1	1	0	2	0	9	3	11
Subcutaneous tissue	6	3	3	2	0	4	3	1	9	8	16
Thyroid gland	14	6	13	5	6	2	8	0	19	10	29
Ureter	2	0	1	0	0	0	0	0	2	0	2
Urinary bladder	10	0	10	3	3	0	3	0	16	3	18
Uterus/cerix	0	0	8	0	0	0	7	1	15	1	16
Zymbal gland	16	2	15	1	1	1	2	0	18	3	20
Totals	225	79	197	58	151	51	201	31			

[a] Positive responses, and includes P, CE, and SE; EE, equivocal responses, and includes those that may have been related to chemical exposure.

[b] Number of individual chemicals that caused positive (POS), equivocal (EE), and either or both responses (POS/EE) in at least one sex of one species.

Table 6. Organs/systems most frequently observed in rats and mice with chemically induced site-specific neoplasia from 379 long-term chemical carcinogenesis studies.

			Rats		Mice			
Organs/systems	Chemicals	% of 379 chemicals	Male	Female	Male	Female	Experiments	% of 1394 experiments
1. Liver	104	27%	38	32	58	75	203	15%
2. Lung	30	8%	5	7	18	21	51	4%
3. Hematopoietic system	29	8%	12	10	8	13	43	3%
Kidney	29	8%	25	9	4	1	39	3%
4. Mammary gland	27	7%	3	22	0	9	34	2%
5. Forestomach	23	6%	15	11	15	16	57	4%
6. Thyroid gland	19	5%	14	13	6	8	41	3%
7. Zymbal gland	18	5%	16	15	1	2	34	2%
8. Urinary bladder	16	4%	10	10	3	3	26	2%
9. Skin	15	4%	14	7	3	2	26	2%
Uterus/cervix	15	4%	0	8	0	7	15	1%
10. Circulatory system	13	3%	4	2	8	9	23	2%
Adrenal gland	13	3%	5	3	5	4	17	1%
Totals			161	149	129	170		

Table 7. Top 10 organs/systems most frequently observed in rats with chemically induced neoplasia from 379 long-term chemical carcinogenesis studies.

Male rats		Female rats			Rats		Unique
Site	Chemicals	Site	Chemicals	Composite sites	Male	Female	chemicals
1. Liver	38	Liver	32	Liver[a]	38	32	44
2. Kidney	25	Mammary gland	22	Kidney[a]	25	9	28
3. Zymbal gland	16	Zymbal gland	15	Mammary gland	3	22	22
4. Forestomach	15	Thyroid gland	13	Zymbal gland[a]	16	15	18
5. Thyroid gland	14	Forestomach	11	Thyroid gland[a]	14	13	17
6. Skin	14	Urinary bladder	10	Hematopoietic system[a]	12	10	17
7. Hematopoietic system	12	Clitoral gland	10	Forestomach[a]	15	11	15
8. Urinary bladder	10	Hematopoietic system	10	Skin	14	7	15
9. Intestines	9	Kidney	9	Urinary bladder	10	10	14
10. Nasal cavity	8	Uterus cervix	8	Clitoral gland	0	10	10
		Oral cavity	8				

[a] Occurs in top 10 in both male and female rats.

Table 8. Top 10 organs/systems most frequently observed in mice with chemically induced neoplasia from 379 long-term chemical carcinogenesis studies.

Male mice		Female mice			Mice		Unique
Site	Chemicals	Site	Chemicals	Composite sites	Male	Female	chemicals
1. Liver	58	Liver	75	Liver[a]	58	75	86
2. Lung	18	Lung	21	Lung[a]	18	21	23
3. Forestomach	15	Forestomach	16	Forestomach[a]	15	16	17
4. Circulatory system	8	Hematopoietic system	13	Hematopoietic system[a]	8	13	15
5. Hematopoietic system	8	Circulatory system	9	Circulatory system[a]	8	9	11
6. Thyroid gland	6	Mammary gland	9	Mammary gland	0	9	9
7. Harderian gland	5	Ovary	8	Thyroid gland[a]	6	8	9
8. Adrenal gland	5	Thyroid gland	8	Ovary	0	8	8
9. Kidney	4	Uterus/cervix	7	Harderian gland[a]	5	6	7
10. Five sites[b]	3	Harderian gland	6	Uterus/cervix	0	7	7

[a] Occurs in top 10 in both male and female mice.
[b] Heart, nasal cavity, preputial gland, skin, urinary bladder.

Comparing the sites of these chemically induced tumors with those recorded for the human population in the United States (Table 9) and worldwide (Table 10) lends further support to the biological conservation among these species. Of course, one has to recognize "life-style" tumor differences such as melanoma of the skin in U.S. females. Some may think it odd to compare site-specific cancers observed in humans with those found in chemically induced cancers in rodents, yet the majority of cancers in humans have been considered to be preventable and hence "environmentally caused." Further, there is little evidence to suggest that any tumor occurring in rodents or in humans does not have some association with "chemical" causes, be it from the diet or from specific chemicals.

In this paper on sites and types of tumors chemically induced in rats and mice (Tables 6–8), five (hematopoietic system, lung, mammary gland, urinary bladder, and uterus) of the most frequently observed tumor sites are the same as those observed in the top 10 sites in the human population of the U.S. (*49*); if one considers the most common tumor types in the world population (*50*) then rodents and humans correspond on 7 (adding esophagus/stomach and liver) of 10. Those tumor sites in rodents lacking "top 10" correlation in humans include kidney (number 11 in the U.S.), thyroid gland, and Zymbal gland). (In this comparison rodent forestomach was taken as associating with human esophagus.)

For all those chemicals or mixtures for which there is evidence of carcinogenicity for humans and that have been studied adequately in experimental animals, all have been shown to cause cancer in a common site in at least one animal species (*4,27,28,51*). For several chemicals the evidence of carcinogenicity in experimental animals preceded evidence obtained from epidemiological studies or case reports (*1,4,52,53*). For these eight chemicals, the major organs showing positive carcinogenic responses in animals included: liver, lung, mammary gland, and skin, each showing a positive response for three of the eight chemicals. For all eight human carcinogens first identified in animals, the organs showing a positive effect in humans were the same as those observed experimentally in either rats or mice or both. Other organs in animals showing positive effects from these eight chemicals included kidney, Zymbal gland, urinary bladder, intestinal tract, nasal cavity, ovary, lymphoma, pituitary gland, and cervix-vagina-uterus.

The overall concordance in carcinogenic response between rats and mice agrees closely with previous estimates (*47,54*), and tends to stay consistently in the range of 75% (Table 4). Importantly, this value is almost

Table 9. Top 12 most frequently observed site-specific cancers in humans in the United States for the 2-year period 1986–1987 (age-adjusted rates per 100,000 population).[a]

A. Cancer incidence rates

	Males and females		Males		Females	
	Site	Rate	Site	Rate	Site	Rate
1.	Breast	61.3	Prostate gland	94.2	Breast	112.1
2.	Lung and bronchus	56.6	Lung and bronchus	82.0	Colon/rectum	41.7
3.	Colon/rectum	49.8	Colon/rectum	61.2	Lung and bronchus	38.1
4.	Prostate gland	38.2	Urinary bladder	32.4	Cervix uteri, corpus and uterus	30.0
5.	Urinary bladder	18.1	Non-Hodgkin's lymphoma	17.1	Ovary	13.9
6.	Cervix uteri, corpus and uterus	16.3	Oral and pharynx	16.4	Non-Hodgkin's lymphoma	11.0
7.	Non-Hodgkin's lymphoma	13.8	Leukemia	13.0	Melanoma of skin	10.0
8.	Melanoma of skin	11.2	Melanoma of skin	12.9	Pancreas	7.6
9.	Oral and pharynx	10.9	Kidney	11.7	Urinary bladder	7.6
10.	Leukemia	9.7	Stomach	10.6	Leukemia	7.4
11.	Pancreas	8.8	Pancreas	10.6	Thyroid gland	6.1
12.	Kidney	8.4	Larynx	8.2	Brain and nervous system	5.8

B. Cancer mortality rates

	Males and females		Males		Females	
	Site	Rate	Site	Rate	Site	Rate
1.	Lung and bronchus	47.4	Lung and bronchus	74.5	Lung and bronchus	27.6
2.	Colon/rectum	20.2	Colon/rectum	24.5	Breast	27.2
3.	Breast	15.3	Prostate gland	24.4	Colon/rectum	16.8
4.	Prostate gland	9.2	Pancreas	10.0	Ovary	7.7
5.	Pancreas	8.4	Leukemia	8.3	Pancreas	7.2
6.	Leukemia	6.3	Stomach	7.2	Cervix uteri, corpus and uterus	6.7
7.	Non-Hodgkin's lymphoma	5.8	Non-Hodgkin's lymphoma	7.1	Leukemia	4.9
8.	Stomach	4.9	Esophagus	5.8	Non-Hodgkin's lymphoma	4.8
9.	Ovary	4.3	Urinary bladder	5.7	Brain and nervous system	3.3
10.	Brain and nervous system	4.1	Brain and nervous system	4.9	Stomach	3.2
11.	Kidney	3.4	Kidney	4.8	Multiple myeloma	2.4
12.	Urinary bladder	3.3	Liver	3.7	Kidney	2.3

[a] Data from Ries et al. (49).

certainly an underestimate of the true underlying interspecies concordance, given the lack of sensitivity or low power for detecting carcinogenic responses for "weak" chemical carcinogens, co-carcinogens, or "promoters." For example, Piegorsch et al. (*55*) demonstrated that even if the underlying interspecies concordance in a particular carcinogenic response for a given set of chemicals is 100%, the maximum level of observable concordance achievable for these chemicals is only about 80%, largely because of the variability in observed tumor responses that can occur by chance, resulting in a small number of false negative (and false positive) outcomes in one of the two species. This important revelation implies that the underlying correlations in carcinogenic response between rats and mice is clearly higher than commonly assumed or reported. Thus, one might consider that the experimentally observed concordance of 75% actually comes closer to a true species correlation of 94%. Similarly, the underlying interspecies correlation in site-specific carcinogenic responses is no doubt higher than would be apparent from an evaluation of the observed associations reported in Table 1.

The excellent correlation between genders within a species led Huff et al. (*2*) to cautiously suggest a possible alternative to the current design, whereby male F344 rats and female B6C3F1 mice could be used and this modified (or reduced) protocol would have identified correctly (from simply a yes-or-no carcinogenicity-point-of-view) 96% of the chemicals so far studied. This would not have allowed the construction of the data in Table 3, however. Thus, this design could be best used either as a carcinogenicity screen or as a model for studying additional chemicals in a class where one already has a good expectation about potential carcinogenicity.

The correlation of carcinogenic responses between rats and mice should be considered quite good (74%), and as mentioned is perhaps as close as one can get to "perfection" under the conditions of these long-term chemical carcinogenesis experiments (*55*). This overall correspondence for rats and mice clearly supports the decision of those in the research and regulatory agencies who early on proposed and actually insisted that carcinogenicity studies must be conducted in both genders of at least two species. We agree that both sexes of two species of rodents should ordinarily continue to be part of the core design strategy for identifying chemical carcinogens that may pose carcinogenic risk to humans (*20,56*); yet, as mentioned above, there will be instances whereby an alternative approach should be given due

consideration. This may appear especially tempting given that the observed correlation between sexes within a species tends to be 85% or above.

Another set of correlation data comes from comparing tumor incidence rates between those site-specific tumors that occur in unexposed (or control) groups and those that are considered to be caused by chemicals. For F344 rats, there appears to be little or no correlation between the tumor rates in control animals and the frequency of site-specific chemically induced carcinogenic effects. Of the top 10 sites of carcinogenicity in male rats (Table 7), all but two (thyroid gland and hematopoietic system) involve tumors with background rates below 5%, and for most sites (forestomach, intestines, kidney, nasal cavity, and urinary bladder) the control rate is less than 1% (*22,57*). Three of the four most frequently occurring tumors in control animals (pheochromocytomas of the adrenal gland, adenomas of the pituitary gland, and interstitial cell tumors of the testes) are not among the frequent sites of chemical carcinogenicity. For female rats the results are quite similar: the most frequent tumor observed in control groups is adenoma of the pituitary gland (*22,57*), which has been considered to show chemically related effects in only a single study (Table 1: 2-mercaptobenzothiazole; two others showed marginal increases). In contrast, chemically induced carcinogenicity is frequently observed for uncommonly occurring tumors in the forestomach, kidney, and urinary bladder (Table 7).

For B6C3F1 mice the results are different: the four most common sites for observed tumors in control male mice (liver, hematopoietic system [malignant lymphoma], lung, and circulatory system [hemangioma-hemangiosarcoma]) are among the five most frequent sites of chemical carcinogenicity (Table 8). Female mice show a similar pattern, although the relatively commonly occurring tumors of the pituitary gland are not among the top 10 tumor sites. Nevertheless, chemical carcinogenicity is often observed in mice at sites having low background rates (*57*), most notably for the forestomach and ovary.

As has been long known, the liver is the most frequent site of chemically caused cancer in laboratory animals (*58*): in our studies 27% (104/379) of the chemicals evaluated caused liver tumors, or in 15% (203/1394) of the individual experiments (Table 6). However, what may not be fully appreciated is the fact that the liver is the most common site of chemically induced cancer for rats as well as mice, an important factor when evaluating the biological significance of these neoplasms. That is, chemically related liver tumor effects in B6C3F1 mice have been discounted by some investigators based in large measure on the relatively high background rate of these neoplasms [31% in male and 8% in female mice; (*57*)]. However, there appears to be little biologic evidence to support this view. Chemically induced liver tumors are more common in female mice than in male mice despite the lower control rate in female mice (Table 6). Further, liver cancers are relatively uncommon in Fischer rats [< 1%; (*22*)], yet the liver remains the most frequent site of chemical carcinogenicity in both species. Thus, the liver is an important site of chemical carcinogenesis in rodents, independent of background rate.

Comparing the correspondence between tumors of the liver with tumors in other organs reveals that a significant association exists for liver tumors in mice and "any other site" tumors in rats. For example, if a chemical produced liver cancer in mice, then that chemical was twice as likely to be a carcinogen in the rat (49/78, 63%) when compared with a chemical not causing liver tumors in mice (73/235, 31%).

However, other site-specific tumors in mice are even more predictive of chemical carcinogenesis in the rat. If one divides the chemicals into three groups—1) those chemicals not causing any carcinogenic effects in mice, 2) those chemicals causing carcinogenic responses in mice only for the liver, and 3) those chemicals causing carcinogenic effects in mice at sites other than the liver—then a clear gradient of predictability becomes obvious: 21% (40/191) of the chemicals not causing any tumors in mice were carcinogenic in rats; 54% (26/48) of the chemicals causing only liver tumors in mice were also carcinogenic in rats, and 76% (56/74) of the chemicals causing cancer in mice at sites other than the liver were likewise carcinogenic in rats.

The influence of the background control rate "inherent" within a particular organ or system has little or no biological impact on the actual "inherent" carcinogenicity of a particular chemical substance. As noted, a "high" background rate does not correspond with a high frequency of chemically related carcinogenic effects. For organs with very high background rates, however, a chemically induced carcinogenic response is difficult or impossible to detect because of the variable range of "control" data and because the statistical and biological limits may have been reached: for instance, the 64 to 98% control tumor incidence for interstitial cell tumors of the testes in Fischer rats essentially precludes this organ as a potential site for detecting a carcinogenic effect. In no case has a chemical been judged to induce this tumor type in this organ.

The findings from long-term chemical carcinogenicity experiments are frequently the major stimulus for initiating the risk assessment process. The four stages are hazard identification, dose-response assessment, exposure assessment, and risk characterization (*6,15,24–26*). Results from these long-term carcinogenesis experiments form the basis for step 1 (and often provide input for step 2) in the four-step process of assessing potential risks to humans from exposure to a particular chemical. Completion of these four steps may result eventually in the activation of a more social, regulatory, and political (risk versus benefit) risk management process for protecting public, environmental, and occupational health. Of course one must evaluate all the available and relevant scientific information before proposing or initiating occupational or public policy.

The results of long-term chemical carcinogenesis

studies and the evidence of carcinogenicity are used to establish public health policies by local, state, and national and international governmental agencies (*1*). Positive carcinogenicity results in these experiments demonstrate that a "chemical" is carcinogenic for laboratory animals under the conditions of the study and in our collective view (*1–3,15,16,23,24,33,34*) indicate that exposure to the "chemical" should be regarded for prudent public health and scientific purposes as being a likely carcinogenic hazard to humans.

Using the experience of the International Agency for Research on Cancer (IARC) over the last 20 years (1972 till now), they have been able to locate carcinogenicity information on only 732 substances. In IARC Monographs Volumes 1–53, 55 "agents" are carcinogenic to humans; 45 are probably carcinogenic to humans; 191 are possibly carcinogenic to humans; 440 cannot be classified as to their individual carcinogenicity to humans; and 1 (caprolactam) is probably not carcinogenic to humans (*51*). Thus of these 732 agents, only 100 (or 14%) are either known as carcinogenic to humans or are strongly suspected of being carcinogenic to humans. Using our qualitative data in Table 3, we estimate that about 25% of chemicals evaluated by us would fit the international definitions either 1) for those chemicals with sufficient evidence of carcinogenicity in experimental animals that would be regarded as if they were carcinogenic to humans (*52*) or/and 2) for those chemicals considered reasonably anticipated to be human carcinogens (*29*).

Qualitative evaluations by chemical show that 52% were considered carcinogenic in at least one of the four experiments (Table 2). Another important view of the overall carcinogenicity of these chemicals is shown by the evaluations based on individual experiments: of the 1394 cases, 459 (or 33%) showed carcinogenicity. One qualitative way to categorize chemical carcinogens is to group them by the strength of the evidence, taking into account the exposure concentrations, the number of positive experimental cells across sexes and species (Table 3), the incidences and types of neoplastic responses, the number of different organs or systems affected, and the latency periods. This is certainly preferred over simply counting and combining the numbers of chemicals causing single-site, single-sex, single-species carcinogens (e.g., allyl isothiocyanate and *d*-limonene) with those causing multiple tumor sites in multiple experiments [e.g., benzene, glycidol, substituted benzidines, and others (*15*)].

Some have interpreted the 50% number of "positives" to claim that there are "too many rodent carcinogens" (*59,60*), and thus that results of carcinogenicity observed in these mammalian bioassays are irrelevent in themselves and predict potential hazard to humans no better than a "coin-toss." We and most others active in the fields of chemical carcinogenesis and public health find no scientific evidence to support this claim. In one sense, the chemicals selected and evaluated so far represent those that for the most part were considered likely of being carcinogenic, and one might have been led to anticipate that a high proportion or even most of the first 300 or so chemicals should indeed have induced cancers in one or more of the experimental groups. This did not happen, and thus active research efforts continue to look for or develop reliable methods to more accurately predict carcinogenic responses in experimental animals and in humans. The best predictive method now available is the long-term chemical carcinogenesis experiments using laboratory animals.

Examining the existing universe of chemicals that may eventually represent potential carcinogenic hazards to humans, Huff and Hoel (*15*) set forth an empirical idea that the percentage of chemicals that one could reasonably anticipate to meet the criteria as human carcinogens (*27,29*) would be substantially lower than currently believed or estimated. Using our data set alone as an example, only 25% of the chemicals would fit these categories.

The data in Table 3 reflect a qualitative aggregation of chemicals by the number of positive experiments. In this way one begins to better differentiate the 50% of chemicals causing cancer in experimental systems. Moreover, from the public health point of view, epidemiological studies could be considered for the 43 chemicals causing cancer in each of the four experimental cells or for the 25 in the three of four grouping. These two classes of chemicals comprise 22% of the number evaluated by us in long-term carcinogenesis studies. Moreover, chemicals "ranked" in this way could allow regulatory and public health organizations the opportunity to direct their efforts toward those chemicals having the greater "strength" of evidence.

Much is being said about the value of knowing the mechanism of carcinogenic action before making public health decisions. However, as most subscribe, mechanism of action is not yet considered to be defined nearly enough to become a significant factor in the evaluations on a global or generic basis; but certainly all relevant biologic information (oncogene activation and tumor suppressor genes, pharmacology and pharmacokinetics, DNA damage and repair, short- and mid-term assay results, among others) should be considered when deciding a particular level (classification or category) of evidence of carcinogenicity (*6,61,62*). At present we are unable to predict the eventual impact some or all of these pieces of information would have on the relative strength or weakness of a particular category of evidence for chemically caused cancers. One of the most important criteria for making these scientific judgments is knowledgeable and objective scientific staff, most preferably those with actual "hands-on" experience in all or at least many of the stages of these studies together with historical knowledge to allow some consistency or trends over time. A multidisciplinary group approach for making these important evaluations—including, at a minimum, toxicology, pathology, statistics, cancer biology, pharmacology-pharmacokinetics, and chemistry—appears to be most advantageous, and typically results in the closest one gets to scientific objectivity (for a very subjective area). Subsequent public

peer-review certainly goes a long way to support and better guarantee objectivity.

This and other information taken together with the strong evidence of correspondence between the chemicals identified as causing cancer in humans and in experimental animal models (*4*) support the public health policy of continuing to use laboratory research and experimental findings as relevant for identifying potential hazardous effects in humans (*1,2*).

Afterword

"This is a time of unprecedentedly rapid advances in the biomedical sciences, including new insights into the influence of the environment on human health. Whereas the major causes of death in past centuries were microbial diseases, today's leading causes of death in the industrialized world are constitutional, degenerative, and neoplastic disorders that are rooted to a large degree in environmental causes. Better understanding of such environmental causes can be expected to enable preventive measures that will yield enormous benefits to human health" (*63*).

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