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 1975 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,
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 ½ 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 non-government 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-

(text continues on page 261)
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 | Chemical | SAL* | RUT* | MR | FR | MM | FM | May have been related? (sex species) | Other sites |
|-------|----------|------|------|----|----|----|----|--------------------------------|------------|
| ADRENAL GLAND | 021 ALDRIN | - | F | E (E) P | N | Y | | | |
| 318 AMPICILLINE TETRABROMIDE | - | G | (EE) NE NE NE | | | | | | |
| 363 BROMOETHANE (ETHYL BROMIDE) | - | I | (EE) EE CE EE | | | | | | |
| 305 CHLORINATED PARAFFINS: C23, 43% CHLORINE | - | G | NE (EE) CE EE | | | | | | |
| 351 P-CHLORAMINILINE HYDROCHLORIDE | - | W | G | CE (EE) SE NE | (MR) | Y | | | |
| 075 CHLOROBENZilate | - | F | (E) (E) P | P | | | | | |
| 085 4-CHLORO-N-PHENYLENEDIAMINE | - | F | (P) N N P | | | | | | |
| 405 C.1. ACID RED 114 | + | W | CE CE | (MR) | (FR) | Y | | | |
| 285 C.1. BASIC RED 9 MONOHYDROCHLORIDE | + | F | CE CE CE CE | (CE) | | | | | |
| 206 1,2-DIBROMO-3-CHLOROPROPANE | + | I | P (P) P | P | | | | | |
| 319 1,4-DICHLOROBENZENE (P-DICHLOROBENZENE) | - | G | CE NE CE CE | (MM) | Y | | | | |
| 402 FURAN | - | G | CE CE (CE) CE | | | | | | |
| 361 HEXACHLOROETHANE | - | G | NE CE | (MR) | | | | | |
| 330 4-HEXYLSORCINOL | - | G | NE NE (EE) NE | | | | | | |
| 332 2-MERCAPTOBENZATIONIAZOLE | - | G | (SE) (SE) NE EE | | | | | | |
| 248 4,4'-METHYLENEDIAMINLINE DIHYDROCHLORIDE | W | W | | | | | | | |
| 313 MIREX | - | F | CE CE | | | | | | |
| 315 OCTYTRACYCLINE HYDROCHLORIDE | - | F | (EE) EE NE NE | | | | | | |
| 070 PARATHION | W | F | (E) E N N | N | | | | | |
| 349 PENTACHLOROPHENOL, DOMICIDE EC-7 | - | F | (CE) CE | | | | | | |
| 349 PENTACHLOROPHENOL, TECHNICAL | - | F | (CE) SE | | | | | | |
| 240 PROPYL GALLATE | - | F | (E) N E N | | | | | | |
| 143 RESERPINE | - | F | (P) P N P | P | | | | | |
| 364 RHODAMINE 6G | - | F | EE (EE) NE NE | | | | | | |
| 033 TETRACHLORVINPHOS | - | F | N (P) P P | P | | | | | |
| 274 TRICLOR(2-ETHYLHEXYLP)PHOSPHATE | - | G | (EE) NE SE SE | | | | | | |
| 303 4-VINYLCYCLOHEXENE | - | G | IS IS IS CE | | | | | | |

Number of Chemicals = 28

| BONE | TOTALS | 14 | 10 | 7 | 5 |

| Number of Chemicals = 3 | TOTALS | 3 | 0 | 0 | 0 |

| BRAIN | TOTALS | 9 | 6 | 2 | 1 |

- 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. *Sex-specific groups that show a marginal increase for this tumor site. **Indicates whether other site-specific cancers were induced; Y, yes; N, no. *NCI or NTP Technical Report number. *Salmonella typhimurium results: +, positive; +W, weakly positive; ?, inconclusive; -, negative. 1Route of exposure: F, feed; G, gavage; I, inhalation; W, drinking water; J, injection; S, skin application. *Sex and species: MR, male rats; FR, female rats; MM, male mice; FM, female mice. *The sex-species animal group in which a carcinogenic response was chemically induced in that particular organ or system. **Totals include positive and equivocal or may have been related responses; under each sex-species column = number of chemicals for that tumor.

(Continued on next page)
| TR No. | Chemical                                               | SAL* | RUT* | MR* | FR | MM | FM | May have been relatedb (sex species) | Otherc sites |
|-------|--------------------------------------------------------|------|------|-----|----|----|----|-----------------------------------|--------------|
|       | **CIRCULATORY SYSTEM**                                 |      |      |     |    |    |    |                                   |              |
| (HEMANGIOMA/HEMANGIOSARCOMA) |                                                                               |      |      |     |    |    |    |                                   |              |
| 233   | 2-BIPHENYLAMINE HYDROCHLORIDE                         | +,* | F    | N   | N  | (E ) | (P ) | N                                 |              |
| 288   | 1,3-BUTADIENE                                          | +   | I    | (CE) | (CE) |     |    | Y                                 |              |
| 169   | P-CHLOROANILINE                                        | +,* | W    | F   | E  | (N) | (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-NITROANTHRACINONE                           | +   | 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  | P  | N  | Y                                 |              |
| 153   | O-TOLUIDINE HYDROCHLORIDE                              | -,* | F    | P   | P  | (P ) | P  | Y                                 |              |
|       | Number of Chemicals = 16                               |      |      |     |    |    |    |                                   |              |
|       | **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'-DIMETHYLIDENE DİHYDROCHLORIDE                     | +,* | W    | CE  | (CE) |     |    | Y                                 |              |
| 374   | GLYCIDOL                                               | +,* | G    | CE  | CE  | CE  | CE  | Y                                 |              |
| 368   | NALIDIXIC ACID                                         | -   | G    | CE  | (CE) | EE  | NE | Y                                 |              |
| 143   | 1,5-NAPHTHALENE DIAMINE                                | +   | 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                               |      |      |     |    |    |    |                                   |              |
|       | **EPIDIDYMIS**                                         |      |      |     |    |    |    |                                   |              |
| 374   | GLYCIDOL                                               | +,* | G    | CE  | CE  | CE  | CE  | Y                                 |              |
|       | Number of Chemicals = 1                                |      |      |     |    |    |    |                                   |              |
|       | **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                                |      |      |     |    |    |    |                                   |              |
|       | **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                      | +,* | G    | P   | P  |     |     | (FM)                             |              |
| 288   | 1,3-BUTADIENE                                          | +   | I    | (CE) | (CE) |     |    | Y                                 |              |
| 300   | 3-CHLORO-2-METHYLPROPENE                                | +,* | G    | (CE) | (CE) | (CE) | (CE) | N                                 |              |
| 095   | 3-CHLOROMETHYLPROPIONIC HYDROCHLORIDE                  | +   | G    | (P ) | (E ) | (P ) | (P ) | N                                 |              |
| 063   | 4-CHLORO-O-PHENYLMEDIAMINE                              | +   | F    | (P ) | (P ) | (P ) | (P ) | Y                                 |              |
| 222   | C.I. DISPERSE YELLOW 5                                 | +   | 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-CHLOROPROPAE                             | +   | 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 ) | Y                                 |              |
| 354   | DIMETHOKANE                                             | +   | G    | NE  | NE  | NE  | (CE) | N                                 |              |
| 360   | N,N-DIMETHYLAMINE                                       | -   | G    | SE  | NE  | NE  | (EE) | Y                                 |              |
| 287   | DIMETHYL HYDROGEN PHOSPHITE                            | +,* | 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 | Chemical | SAL$^*$ | RUT$^*$ | Levels of evidence of carcinogenicity$^a$ | May have been related$^b$ (sex species) | Other$^c$ sites |
|-------|----------|---------|---------|---------------------------------|---------------------------------|--------------|
| 259   | ETHYL ACRYLATE | +w, i, i | G | (P) (P) (P) (P) | N | |
| 382   | FURFURAL | ? , i | G | SE NE CE SE | (FM) | Y |
| 374   | GLYCIDOL | +, + | G | CE (CE) CE CE | Y | |
| 340   | IOCIDATED GLYCEROL | + | G | SE NE SE | (FM) | Y |
| 140   | PIVALACTONE | G | (P) (P) N N | N | |
| 115   | SULFATE | + | F | (P) P P | Y | |
| 399   | TITANOCENE DICHLORIDE | + | G | (EE) (EE) | N | |
| 034   | TRIFURALIN | w | F | N N N | 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**

| No | Chemical | SAL$^*$ | RUT$^*$ | Levels of evidence of carcinogenicity$^a$ | May have been related$^b$ (sex species) | Other$^c$ sites |
|----|----------|---------|---------|---------------------------------|---------------------------------|--------------|
| 091 | CLONITALID | 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**

| TR No | Chemical | SAL$^*$ | RUT$^*$ | Levels of evidence of carcinogenicity$^a$ | May have been related$^b$ (sex species) | Other$^c$ sites |
|-------|----------|---------|---------|---------------------------------|---------------------------------|--------------|
| 289   | BENZENE | - | G | CE CE (CE) CE | Y | |
| 100   | COPPER | + | F | P P P | Y | |
| 326   | ETHYLENE OXIDE | I | G | CE (CE) (CE) | Y | |
| 152   | ETHYL TELLURAC | - | F | E N (E) (E) | Y | |
| 374   | GLYCIDOL | +, + | G | CE CE (CE) CE | Y | |
| 330   | 4-HYDROXYCINOL | - | G | NE NE (EE) NE | N | |
| 340   | IOCIDATED GLYCEROL | + | G | SE NE (EE) (EE) | Y | |
| 352   | 3,4-DIMETHYLACRYLAMIDE | - | G | NE NE (CE) NE | Y | |
| 205   | 4,4'-OXIDIANILINE | + | 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**

| TR No | Chemical | SAL$^*$ | RUT$^*$ | Levels of evidence of carcinogenicity$^a$ | May have been related$^b$ (sex species) | Other$^c$ sites |
|-------|----------|---------|---------|---------------------------------|---------------------------------|--------------|
| 288   | 1,3-BUTADIENE | + | I | (CE) (CE) | Y | |
| 059   | ESTRADIOL MUSTARD | G | 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)**

| TR No | Chemical | SAL$^*$ | RUT$^*$ | Levels of evidence of carcinogenicity$^a$ | May have been related$^b$ (sex species) | Other$^c$ sites |
|-------|----------|---------|---------|---------------------------------|---------------------------------|--------------|
| 394   | ACETAMINOPHEN (4-HYDROXYACETANILIDE) | - | F | NE (EE) NE NE | N | |
| 253   | ALLY ISOLYSERATE | - | G | (P) N N (P) | N | |
| 144   | 2-AMINOANTHRACINE | + | F | P IS P | Y | |
| 053   | 2-AMINO-5-NITRODIAZOLE | + | F | P N N N | N | |
| 216   | 11-AMINoundecanonic ACID | - | F | P N (E) | Y | |
| 318   | AMPICILLIN TRICARATE | - | G | (EE) NE NE NE | Y | |
| 042   | 5-ACETYLDINE | + | J | IS IS IS (P) | N | |
| 289   | BENZENE | - | G | CE CE (CE) (CE) | Y | |
| 215   | BISPHENOL A | - , i | F | (E) N N N | Y | |
| 288   | 1,3-BUTADIENE | + | I | (CE) (CE) | Y | |
| 213   | BUTYL BENZYL PHthalate | - , i | 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) | |
| 305   | CHLORINATED PARAFFINS: C23, 43% CHLORINE | - | G | CE CE EE | EE | |
| 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 | (FR) | Y |
| 134   | C.I. VAT YELLOW 4 | - , i | F | N N (P) N | N | |
| 242   | DIALYL PHthalate | - | G | (E) E | N | |
| 284   | DIALYL PHthalate | - , i | G | NE (EE) | Y | |
| 162   | 2,4-DIAMINOTOLUENE | + | F | P P N P | (FM) | Y |
| 123   | 2,7-DICHLOOROBENZO-P-DIOXIN | - | F | N N (E) N | Y | |
| 342   | DICHLOOROVS | + | G | (SE) SE SE CE | Y | |
| 128   | 3,3'-DIMETHOXYBENZIDINE-4,4'-DIOISOCYANATE | F | (P) P N N | Y | |
| 390   | 3,3'-DIMETHYLBENZIDINE DIOHYDROCHLORIDE | + | W | CE CE | (FR) | Y |
| 323   | DIMETHYL METHYLPHOSPHONATE | - | G | SE NE IS NE | (MR) | |
| 298   | DIMETHYL MORPHOLINOPHOSPHORAMIDATE | - | G | (SE) (SE) NE NE | N | |
| 059   | ESTRADIOL MUSTARD | G | N N (P) | Y | |
| 326   | ETHYLENE OXIDE | I | G | CE CE | Y | |
| 402   | FURAN | - | G | (CE) (CE) CE CE | Y | |

(Continued on next page)
| TR No. | Chemical                          | SAL* | RUT† | Levels of evidence of carcinogenicity* | May have been related† (sex species) | Other‡ sites |
|--------|-----------------------------------|------|------|---------------------------------------|-------------------------------------|-------------|
| 374    | GLYCIDOL                          | +,*  | G    | CE (CE) CE CE                         | Y                                   |             |
| 366    | HYDROQUINONE                      | -    | G    | SE (SE) NE SE                         | Y                                   |             |
| 078    | 1CHF-159                          | J    | E    | E (E) (E)                             | Y                                   |             |
| 018    | 1PD (3,3'-IMINOBIS-1-PROPAOL DIMETHANESULF) | J    | E    | E (E) (E)                             | Y                                   |             |
| 340    | 1DIODINATED Glycerol              | +    | G    | SE NE NE SE                           | Y                                   |             |
| 291    | ISOPHORONE                        | -    | G    | NE (EE) NE                            | Y                                   |             |
| 032    | ISOPHOSPHAMIDE                    | J    | N    | P (P)                                 | Y                                   |             |
| 039    | LASIOCARPINE                      | +    | F    | P (P)                                 | Y                                   |             |
| 332    | 2-MERCAPTOBENZOTHIAZOLE           | ?,*  | G    | SE NE NE EE                           | Y                                   |             |
| 248    | 4,4'-METHYLENEDIAMININE DIHYDROCHLORIDE | +    | W    | P P P (P)                             | Y                                   |             |
| 313    | MIREX                             | -    | F    | CE (CE)                               | Y                                   |             |
| 060    | PHENESTERIN                       | +    | G    | W P (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                           | Y                                   |             |
| 155    | 2,4,6-TRICHLOOROPHENOL            | -    | F    | (P) N P                               | Y                                   |             |
| 058    | TRISAZIRIDIDINYL-PHOSPHINE SULFIDE| +    | J    | (P) P (P) (P)                         | Y                                   |             |
| 391    | TRIS(2-CHLOROETHYL) PHOSPHATE     | -    | G    | CE CE EE EE                           | (MR) (FR)                           |             |

Number of Chemicals = 50

| TOTALS | 18 | 18 | 14 | 17 |

**INTESTINE**

| TR No. | Chemical                          | SAL* | RUT† | Levels of evidence of carcinogenicity* | May have been related† (sex species) | Other‡ sites |
|--------|-----------------------------------|------|------|---------------------------------------|-------------------------------------|-------------|
| 038    | AROCLOR 1254                      | -    | F    | (E) (E)                               | Y                                   |             |
| 295    | ASBESTOS, CHRYSOTILE(IR)          | -    | F    | (SE) NE                               | N                                   |             |
| 321    | BROMODICHLOROMETHANE              | -    | G    | (CE) CE CE                            | Y                                   |             |
| 015    | CAPTAN                            | +    | F    | N N (P) (P)                           | Y                                   |             |
| 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                              | Y                                   |             |
| 099    | PHENAZOPYRIDE HYDROCHLORIDE       | ?    | F    | (P) P (P) N P                        | Y                                   |             |
| 005    | PROFLAVIN HYDROCHLORIDE           | -    | F    | (E) N E E                            | Y                                   |             |
| 047    | 4,4'-TRIDIOANILINE                | +    | F    | (P) P P P                            | Y                                   |             |
| 350    | TRIBROMOMETHANE                   | ?,*  | G    | (SE) CE NE                            | N                                   |             |

Number of Chemicals = 13

| TOTALS | 11 | 8 | 1 | 1 |

**KIDNEY**

| TR No. | Chemical                          | SAL* | RUT† | Levels of evidence of carcinogenicity* | May have been related† (sex species) | Other‡ sites |
|--------|-----------------------------------|------|------|---------------------------------------|-------------------------------------|-------------|
| 111    | 1-AMINO-2-METHYLANTHRACINONE       | +    | F    | (P) P N P                             | Y                                   |             |
| 339    | 2-AMINO-4-NITROPHENOL              | *,*  | G    | (SE) NE NE NE                         | N                                   |             |
| 089    | 0-ANISIDINE DIHYDROCHLORIDE        | ?,*  | F    | (P) P P P                            | N                                   |             |
| 067    | ASPARIN, PHENACETIN, AND CAFFEINE  | -    | F    | N (E) NE                               | Y                                   |             |
| 370    | BENZOFURAN                        | -    | G    | NE (SE) CE                             | CE                                  |             |
| 321    | BROMODICHLOROMETHANE              | -    | G    | (CE) (CE) (CE)                        | Y                                   |             |
| 308    | CHLORINATED PARAFFINS: C12, 60% CHLORINE | -    | G    | (CE) CE CE                            | Y                                   |             |
| 041    | CHLOROTHALONIL                    | -    | F    | (P) (P) N P                           | N                                   |             |
| 335    | C. I. ACID ORANGE 3               | +    | G    | NE (CE) NE                            | N                                   |             |
| 411    | C. I. PI GMENT RED 23             | -    | G    | (EE) NE NE                            | N                                   |             |
| 196    | CINNAMYL ANTHRAVILATE             | -    | F    | (P) P N P                             | Y                                   |             |
| 401    | 2,4-DIAMINOPHENOL DIHYDROCHLORIDE | +    | G    | NE NE (SE) NE                         | N                                   |             |
| 319    | 1,4-DICHLOROBENZENE (P-DICHLOROBENZENE) | -    | G    | (CE) NE CE                            | Y                                   |             |
| 323    | DIMETHYL METHYLPHOSPHONATE        | -    | G    | (SE) NE IS                             | Y                                   |             |
| 382    | FURFURAL                          | ?,*  | G    | SE NE CE SE                           | (MM)                                |             |
| 356    | FUROSEMICIDE                      | -    | F    | (EE) NE SE                            | Y                                   |             |
| 252    | GERANYL ACETATE                   | -    | G    | N N N (MR)                             | Y                                   |             |
| 361    | HEXACHLOROPHENE                   | ?,*  | G    | (SE) NE                                | Y                                   |             |
| 366    | HYDROQUINONE                      | -    | G    | (SE) NE                                | SE                                  |             |
| 291    | ISOPHORONE                        | -    | G    | (SE) NE EE                            | Y                                   |             |
| 347    | D-LIMONENE                        | -    | G    | (CE) NE                                | N                                   |             |
| 359    | 8-METHOXYPORALEN                  | -    | G    | (CE) NE                                | Y                                   |             |
| 369    | ALPHA-METHYLPHENYL ALCOHOL        | -    | G    | (SE) NE                                | N                                   |             |
| 348    | METHYLDEPA SESQUIH YDRATE         | -    | F    | NE NE (EE)                             | N                                   |             |
| 313    | MIREX                             | -    | F    | (CE) CE                               | Y                                   |             |
| 266    | MONUROX                           | -    | F    | (CE) NE NE                            | Y                                   |             |
| 006    | NITRILITRIACETIC ACID (NTA)       | +    | F    | (P) P P (P) (P)                       | Y                                   |             |
| 006    | NITRILITRIACETIC ACID TRISODIUM MONOHYDRATE | +    | F    | (E) E N N                             | Y                                   |             |
| 341    | NITROFURANTOIN                    | +,*  | F    | (SE) NE NE                            | C E                                |             |
| 358    | QCIRATOKIN A                      | -    | G    | (CE) (CE)                             | Y                                   |             |
| 367    | PHENYL BUTAZONE                   | -    | G    | (EE) SE NE                            | (FR)                                |             |
| 333    | N-PHENYL-2-NAPHTHYLAMINE           | -    | F    | NE NE (EE)                             | N                                   |             |
## CHEMICALS AND SITE-SPECIFIC NEOPLASIA

Table 1. (continued)

| TR No | Chemical | SAL | RUT | Levels of evidence of carcinogenicity | May have been related to (sex species) | Other sites |
|-------|----------|-----|-----|--------------------------------------|----------------------------------------|------------|
| 409   | QUERCETIN | +   | F   | (SE) NE                               | N                                      | Y          |
| 311   | TETRACHLOROETHYLENE | -   | I   | (CE) SE CE CE CE                      | Y                                      | N          |
| 391   | TRIS(2-CHLOROETHYL) PHOSPHATE | -   | G   | (CE) (CE) (CE) EE                    | Y                                      | N          |
| 076   | TRIS(2,3-DIBROMOPROPYL) PHOSPHATE | +   | F   | (P) (P) (P) P                        | Y                                      | N          |

Number of Chemicals = 37

**LIVER**

| TR No | Chemical | SAL | RUT | Levels of evidence of carcinogenicity | May have been related to (sex species) | Other sites |
|-------|----------|-----|-----|--------------------------------------|----------------------------------------|------------|
| 021   | ALDRIN   | -   | F   | E E (P) N                             | Y                                      | N          |
| 144   | 2-AMINOANTHRAQUINONE | +   | F   | (P) IS (P) P                         | Y                                      | N          |
| 093   | 3-AMINO-9-ETHYLCARBAZOLE HCL | +   | F   | (P) (P) (P) P                       | Y                                      | N          |
| 111   | 1-AMINO-2-METHYLANTHRAQUINONE | +   | F   | (P) (P) N (P)                       | Y                                      | N          |
| 216   | 11-AMINONITRILEACID | -   | F   | (P) N E N                            | Y                                      | N          |
| 038   | AROCLOR 1254 | -   | F   | (E) (E)                              | Y                                      | N          |
| 370   | BENOZOFURAN | -   | G   | NE SE (CE) (CE)                      | Y                                      | N          |
| 250   | BENZYL ACETATE | -   | G   | EE NE SE (SE) (SE)                 | Y                                      | N          |
| 239   | BIS(2-CHLORO-1-METHYETHYL) ETHER | +w,+w | G   | (P) P                                | Y                                      | N          |
| 321   | BROMODICHLOOROMETHANE | -   | G   | CE CE CE CE Y                       | Y                                      | N          |
| 288   | 1,3-BUTADIENE | +   | I   |                                      | Y                                      | N          |
| 025   | CHLORAMEN | +   | F   | N N (E) (P)                         | Y                                      | N          |
| 008   | CHLORODINE (ANALYTICAL GRADE) | +   | F   | N N (P) (P)                          | Y                                      | N          |
| 304   | CHLORENDOIC ACID | -   | F   | (CE) (CE) (CE) NE                 | Y                                      | N          |
| 308   | CHLORINATED PARAFFINS: C12, 60% CHLORINE | -   | G   | (CE) (CE) (CE) (CE)                | Y                                      | N          |
| 305   | CHLORINATED PARAFFINS: C25, 43% CHLORINE | -   | G   | NE EE CE (EE)                      | Y                                      | N          |
| 351   | P-CHLOROANILINE HYDROCHLORIDE | +,+w | G   | CE (EE) NE (EE)                 | Y                                      | N          |
| 261   | CHLOROBENZENE | -   | G   | (E) N N N                            | Y                                      | N          |
| 075   | CHLOROBENZILATE | -   | F   | E E (P) (P)                         | Y                                      | N          |
| 282   | CHLORODIBROMOMETHANE | -   | G   | NE NE (EE) (SE)                    | Y                                      | N          |
| 346   | CHLOROETHANE | -   | G   |                                      | Y                                      | N          |
| 085   | 4-CHLORO-N-PHENYLENEDIAMINE | +   | F   | P N N (P)                           | Y                                      | N          |
| 063   | 4-CHLORO-P-PHENYLENEDIAMINE | +   | F   | P P (P) (P)                         | Y                                      | N          |
| 187   | 5-CHLORO-O-TOLUIDINE | -   | F   | N N (P) (P)                         | Y                                      | N          |
| 405   | C.I. ACID RED 114 | +   | W   | (CE) (CE)                           | Y                                      | N          |
| 285   | C.I. BASIC RED 9 MONOHYDROCHLORIDE | +   | F   | (CE) (CE) (CE) (CE)                 | Y                                      | N          |
| 108   | C.I. DIRECT BLUE 38 | +   | F   | (P) (P)                             | Y                                      | N          |
| 108   | C.I. DIRECT BLUE 6 | -   | F   | (P) (P)                             | Y                                      | N          |
| 397   | C.I. DIRECT BLUE 15 | -   | W   | (CE) (CE)                           | Y                                      | N          |
| 108   | C.I. DIRECT BROWN 95 | +w,+w | F   | N (P)                               | Y                                      | N          |
| 299   | C.I. DISPERSE BLUE 1 | +   | F   | CE CE (EE) NE                       | Y                                      | N          |
| 222   | C.I. DISPERSE YELLOW 3 | +   | F   | (P) N N (P)                         | Y                                      | N          |
| 226   | C.I. SOLVENT YELLOW 14 | +   | F   | (P) (P) N N                         | Y                                      | N          |
| 196   | CINNAMYL ANTHRAILATE | -   | F   | P N (P) (P)                         | Y                                      | N          |
| 142   | P-CRESIDINE | -   | F   | (P) N (P)                           | Y                                      | N          |
| 100   | CUFERON | +   | F   | (P) (P) P P                         | Y                                      | N          |
| 083   | DAMINOZIDE | -   | F   | N P (E) N                            | Y                                      | N          |
| 225   | D & C RED NO. 9 | +w | F   | (P) (E) N                            | Y                                      | N          |
| 309   | DEACETROBROMINPHENYL OXIDE | -   | F   | (SE) (SE) (EE) (EE)                  | Y                                      | N          |
| 162   | 2,4-DIAMINOTOLUENE | +   | F   | (P) (P) (P) N                       | Y                                      | N          |
| 086   | 1,2-DICBROMOMETHANE | +   | G   | P P P P                             | Y                                      | N          |
| 319   | 1,4-DICHLOROBENZENE (P-DICHLOROBENZENE) | -   | G   | CE NE (CE) (CE)                     | Y                                      | N          |
| 123   | 2,7-DICHLOROBENZO-P-DIOXIN | -   | F   | N N (E) N                            | Y                                      | N          |
| 131   | P-DICHLORODIPHENOLDICHLOROETHYLENE | +   | F   | N N (P) (P)                         | Y                                      | N          |
| 219   | 2,6-DICHLORO-P-PHENYLENEDIAMINE | +   | F   | N N (P) (P)                         | Y                                      | N          |
| 263   | 1,2-DICHLOROPROPANE (PROPYLENE DICHLORIDE) | +w,+w | G   | NE EE (SE) (SE)                     | Y                                      | N          |
| 269   | 1,3-DICHLOROPROPENE (TELONE II) | +   | G   | (CE) SE IS (CE)                      | Y                                      | N          |
| 099   | DIOCOFOL | -   | F   | N N (P) N                            | Y                                      | N          |
| 379   | DIOETHYLACETATE | -   | F   | N N (E) N                            | Y                                      | N          |
| 212   | D1(2-ETHYLHEXYL)ADIPATE | +w,+w | F   | N (P) N                                | Y                                      | N          |
| 217   | D1(2-ETHYLHEXYL)PHTHALATE | +w,+w | F   | (P) (P) P (P)                      | Y                                      | N          |
| 156   | D1(P-ETHYLENPHENYL)DICHLOROETHANE | -   | F   | N N N (E)                           | Y                                      | N          |
| 372   | 3,3'-DIMETHOXYBENZENIDIH YDROCHLORIDE | +,+w | W   | (CE) (CE)                           | Y                                      | N          |
| 390   | 3,3'-DIMETHYLBENZENIDIH YDROCHLORIDE | +   | W   | (CE) (CE)                           | Y                                      | N          |
| 080   | 1,4-DIOXANE | -   | W   | P (P) (P) (P)                        | Y                                      | N          |
| 132   | 2,5-DIETHOBIUREA | -   | F   | N N N (E)                            | Y                                      | N          |
| 308   | ETHYLEN THIOUREA (ETU) | -   | F   | (E) (E)                              | Y                                      | N          |
| 223   | EUGENOL | -   | F   | N N (E) (E)                          | Y                                      | N          |
| 195   | FLUORUMETURON | -   | F   | N N (E) N                            | Y                                      | N          |
| 402   | FURAN | -   | G   | (CE) (CE) (CE) (CE)                  | Y                                      | N          |
| 362   | FURFURAL | -   | G   | (SE) (EE) (SE) (EE)                  | Y                                      | N          |
| 374   | GLYCERYL | +   | G   | CE CE CE CE (E)                      | Y                                      | N          |
| 271   | HC BLUE 1 | +   | F   | (EE) (EE) (EE) (EE)                 | Y                                      | N          |
| 281   | HC RED 3 | +   | G   | NE NE (EE) IS                       | Y                                      | N          |

(Continued on next page)
Table 1. (continued)

| TR No | Chemical                                    | SAL* | RUT* | Levels of evidence of carcinogenicity* | May have been related* (sex species) | Other* sites |
|-------|---------------------------------------------|------|------|----------------------------------------|--------------------------------------|-------------|
| 009   | HEPTACHLOR                                 | N    | N    | E (P) (P)                              | Y                                    |             |
| 198   | 1,2,3,6,7,8-HEXACHLORODIBENZO-P-DIOXIN      | N    | N    | E (P) (P)                              | Y                                    |             |
| 068   | HEXACHLOROTHANE                            | N    | N    | E (P) (P)                              | Y                                    |             |
| 092   | HYDRAZOBENZENE                            | F    | E    | N (P)                                  | Y                                    |             |
| 357   | HYDROCHLOROTHIAZIDE                       | F    | E    | N (EE) NE                               | Y                                    |             |
| 366   | HYDROQUINONE                               | G    | E    | SE NE SE (EE)                          | Y                                    |             |
| 291   | ISOPHORONE                                 | G    | E    | SE NE (EE)                             | Y                                    |             |
| 039   | LASIOCARPINE                               | F    | E    | N (P)                                  | N                                    |             |
| 332   | 2-MERCAPTOBENZOTHIAZOLE                    | G    | E    | SE NE (EE)                             | Y                                    |             |
| 328   | Methyl Carbamate                           | G    | E    | (CE) (CE) NE                           | N                                    |             |
| 186   | 4,4'-METHYLENEDIANILINE, N,N-DIMETHYL)BENZENAMINE | F    | E    | N (P)                                  | Y                                    |             |
| 306   | METHYLENE CHLORIDE                         | F    | E    | N (P)                                  | Y                                    |             |
| 264   | 4,4'-METHYLENEDIAMINE DINYDROCHLORIDE       | F    | E    | N (P)                                  | Y                                    |             |
| 029   | 2-METHYL-1-NITROANILAMONIQUINONE            | F    | E    | N (P)                                  | Y                                    |             |
| 352   | N-METHYLOLACRYLAMIDE                       | G    | E    | SE NE (EE)                             | Y                                    |             |
| 181   | MICHELIR'S KETONE                          | F    | E    | N (P)                                  | Y                                    |             |
| 313   | NIREX                                     | F    | E    | (CE) (CE)                              | Y                                    |             |
| 266   | MONKURON                                  | F    | E    | N (P)                                  | Y                                    |             |
| 143   | 1,5-NAPHTHALENEDIAMINE                     | F    | E    | N (P)                                  | Y                                    |             |
| 146   | NITRANITROACETAMIDE                        | F    | E    | N (P)                                  | Y                                    |             |
| 118   | 5-NITROACETAMIDE                           | F    | E    | N (P)                                  | Y                                    |             |
| 133   | 5-NITRO-P-ACETOPHENETIDE                   | F    | E    | N (P)                                  | Y                                    |             |
| 127   | 5-NITRO-ANISIDINE                          | F    | E    | N (P)                                  | Y                                    |             |
| 116   | 5-NITROBENZIMIDAZOLE                       | F    | E    | N (P)                                  | Y                                    |             |
| 184   | NITROFEN                                  | F    | E    | N (P)                                  | Y                                    |             |
| 026   | NITROFEN                                  | F    | E    | IS (IS)                                 | Y                                    |             |
| 169   | 2-NITRO-P-PHENYLENEDIAMINE                  | F    | E    | N (P)                                  | Y                                    |             |
| 052   | 3-NITROPROPIONIC ACID                      | G    | E    | N (P)                                  | Y                                    |             |
| 190   | P-NITROSODIPHENYLAMINE                     | F    | E    | N (P)                                  | Y                                    |             |
| 107   | 5-NITRO-O-TOLUIDINE                        | F    | E    | N (P)                                  | Y                                    |             |
| 205   | 4,4'-OXYDIAMINILINE                        | F    | E    | N (P)                                  | Y                                    |             |
| 349   | PENTACHLOROPHENOL, DOWIDEC-7               | F    | E    | N (P)                                  | Y                                    |             |
| 349   | PENTACHLOROPHENOL, TECHNICAL               | F    | E    | N (P)                                  | Y                                    |             |
| 099   | PHENAZOPYRIDINE HYDROCHLORIDE              | F    | E    | N (P)                                  | Y                                    |             |
| 367   | PHENYLButAZONE                             | F    | E    | N (P)                                  | Y                                    |             |
| 023   | PILORAM                                   | F    | E    | N (P)                                  | Y                                    |             |
| 124   | PIPERONYL SULFOXIDE                       | F    | E    | N (P)                                  | Y                                    |             |
| 244   | POLYBROMINATED BIPHENYL MIX (FFI)          | F    | E    | N (P)                                  | Y                                    |             |
| 395   | PROBECICID                                 | F    | E    | N (P)                                  | Y                                    |             |
| 005   | PROFLAVIN HYDROCHLORIDE                    | F    | E    | N (P)                                  | Y                                    |             |
| 194   | SELENIUM SULFIDE                           | F    | E    | N (P)                                  | Y                                    |             |
| 209   | 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN        | F    | E    | N (P)                                  | Y                                    |             |
| 027   | 1,1,2,2-TETRACHLOROTHANE                   | F    | E    | N (P)                                  | Y                                    |             |
| 013   | TETRACHLOROETHYLENE                       | F    | E    | N (P)                                  | Y                                    |             |
| 311   | TETRACHLOROETHERYLENE                     | F    | E    | N (P)                                  | Y                                    |             |
| 033   | TETRACHLORVINPHOS                          | F    | E    | N (P)                                  | Y                                    |             |
| 047   | 4,4'-THIODIOLANILINE                      | F    | E    | N (P)                                  | Y                                    |             |
| 251   | 2,4 & 2,6-TOLUENE DIISOCYANATE             | F    | E    | N (P)                                  | Y                                    |             |
| 153   | 0-TOLUIDINE HYDROCHLORIDE                  | F    | E    | N (P)                                  | Y                                    |             |
| 037   | TOXAPHENE                                  | F    | E    | N (P)                                  | Y                                    |             |
| 074   | 1,1,2-TRICHLOROTHANE                       | F    | E    | N (P)                                  | Y                                    |             |
| 002   | TRICHLOROETHYLENE                          | F    | E    | N (P)                                  | Y                                    |             |
| 243   | TRICHLOROETHYLENE                          | F    | E    | N (P)                                  | Y                                    |             |
| 155   | 2,4,6-TRICHLOROPHENOL                     | F    | E    | N (P)                                  | Y                                    |             |
| 034   | TRIFLURALIN                                | F    | E    | N (P)                                  | Y                                    |             |
| 160   | 2,4,5-TRIMETHYLAMINE                      | F    | E    | N (P)                                  | Y                                    |             |
| 076   | TRIS(2,3-DIBROMOPROPYL) PHOSPHATE          | F    | E    | N (P)                                  | Y                                    |             |
| 274   | TRIS(2-ETHYLHEXYL)PHOSPHATE                | F    | E    | N (P)                                  | Y                                    |             |
| 278   | 2,6-XYLIDINE                               | F    | E    | N (P)                                  | Y                                    |             |
| 235   | ZEARALENONE                                | F    | E    | N (P)                                  | Y                                    |             |

Number of Chemicals = 124

TOTALS 44 36 74 83

LUNG

| TR No | Chemical                             | SAL* | RUT* | Levels of evidence of carcinogenicity* | May have been related* (sex species) | Other* sites |
|-------|--------------------------------------|------|------|----------------------------------------|--------------------------------------|-------------|
| 289   | BENZENE                              | G    | E    | CE (EE) CE (EE)                        | Y                                    |             |
| 370   | BENZOFURAN                           | G    | E    | CE (EE) CE (EE)                        | Y                                    |             |
| 088   | 1,2,3-BENZOTRIAZOLE                   | F    | E    | E (EE)                                 | Y                                    |             |
| 239   | BIS(2-CHLORO-1-METHYLETHYL) ETHER     | F    | E    | E (EE)                                 | Y                                    |             |
| 363   | BROMOMETHANE (ETHYL BROMIDE)         | F    | E    | E (EE)                                 | Y                                    |             |
| 288   | 1,3-BUTADIENE                        | F    | E    | E (EE)                                 | Y                                    |             |

Y
| TR No* | Chemical | SAL* | RUT* | Levels of evidence of carcinogenicity* | May have been related to* (sex species) | Other* sites |
|-------|----------|------|------|----------------------------------------|----------------------------------------|------------|
| 304   | CHLORDIEN ACID | - | F | CE CE CE NE | (MR) | Y |
| 305   | C.I. ACID RED 116 | + | W | CE (CE) (CE) | | |
| 299   | C.I. DISPERSE BLUE 1 | + | F | CE CE (EE) NE | (MR) | Y |
| 206   | 1,2-DIBROMO-3-CHLOROPROPANE | + | I | P P P P | | |
| 068   | 1,2-DIBROMOTHDANE | + | G | P P P P | | |
| 210   | 1,2-DIBROMOETHANE | + | I | P P P P | | |
| 269   | 1,3-DIBROMOPROPANE (TELONE II) | + | G | CE SE IS (CE) | | |
| 390   | 3,3'-DIMETHYLBENZIDINE DIHYDROCHLORIDE | + | W | (CE) (CE) | | |
| 287   | DIMETHYL HYDROGEN PHOSPHITE | +W | G | (CE) (EE) NE NE | | |
| 121   | DIMETHYL TEREPTHALATE | - | F | N N (E) N | | |
| 355   | DIPHENYLDIMARINE HYDROCHLORIDE | - | F | (EE) EE NE NE | | |
| 329   | 1,2-EPOXYBUTANE | + | I | (CE) EE NE NE | | |
| 059   | ESTRADIOLE MUSTARD | - | G | N N (P) P | | |
| 326   | ETHYLENE OXIDE | - | I | (CE) (CE) | | |
| 374   | GLYCIDOL | + | G | CE CE (CE) CE | | |
| 271   | 1,1-DICHLOROETHANE | + | F | EE (SE) CE CE | | |
| 359   | 8-METHOXYPSORALEN | + | G | CE NE | (MR) | Y |
| 306   | METHYLENE CHLORIDE | + | I | SE CE (CE) (CE) | | |
| 352   | N-METHYLACRYLAMIDE | - | G | NE CE (CE) (CE) | | |
| 410   | NAPHTHALENE | - | I | | | |
| 141   | 1,5-NAPHTHALEDIHYDRAZINE | + | F | N P P P | | |
| 118   | 5-NITROACETOPHENONE | + | F | (P) (P) N P | | |
| 060   | PHENESTERIN | - | G | N P P P | | |
| 019   | PROCARBAZINE HYDROCHLORIDE | - | F | P P P P | | |
| 194   | SELENIUM SULFIDE | + | G | P N N P | | |
| 185   | STYRENE | - | G | N N (E) N | | |
| 115   | SULFATE | + | F | P P (P) P | | |
| 386   | TETRANITROMETHANE | + | I | (CE) (CE) (CE) (CE) | | |
| 034   | TRIFLURALIN +W | F | N N N N P | | |
| 160   | 2,4,5-TRIMETHYLANILINE | + | F | P P E P | | |
| 076   | TRIS(2,3-DIBROMOPROPYL) PHOSPHATE | | F | P P (P) P | | |
| 362   | 4-VINYL-1-CYCLOXENENE DIOXIDE | + | S | CE CE CE CE | (FM) | |
| 239   | ZIRAM | + | F | N N (E) | | |

Number of Chemicals = 40

**Table 1. (continued)**

| TR No* | Chemical | SAL* | RUT* | Levels of evidence of carcinogenicity* | May have been related to* (sex species) | Other* sites |
|-------|----------|------|------|----------------------------------------|----------------------------------------|------------|
| 049   | ACRONYCINE | J | P (P) | IS IS | | |
| 289   | BENZENE | - | G | CE CE CE CE (CE) | | |
| 288   | 1,3-BUTADIENE | + | I | | | |
| 379   | 2,3-CLORACETOPHENONE (CN) | - | I | NE (EE) NE NE | | |
| 405   | C.I. ACID RED 114 | + | W | CE CE | (FR) | | |
| 285   | C.I. BASIC RED 9 MONOHYDROCHLORIDE | + | F | CE CE CE CE | (FR) | | |
| 091   | CLOMITRAT | F | N (E) IS N | | |
| 207   | CTMEMBENE | F | J | P (P) | | |
| 162   | 2,4-DIAMINOTOLUENE | + | F | P (P) | | |
| 028   | 1,2-DICLORO-EUROPAPROPANE | + | G | P (P) | | |
| 210   | 1,2-DIBROMOTHDANE | + | I | P P (P) | | |
| 066   | 1,1-DICHROMETHANE | - | G | N (E) N E | | |
| 055   | 1,2-DICHLOROTHDANE | - | G | P P (P) | | |
| 263   | 1,2-DICHROMOPROPANE (PROPYLE DICHROMATE) | +W | G | NE (EE) SE SE | | |
| 342   | DICHLORVOS | + | G | SE (EE) SE CE | | |
| 372   | 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE | +,+ | W | CE (CE) | | |
| 390   | 3,3'-DIMETHYLBENZIDINE DIHYDROCHLORIDE | + | W | CE (CE) | | |
| 054   | 2,4-DINITROTOLUENE | + | F | P (P) N N | | |
| 326   | ETHYLENE OXIDE | I | | CE (CE) | | |
| 356   | FUROSEMED | E | | EE NE NE (SE) | | |
| 374   | GLYCIDOL | + | G | (CE) (CE) CE (CE) | | |
| 092   | HYDRAZOBENZONE | + | F | P (P) N P | | |
| 032   | ISOPHOSPHAMIDE | J | N (P) N | | |
| 306   | METHYLENE CHLORIDE | +, I | (SE) (CE) CE CE | | |
| 146   | NITRIDE | F | N (P) P E | | |
| 118   | 5-NITROACETOPHENONE | + | F | P (P) N P | | |
| 337   | NITROFURAZONE | + | F | EE (CE) NE CE | | |
| 358   | OCHROTOKIN A | - | G | CE (CE) | | |
| 060   | PHENESTERIN | - | G | N (P) P P | | |
| 019   | PROCARBAZINE HYDROCHLORIDE | - | J | (P) (P) | | |
| 193   | RESERPINE | - | F | N N | | |
| 115   | SULFATE | + | F | P (P) P P | | |
| 251   | 2,4- & 2,6-TOLUENE DIISOCYANATE | + | G | P (P) N P | | |
| 153   | O-TOLUIDINE HYDROCHLORIDE | - | F | P (P) P P | | |

Number of Chemicals = 34

| TOTALS | 3 | 9 | 0 | 9 |

(Continued on next page)
Table 1. (continued)

| TR No | Chemical Name | SAL* | RUT* | Levels of evidence of carcinogenicity* | May have been related* (sex species) | Other sites |
|-------|---------------|------|------|---------------------------------------|---------------------------------------|------------|
|       |               |      |      | MR* | FR | MM | FM |                     |                        |            |
| 049   | ACRYNONE      | J    |      | (P) | (P) | IS | IS |                     |                        | Y           |
| 207   | CTENBENA      | J    |      | P   | N  | N  | N  |                     |                        | Y           |
| 210   | 1,2-DIBROMOETHANE | I   |      | P   | P  | P  | P  |                     |                        | Y           |
| 372   | 3,3′-DIMETHYLBENZIDINE DIHYDROCHLORIDE | *+,*+ |      | W  | (CE) | CE | CE |                     |                        | Y           |
| 390   | 3,3′-DIMETHYLBENZIDINE DIHYDROCHLORIDE | +   |      | W  | (CE) | CE | CE |                     |                        | Y           |
| 152   | ETHYL TELLURAC  | I    |      | F   | (E) | E  | E  |                     |                        | Y           |
| 374   | GLYCIDOL      | J    |      | (P) | (P) | (P) | (P) |                     |                        | N           |
| 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 | +    |      | F   | (P) | P  | P  | P  |                     |                        | Y           |
| 153   | 0-TOLUIDINE HYDROCHLORIDE | -,* |      | F   | (P) | (P) | (P) | (P) |                     |                        | Y           |

Number of Chemicals = 11

NASAL CAVITY

| TR No | Chemical Name | SAL* | RUT* | Levels of evidence of carcinogenicity* | May have been related* (sex species) | Other sites |
|-------|---------------|------|------|---------------------------------------|---------------------------------------|------------|
| 376   | ALLYL GLYCIDYL ETHER | + | I | (EE) | (EE) | NE | (EE) | EE |                     |                        | W           |
| 142   | P-CRESIDINE | + | F | (P) | (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  | P  |                     |                        | Y           |
| 316   | DIMETHYLVINYL CHLORIDE (DMVC) | -,* | G | (CE) | (CE) | CE | CE | CE |                     |                        | Y           |
| 080   | 1,4-DIOXANE | + | W | (P) | (P) | P  | P  | P  |                     |                        | Y           |
| 329   | 1,2-EPOXYBUTANE | + | I | (CE) | (EE) | NE | NE | Y  |                     |                        | 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) | (P) | (P) |                     |                        | Y           |

Number of Chemicals = 10

ORAL CAVITY

| TR No | Chemical Name | SAL* | RUT* | Levels of evidence of carcinogenicity* | May have been related* (sex species) | Other sites |
|-------|---------------|------|------|---------------------------------------|---------------------------------------|------------|
| 289   | BENZENE | - | G | (CE) | (CE) | CE | CE | CE |                     |                        | Y           |
| 405   | C.I. ACID RED 114 | + | W | CE | (CE) | CE | (MR) |                     |                        | Y           |
| 397   | C.I. DIRECT BLUE 15 | - | W | (CE) | (CE) | CE | CE | CE |                     |                        | Y           |
| 206   | 1,2-DIBROMO-3-CHLOROPROPANE | + | I | (P) | (P) | P  | P  | P  |                     |                        | Y           |
| 372   | 3,3′-DIMETHOXYBENZIDINE DIHYDROCHLORIDE | *+,*+ | W | (CE) | (CE) | CE | CE | CE |                     |                        | Y           |
| 390   | 3,3′-DIMETHYLBENZIDINE DIHYDROCHLORIDE | + | W | (CE) | (CE) | CE | CE | CE |                     |                        | Y           |
| 316   | DIMETHYLVINYL CHLORIDE (DMVC) | -,* | G | (CE) | (CE) | CE | CE | CE |                     |                        | Y           |
| 374   | GLYCIDOL | *+ | G | CE | (CE) | CE | CE | CE |                     |                        | Y           |

Number of Chemicals = 8

OVARY

| TR No | Chemical Name | SAL* | RUT* | Levels of evidence of carcinogenicity* | May have been related* (sex species) | Other sites |
|-------|---------------|------|------|---------------------------------------|---------------------------------------|------------|
| 289   | BENZENE | - | G | CE | CE | CE | CE | CE | (MR) |                     |                        | Y           |
| 288   | 1,3-BUTADIENE | + | I | CE | CE | CE | CE | CE |                     |                        | Y           |
| 352   | N-METHYLACRYLAMIDE | - | G | NE | NE | CE | CE | CE |                     |                        | Y           |
| 118   | 5-NITROGENAPHTHEN | + | F | P  | P  | N  | P  | P  |                     |                        | Y           |
| 341   | NITROFURANTOIN | +,*+ | F | SE | NE | NE | CE | CE |                     |                        | Y           |
| 337   | NITROFURAZONE | + | F | EE | CE | CE | NE | CE |                     |                        | Y           |
| 303   | 4-VINYLCYCLOHEXENE | -,* | G | IS | IS | IS | IS | CE |                     |                        | Y           |
| 362   | 4-VINYL-1-CYCLOHEXENE DIEPOXIDE | + | S | CE | CE | CE | CE | CE |                     |                        | Y           |

Number of Chemicals = 8

PANCREAS

| TR No | Chemical Name | SAL* | RUT* | Levels of evidence of carcinogenicity* | May have been related* (sex species) | Other sites |
|-------|---------------|------|------|---------------------------------------|---------------------------------------|------------|
| 334   | 2-Amino-5-NITROPHENOL | + | G | (SE) | NE | NE | NE | NE |                     |                        | Y           |
| 069   | AZINPHOSMETHYL | +W,+ | F | (E) | N  | N  | N  | N  |                     |                        | Y           |
| 250   | BENZYL ACETATE | - | G | (EE) | NE | SE | SE | Y  |                     |                        | Y           |
| 304   | CHLORENACID | + | F | (CE) | CE | CE | CE | Y  |                     |                        | Y           |
| 329   | C.I. DISPERSE BLUE 1 | + | F | (CE) | CE | EE | NE | Y  |                     |                        | Y           |
| 196   | CINNAMYL ANTHRANILATE | - | F | (P) | N  | P  | P  | P  |                     |                        | Y           |
| 342   | DICHLORVOS | + | G | (SE) | (EE) | SE | CE | Y  |                     |                        | Y           |
| 331   | MALONALDEHYDE, SODIUM SALT | - | G | CE | CE | NE | NE | (MR) |                     |                        | Y           |
| 332   | 2-MERCAPTOBENZOTHIAZOLE | ?,,* | G | (SE) | SE | NE | EE | Y  |                     |                        | Y           |
| 026   | NITROFEN | F | IS | (P) | P  | P  | P  | P  |                     |                        | Y           |
| 052   | 3-NITROPROPIONIC ACID | + | G | (E) | N  | N  | N  | N  |                     |                        | Y           |
| 240   | PROPYL GALLATE | - | F | (E) | N  | E  | N  | Y  |                     |                        | Y           |
| 345   | ROXARSONE | - | F | (EE) | NE | NE | NE | N  |                     |                        | N           |
| 251   | 2,4- & 2,6-TOLUENE DIISOCYANATE | + | G | (P) | (P) | N  | P  | P  |                     |                        | Y           |

Number of Chemicals = 14

Y = Yes, NE = Not Established, W = Wound, MR = Malignant Rhabdoid Tumor, CE = Carcinoma Erythroleucocytic, SE = Sarcoma Erythroleucocytic, EE = Erythroleucocytic Sarcoma
Table 1. (continued)

| TR No. | Chemical                               | SAL* | RUT* | Levels of evidence of carcinogenicity* | May have been related* (sex species) | Other sites |
|--------|----------------------------------------|------|------|--------------------------------------|-------------------------------------|-------------|
|        |                                        |      |      |                                      |                                     |             |
| 320    | ROSENFÜHR Un然 or DIPHENHYDRAMINE HYDROCHLORIDE | -    | F    | (EE) NE NE NE                        |                                     |             |
|        | Number of Chemicals = 1               |      |      |                                      |                                     |             |
| 355    | DIPHENHYDRAMINE HYDROCHLORIDE         | -    | F    | EE (EE) NE NE                        |                                     | Y           |
| 388    | ETHYLENE THIOUREA (ETU)                | -    | F    | EE CE CE (CE) CE                    |                                     | Y           |
| 332    | 2-MERCAPTOBENZOTHIAZOLE                | -    | F    | EE (EE) NE NE                        |                                     |             |
| 315    | OXYTETRACYCLINE HYDROCHLORIDE         | -    | F    | EE (EE) NE NE                        |                                     | Y           |
| 335    | 3,3'-DIMETHOXYBENZIDINE-4,4'-DIISOCYANATE | +    | F    | (P ) P P P                          |                                     |             |
|        | Number of Chemicals = 6               |      |      |                                      |                                     |             |
| 334    | 2-AMINO-5-NITROPHENOL                  | +    | G    | SE NE NE NE (MR)                    |                                     | Y           |
| 289    | BENZENE                                | -    | G    | CE CE (CE) CE                       |                                     |             |
| 288    | 1,3-BUTADIENE                          | +    | F    | CE CE NE (MR)                       |                                     |             |
| 304    | CHLOROEOIC ACID                        | -    | F    | CE CE NE (MR)                       |                                     |             |
| 397    | C.I. DIRECT BLUE 15                   | +    | F    | CE CE CE                            |                                     |             |
| 406    | 2,4-DIAMINOANISOLE SULFATE             | +    | F    | (P ) P P P                          |                                     |             |
| 372    | 3,3'-DIMETHYLBENZIDINE DIHYDROCHLORIDE | +    | W    | (CE) CE                             |                                     |             |
| 390    | 3,3'-DIMETHYLBNZIDINE DIHYDROCHLORIDE  | +    | W    | (CE) CE                             |                                     |             |
| 316    | DIMETHYLVINYL CHLORIDE (DMVC)          | -    | G    | CE CE (CE) CE                       |                                     |             |
| 291    | ISOPHORENE                             | -    | G    | (SE) NE EE NE                       |                                     |             |
| 385    | 2-MERCAPTOBENZOTHIAZOLE                | -    | F    | (CE) SE NE EE                       |                                     |             |
| 333    | NALIDIXIC ACID                         | -    | F    | (CE) CE EE                           |                                     |             |
| 310    | PROPYL GALLATE                         | -    | F    | (E ) N E N                          |                                     |             |
| 058    | TRIS(AZIRIDINYL)-PHOSPHINE SULFIDE     | +    | J    | P P (P ) P                          |                                     |             |
|        | Number of Chemicals = 16              |      |      |                                      |                                     |             |
| 193    | RESERPINE                              | -    | F    | P N (P ) P                           |                                     | Y           |
|        | Number of Chemicals = 1               |      |      |                                      |                                     |             |
| 093    | 3-AMINO-9-ETHYLCARBAZOLE HCL           | +    | F    | (P ) P P P                          |                                     | Y           |
| 289    | BENZENE                                | -    | G    | (EE) CE CE CE                       |                                     |             |
| 346    | CHLORTHEAHE                           | +    | I    | (EE) EE IS CE                       |                                     |             |
| 405    | C.I. ACID RED 114                     | +    | W    | (CE) CE                             |                                     |             |
| 285    | C.I. BASIC RED 9 MONOXYDROCHLORIDE    | +    | F    | (CE) CE CE                          |                                     |             |
| 397    | C.I. DIRECT BLUE 15                   | +    | W    | (CE) CE                             |                                     |             |
| 084    | 2,4-DIAMINOANISOLE SULFATE             | +    | F    | (P ) P P P                          |                                     |             |
| 310    | DIESEL FUEL MARINE                     | +    | S    | (EE) (EE)                           |                                     |             |
| 372    | 3,3'-DIMETHYLBENZIDINE DIHYDROCHLORIDE | +    | W    | (CE) CE                             |                                     |             |
| 128    | 3,3'-DIMETHYLBENZIDINE-4,4'-DIISOCYANATE | +    | F    | (P ) P N N                          |                                     |             |
| 390    | 3,3'-DIMETHYLBENZIDINE DIHYDROCHLORIDE | +    | W    | (CE) CE                             |                                     |             |
| 054    | 2,4-DINITROTOUENOE                     | +    | F    | (P ) P N N                          |                                     |             |
| 103    | FETHIONL                               | -    | G    | N N N N N                           |                                     |             |
| 252    | GERANYL ACETATE                        | +    | G    | N N N N (MR)                        |                                     |             |
| 374    | GLYCOLID                               | +    | G    | (CE) CE (CE) CE                     |                                     |             |
| 146    | NITRIZIDE                              | +    | F    | N (P ) P E                          |                                     |             |
| 127    | 5-NITRO-O-AMISIDINE                    | +    | F    | (P ) P E P                          |                                     |             |
| 337    | NITROFURAZONE                          | +    | F    | (EE) CE NE                          |                                     |             |
| 364    | RHODAMINE 6G                           | -    | F    | (EE) EE NE                           |                                     |             |
| 058    | TRIS(AZIRIDINYL)-PHOSPHINE SULFIDE     | +    | J    | (P ) (P ) (P ) P                    |                                     |             |
| 362    | 3,3'-DIMETHYLBENZIDINE DIHYDROCHLORIDE | +    | S    | (CE) (CE) (CE) CE                   |                                     |             |
|        | Number of Chemicals = 21               |      |      |                                      |                                     |             |
| 130    | ANILINE HYDROCHLORIDE                  | +    | F    | (P ) (P ) N N                       |                                     |             |
| 154    | AZOBENZENE                             | +    | F    | (P ) (P ) N N                       |                                     |             |
| 189    | P-CHLOROANILINE                        | -    | F    | (E ) N E E                          |                                     |             |
| 351    | P-CHLOROANILINE HYDROCHLORIDE          | -    | G    | (CE) (EE) (SE) NE                   |                                     |             |
| 225    | D & C RED NO. 9                       | +    | F    | (P ) E N N                          |                                     |             |

(Continued on next page)
| TR No | Chemical                              | SAL | RUT | Levels of evidence of carcinogenicity | May have been related (sex species) | Other sites |
|-------|---------------------------------------|-----|-----|--------------------------------------|-------------------------------------|------------|
|       |                                       |     |     | MR FR MM FM                           |                                      |            |
| 360   | N,N-DIMETHYLAMLINE                    | -   | G   | (SE) NE NE EE                        | Y                                   |            |
| 349   | PENTACHLOROPHENOL, DOMICIDE EC-7      | -   | F   |      CE (CE)                         | Y                                   |            |
| 347   | PENTACHLOROPHENOL, TECHNICAL         | -   | F   |      CE (SE)                         | Y                                   |            |
| 016   | PHOSPHAMIDON                          | +   | F   |      (E ) E N                        | Y                                   |            |
| 020   | 4,4'-SULFONYLIDIANILINE (DAPSONE)    | -   | F   |      (P ) N N                        | N                                   |            |
| 153   | 0-TOLUIDINE HYDROCHLORIDE             | -,+ | F   |      (P ) (P) P                       | Y                                   |            |
|       |                                       |     |     |                                      |                                      |            |
|       |                                       |     |     |                                      | Number of Chemicals = 11            |            |
|       |                                       |     |     |                                      | SUMS 9 4 1 2                        |            |
|       |                                       |     |     |                                      |                                      |            |
|       |                                       |     |     |                                      | SUBCUTANEOUS TISSUE                 |            |
|       |                                       |     |     |                                      |                                      |            |
| 234   | ALLYL ISOTHIOCYANATE                  | +W,-| G   |      P (E ) N                        | Y                                   |            |
| 285   | C.I. BASIC RED 9 MONOHYDROCHLORIDE   | +   | F   |      (CE) CE CE                      | Y                                   |            |
| 210   | 1,2-DIBROMOETHANE                    | +   | I   |      P P P (P)                       | Y                                   |            |
| 055   | 1,2-DICHLORODETHANE                  | +   | G   |      (P ) P P                        | Y                                   |            |
| 374   | GLYCIDOL                             | +,+ | G   |      CE CE CE                        | Y                                   |            |
| 018   | IPD (3,3'-IMINOBIS-1-PROPANOL DIMETHANESULF | +   | J   |      E E (E ) (E )                   |                                    |            |
| 291   | ISOPROCHLORONE                       | -   | G   |      SE NE EE                        | Y                                   |            |
| 359   | 8-METHOXYPSORALEN                    | +   | G   |      SE (MR)                         | Y                                   |            |
| 029   | 2-METHYL-1-NITROANTHRAQUINONE         | +   | F   |      (P ) (P) P                      | Y                                   | (MR)       |
| 368   | MALIDIC ACID                         | -   | F   |      CE CE (EE)                      | Y                                   |            |
| 341   | NITROFURANATIN                      | +,+ | F   |      SE NE CE                        | Y                                   | (MR)       |
| 201   | 2,3,7-TETRACHLORIDIBENZO-P-DIOXIN   | +   | S   |      (E ) (P)                        | N                                   |            |
| 251   | 2,4- & 2,6-TOLUENE DISOCYANATE       | +   | G   |      (P ) (P) N                      | Y                                   |            |
| 153   | O-TOLUIDINE HYDROCHLORIDE            | -,+ | F   |      (P ) P P                        | Y                                   |            |
| 081   | TRIMETHYLPHOSPHATE                   | +   | G   |      (P ) N P                        | N                                   |            |
| 278   | 2,6-XYLIDINE                         | +,W,+W | F |      P P (MR) (FR)                   | Y                                   |            |
|       |                                       |     |     |                                      |                                      |            |
|       |                                       |     |     |                                      | Number of Chemicals = 16            |            |
|       |                                       |     |     |                                      | SUMS 9 5 4 4                        |            |
|       |                                       |     |     |                                      | THYROID GLAND                       |            |
|       |                                       |     |     |                                      |                                      |            |
| 021   | ALDRIN                                | -   | F   |      (E ) (E ) P                     | Y                                   |            |
| 112   | 3-AMINO-4-ETHOXACETANILIDE            | +   | F   |      N N (P) N                       | N                                   |            |
| 089   | O-ANISIDINE HYDROCHLORIDE             | ?,+ | F   |      (P ) P P                        | Y                                   |            |
| 069   | AZINPHOSMETHYL                       | +W,+ | F |      (E ) N N                        | Y                                   |            |
| 308   | CHLORINATED PARAFFINS: C12, 6% CHLORINE| -   | G   |      CE CE CE                        | Y                                   |            |
| 285   | C.I. BASIC RED 9 MONOHYDROCHLORIDE   | +   | F   |      (CE) CE CE                      | Y                                   |            |
| 309   | DECADECABROMOPHENYL OXIDE             | +   | F   |      SE SE CE                        | Y                                   |            |
| 084   | 2,4-DIAMINOANISOLE SULFATE           | -   | F   |      (P ) (P) (P) (P)               | Y                                   |            |
| 149   | N,N'-DIETHYLTHIOUREA                 | -   | F   |      (P ) (P) N                      | N                                   |            |
| 388   | ETHEYLENE THIOUREA (ETU)              | -,+ | F   |      (CE) CE CE                      | Y                                   |            |
| 374   | GLYCIDOL                             | +,+ | G   |      (CE) CE CE                      | Y                                   |            |
| 271   | HC BLUE 1                             | -   | F   |      EE SE CE                        | (MM)                                |            |
| 009   | HEXACHLOROBENZOTECHLORIDE             | -   | F   |      N (E ) P                        | Y                                   |            |
| 340   | IODINATED GLYCEROL                   | +   | G   |      (SE) NE SE                      | Y                                   |            |
| 331   | MALONALDEHYDE, SODIUM SALT           | -   | G   |      (CE) CE NE                      | Y                                   |            |
| 186   | 4,4'-METHYLENEDIISWN,DIMETHYL)BENZENAMINE| +   | F   |      (P ) (P) E                      | Y                                   |            |
| 248   | 4,4'-METHYLENEDIAMINYL DIOHYDROCHLORIDE| +,+ | W |      (P ) (P) (P) (P)               | Y                                   |            |
| 143   | 1,5-NAPHTHALENEAMINE                  | +   | F   |      N (P) (P) (P)                   | Y                                   |            |
| 205   | 4,4'-OXYDIJNILE                       | +   | F   |      (P ) (P) P                      | Y                                   |            |
| 016   | PHOSPHAMIDON                          | +   | F   |      (E ) E N                        | Y                                   |            |
| 231   | STANNOUS CHLORIDE                    | -   | F   |      (E ) N N                        | Y                                   |            |
| 209   | 2,1,7,7-BTETRACHLORIDIBENZO-P-DIOXIN | -   | G   |      (P ) (P) P                      | Y                                   |            |
| 131   | TETRACHLORODIPHENYLETHANE             | -   | F   |      (E ) N N                        | Y                                   |            |
| 033   | TETRACHLORVINPHOS                    | -   | F   |      N (P) P                         | Y                                   |            |
| 047   | 4,4'-THIODIANILINE                   | +   | F   |      (P ) (P) (P) (P)               | Y                                   |            |
| 057   | TOXAPHENE                            | +   | F   |      (E ) (E ) P                     | Y                                   |            |
| 129   | TRIMETHYLTHIOUREA                    | -   | F   |      N (P) N                         | Y                                   |            |
| 391   | TRIS(2-CHLOROETHYL) PHOSPHATE         | -   | G   |      CE CE EE EE                    | (MR) (FR)                           |            |
| 238   | ZIRAM                                | +   | F   |      (P ) N N                        | Y                                   |            |
|       |                                       |     |     |                                      |                                      |            |
|       |                                       |     |     |                                      | Number of Chemicals = 29            |            |
|       |                                       |     |     |                                      | SUMS 20 18 8 8                      |            |
|       |                                       |     |     |                                      | URETER                              |            |
|       |                                       |     |     |                                      |                                      |            |
| 006   | NITROLATRIACETIC ACID (NTA)           | -   | F   |      (P ) P P                        | Y                                   |            |
| 006   | NITROLATRIACETIC ACID TRISODIUM MONOHYDRATE| - | F |      (P ) (P)                       | Y                                   |            |
|       |                                       |     |     |                                      |                                      |            |
|       |                                       |     |     |                                      | Number of Chemicals = 2              |            |
|       |                                       |     |     |                                      | SUMS 2 1 0 0                        |            |
|       |                                       |     |     |                                      | URINARY BLADDER                     |            |
|       |                                       |     |     |                                      |                                      |            |
| 234   | ALLYL ISOTHIOCYANATE                 | +W,-| G   |      (P ) E N                        | Y                                   |            |
| 094   | 4-AMINO-2-NITROPHENOL                | +   | F   |      (P ) (E) N                      | N                                   |            |

| Table 1. (continued) |
### Table 1. (continued)

| TR No | Chemical | SAL* | RUT* | MRa | FR | MM | FM | May have been related* (sex species) | Other* sites |
|-------|----------|------|------|------|----|----|----|--------------------------------------|-------------|
| 216   | 11-MINOUNDECA NOIC ACID | -    | F    | (P ) | E  | N  | 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  | Y                                   |             |
| 063   | 4-CHLORO-O-PHENYLENEDIAMINE | +   | F    | (P) | (P) | P  | P  | Y                                   |             |
| 299   | C.I. DISPERSE BLUE 1 | +   | G    | (P) | (P) | IS  | N  | Y                                   |             |
| 155   | 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   | MELANINE | -   | F    | (P) | N   | N  | N  | 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                                   |             |
| 164   | N-NITROSO2PHENYLAMINE | -   | F    | (P) | (P) | N  | N  | Y                                   |             |
| 153   | O-TOLUIDINE HYDROCHLORIDE | -,+ | F    | P   | (P) | P  | P  | Y                                   |             |

Number of Chemicals = 18

### UTERUS/CERVIX

| TR No | Chemical | SAL* | RUT* | MRa | FR | MM | FM | May have been related* (sex species) | Other* sites |
|-------|----------|------|------|------|----|----|----|--------------------------------------|-------------|
| 093   | 3-AMINO-9-ETHYLCARBazoLE HCL | +   | F    | P   | (P) | P  | P  | Y                                   |             |
| 363   | BROMETHANE (ETHYL BROMIDE) | -,+ | I    | SE  | EE  | EE  | (CE) | Y                                   |             |
| 346   | CHLOROETHANE | +   | I    | EE  | EE  | IS  | (CE) | Y                                   |             |
| 083   | DAMINIZIDE | -   | F    | N   | (P) | E  | N  | Y                                   |             |
| 066   | 1,1-DICHLOROETHANE | -   | G    | N   | E   | N  | (E) | Y                                   |             |
| 055   | 1,2-DICHLOROETHANE | +   | P    | P   | P   | P  | (P) | Y                                   |             |
| 372   | 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE | +,+ | W    | CE  | CE  | CE  | (CE) | Y                                   |             |
| 128   | 3,3'-DIMETHOXYBENZIDINE-4,4'-DIISOCYANATE | +   | F    | P   | (P) | N  | N  | Y                                   |             |
| 326   | ETHYLENE OXIDE | -   | I    | CE  | CE  | (CE) | Y | Y                                   |             |
| 374   | GLYCIDOL | +,+ | G    | CE  | CE  | CE  | (CE) | Y                                   |             |
| 078   | ICRF-159 | +   | J    | N   | (P) | N  | P  | Y                                   |             |
| 032   | ISOPHOSPHAMIDE | +   | F    | N   | (P) | P  | P  | Y                                   |             |
| 143   | 1,5-NAPHTHALENE DIAMINE | +   | 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

### ZYMBALE GLAND

| TR No | Chemical | SAL* | RUT* | MRa | FR | MM | FM | May have been related* (sex species) | Other* sites |
|-------|----------|------|------|------|----|----|----|--------------------------------------|-------------|
| 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) | 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) | 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  | CE  | (CE) | Y                                   |             |
| 128   | 3,3'-DIMETHOXYBENZIDINE-4,4'-DIISOCYANATE | +   | F    | (P) | (P) | N  | N  | Y                                   |             |
| 390   | 3,3'-DIMETHYLBENZIDINE DIHYDROCHLORIDE | +   | W    | CE  | CE  | 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-NITROACENAPHTHENNE | +   | F    | (P) | (P) | N  | P  | Y                                   |             |
| 127   | 5-NITRO-O-ANISIDINE | +   | F    | (P) | (P) | E  | P  | Y                                   |             |
| 365   | PENTAYRTHRTOL TETRANITRATE | -   | F    | (EE) | (EE) | NE  | NE  | Y                                   |             |
| 047   | 4,4'-TRIODIANILINE | +   | F    | (P) | (P) | P  | P  | Y                                   |             |
| 057   | BETA-THIOGUANIDINE DEOXYRIBOSIDE | -   | J    | (E) | (P) | IS  | IS  | Y                                   |             |
| 058   | TRIS(2ZIREDINYL)-PHOSPHINE SULFIDE | +   | J    | (P) | (P) | P  | P  | Y                                   |             |

Number of Chemicals = 20

### NO SITE

| TR No | Chemical | SAL* | RUT* | MRa | FR | MM | FM | May have been related* (sex species) | Other* sites |
|-------|----------|------|------|------|----|----|----|--------------------------------------|-------------|
| 050   | ACETOHEXAMIDE | -   | F    | N   | N  | N  | N  | N                                   |             |
| 230   | AGAR | -    | F    | N   | N  | N  | N  | Y                                   |             |
| 136   | ALDICARB | -    | F    | N   | N  | N  | N  | N                                   |             |
| 387   | DL-AMPHETAMINE SULFATE | -   | F    | NE  | NE  | N  | N  | Y                                   |             |
| 104   | ANILAZINE | -    | F    | N   | N  | N  | N  | Y                                   |             |
| 036   | O-ANTHRANILIC ACID | -    | F    | N   | N  | N  | N  | Y                                   |             |
| 279   | ASBESTOS, ANOSITE | -    | F    | N   | N  | N  | N  | Y                                   |             |

(Continued on next page)
| TR No | Chemical Name                     | SAL | RUT | MR² | FR | MM | FM | Other sites |
|-------|-----------------------------------|-----|-----|-----|----|----|----|-------------|
| 295   | Asbestos, Chrysotile(SR)          | F   | NE  | NE  | N  |     |    |             |
| 260   | Asbestos, Crocidolite             | F   | N   | N   | N  |     |    |             |
| 277   | Asbestos, Tremolite               | F   | N   | N   | N  |     |    |             |
| 247   | L-Ascorbic Acid                   | +W  |     | NE  | N  |     |    |             |
| 204   | Benzoin                          |     |     |     | N  |     |    |             |
| 343   | Benzyl Alcohol                    |     |     |     | N  |     |    |             |
| 191   | Bis(2-Chloro-1-Methylethyl) Ether | +W  |     |     | N  |     |    |             |
| 324   | Boric Acid                        |     |     |     | N  |     |    |             |
| 150   | Butylated Hydroxytoluene          |     |     |     | N  |     |    |             |
| 312   | N-Butyl Chloride                  |     |     |     | N  |     |    |             |
| 163   | Calcium Cyanide                   |     |     |     | N  |     |    |             |
| 214   | Caprolactam                       |     |     |     | N  |     |    |             |
| 173   | Carbromal                         |     |     |     | N  |     |    |             |
| 381   | D-Carvone                         |     |     |     | N  |     |    |             |
| 294   | Chlorinated Trisodium Phosphate   | +W  |     | IS  | N  |     |    |             |
| 177   | 4-(Chloracetyl)Acetanilide        | +   | F   | N   | N  |     |    |             |
| 377   | O-Chlorobenzalmalon Nitrite (CS)  | +   | I   | NE  | N  |     |    |             |
| 275   | 2-Chloroethanol (Ethylene Chlorohydrin) | +,+,+ | S | NE  | N  |     |    |             |
| 158   | 2-Chloroethyltrimethylammonium Chloride | +,+ | F | N   | N  |     |    |             |
| 178   | 2-Chloromethylpyridine Hydrochloride | +  | G   | N   | N  |     |    |             |
| 113   | 2-Chloro-P-Phenylenediamine Sulfate | +  | F   | N   | N  |     |    |             |
| 153   | Chloropiricin                      |     |     |     | N  |     |    |             |
| 145   | 3-Chloro-P-Toluidine               | +,+ | G   | IS  | N  |     |    |             |
| 317   | Chlorpheniramine Maleate           |     |     |     | N  |     |    |             |
| 105   | Chlorpropamide                    |     |     |     | N  |     |    |             |
| 211   | C.I. Acid Orange 10               |     |     |     | N  |     |    |             |
| 220   | C.I. Acid Red 14                  |     |     |     | N  |     |    |             |
| 096   | Coumarophis                       |     |     |     | N  |     |    |             |
| 030   | Diarylamilide Yellow              |     |     |     | N  |     |    |             |
| 137   | Diazinom                          |     |     |     | N  |     |    |             |
| 122   | Dibenzo-P-Dioxin                  |     |     |     | N  |     |    |             |
| 183   | Dibutyltin Diacetate              |     |     |     | N  |     |    |             |
| 255   | 1,2-Dichlorobenzene (D-Dichlorobenzene) | -  | G   | N   | N  |     |    |             |
| 131   | Dichlorodiphenyltrichloroethane (DDT) | -  | F   | N   | N  |     |    |             |
| 353   | 2,4-Dichlorophenol                |     |     |     | N  |     |    |             |
| 101   | Dichlorvos                        |     |     |     | N  |     |    |             |
| 056   | N,N'-Dicycleyxylthiourea          |     |     |     | N  |     |    |             |
| 022   | Dieldrin                          |     |     |     | N  |     |    |             |
| 004   | Dimethate                         | +,+ | F   | N   | N  |     |    |             |
| 171   | 2,4-Dimethoxyaniline Hydrochloride | +  | F   | N   | N  |     |    |             |
| 125   | Dioxathion                        | +   | F   | N   | N  |     |    |             |
| 062   | Endosulfan                        | +   | F   | IS  | N  | IS  |    |             |
| 012   | Endrin                            | -   | F   | N   | N  |     |    |             |
| 307   | Epheedrine Sulfate                | -   | F   | NE  | N  |     |    |             |
| 338   | Erythromycin Stearate             | -   | F   | NE  | N  |     |    |             |
| 046   | Ethionamide                       | -   | F   | N   | N  |     |    |             |
| 208   | FD & C Yellow No. 6               | -   | F   | N   | N  |     |    |             |
| 101   | Formulated Fenaminosulf           | +   | F   | N   | N  |     |    |             |
| 252   | Geranyl Acetate                   | -   | G   | N   | N  |     |    |             |
| 229   | Guar Gum                          | -   | F   | N   | N  |     |    |             |
| 227   | Gum Arabic                        | -   | F   | N   | N  |     |    |             |
| 293   | HC Blue 2                         | +   | F   | NE  | N  |     |    |             |
| 202   | 1,2,3,6,7,8-Hexachlorodibenzo-P-Dioxin | +  | S   | N   | N  |     |    |             |
| 040   | Hexachlorophene                   | -   | F   | N   | N  |     |    |             |
| 276   | 8-Hydroxyquinoline                | +   | F   | NE  | N  |     |    |             |
| 110   | Iodoform                          | +,+ | G   | N   | N  |     |    |             |
| 151   | Lead Dimethyldithiocarbamate       | +   | F   | N   | N  |     |    |             |
| 014   | Lindane                           | -   | F   | N   | N  |     |    |             |
| 175   | Lithocholic Acid                  | -   | G   | N   | N  |     |    |             |
| 221   | Locust Bean Gum                   | -   | F   | N   | N  |     |    |             |
| 135   | Malaoxon                          | -   | F   | N   | N  |     |    |             |
| 024   | Malathion                         | -   | F   | N   | N  |     |    |             |
| 192   | Malathion                         | -   | F   | N   | N  |     |    |             |
| 236   | D-Mannitol                        | +,+ | F   | N   | N  |     |    |             |
| 098   | DL-Menthol                        | +   | F   | N   | N  |     |    |             |
| 033   | Methoxychlor                      | +   | F   | N   | N  |     |    |             |
| 385   | Methoxy Bromide                   | +   | I   | NE  | N  |     |    |             |
| 314   | Methyl Methacrylate               | +   | I   | NE  | N  |     |    |             |
| 157   | Methyl Parathion                  | +   | F   | N   | N  |     |    |             |
| 147   | Methylcarbath                     | +   | F   | N   | N  |     |    |             |
| 396   | Monochloroacetic Acid             | -   | G   | NE  | N  |     |    |             |
Table 1. (continued)

| TR No | Chemical                                               | SAL | RUT | Levels of evidence of carcinogenicity | May have been related to carcinogenicity (sex species) | Other sites |
|-------|--------------------------------------------------------|-----|-----|--------------------------------------|------------------------------------------------------|-------------|
| 168   | N-(1-NAPHTHYL)ETHYLENEDIAMINE DIHYDROCHLORIDE          | +   | F   | N N N N                             | N                                                    |             |
| 310   | NAVY FUELS JP-5                                       | -   |     | S                                   | NE NE NE                                             |             |
| 109   | 4-NITROANTHRANILIC ACID                               | +   | F   | N N N N                             | N                                                    |             |
| 064   | 1-NITROPHENPROPYL                                  | *   |     | F                                   | N N N N                                              |             |
| 180   | 4-NITRO-O-PHENYLENEAMINE                             | +, * | F   | N N N N                             | N                                                    |             |
| 170   | BETA-NITROSTYRENE                                        | +W, - | G   | N N N N                             | N                                                    |             |
| 336   | PENICILLIN VK                          | -   |     | G                                   | NE NE NE                                             |             |
| 061   | PENTACHLORONITROBENZENE                             | -   | F   | N N N N                             | N                                                    |             |
| 325   | PENTACHLORONITROBENZENE                             | -   | F   | N N N N                             | N                                                    |             |
| 007   | PHENENONE 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   | N N N N                             | NE NE NE                                             | N           |
| 141   | 1-PHENYL-3-METHYL-5-PYRAZOLONE                        | -   | F   | N N N N                             | N                                                    |             |
| 301   | 0-PHENYLPHENOL                                       | +W, - | S   | N                                   | NE NE NE                                             |             |
| 062   | N-PHENYL-P-PHENYLENEDIAMINE                           | -   | F   | N N N N                             | N                                                    |             |
| 148   | 1-PHENYL-2-TIOLUREA                                   | -   | F   | N N N N                             | N                                                    |             |
| 017   | PHOTODIODRIN                                         | +   | F   | N N N N                             | N                                                    |             |
| 161   | PHTHALAMIDE                                           | -   | F   | N N N N                             | N                                                    |             |
| 159   | PHTHALIC ANHYDRIDE                                    | "   | F   | N N N N                             | N                                                    |             |
| 120   | PIPERONYLBUTOXIDE                                     | +   | F   | N N N N                             | N                                                    |             |
| 272   | PROPYLENE                                            | +   | I   | NE NE NE                             | N                                                    |             |
| 154   | PYRAZINAMIDE                                         | -   | F   | N N N IS                             | N                                                    |             |
| 077   | PYRIMETHANINE                                        | -   | G   | NE NE NE                             | N                                                    |             |
| 403   | RESORCINOL                                           | -   | F   | N IS H                               | N                                                    |             |
| 197   | SELENIUM SULFIDE                                     | +   | S   | N                                   | N                                                    |             |
| 199   | SELSUN                                               | -   | S   | N                                   | N                                                    |             |
| 389   | SODIUM AZIDE                                         | +   | G   | NE NE                                | N                                                    |             |
| 172   | SODIUM DIETHYLDITHIOCARBAMATE                         | -   | F   | N N N N                             | N                                                    |             |
| 373   | SUCINIC ANHYDRIDE                                     | "   | G   | NE NE NE                             | NE NE NE                                             |             |
| 138   | SULFISOKAZOLE                                        | -   | 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   | N N N N                             | NE NE NE                                             | N           |
| 166   | TETRACHLOROTHIURAM DISULFIDE                          | -   | F   | N N N N                             | N                                                    |             |
| 296   | TETRACHLORO(N-HYDROXYMETHYL)PHOSPHONIUM CHLORIDE     | -   | F   | N N N N                             | NE NE NE                                             | N           |
| 296   | TETRACHLORO(N-HYDROXYMETHYL)PHOSPHONIUM SULFATE      | -   | F   | N N N N                             | NE NE NE                                             | N           |
| 097   | TITANIUM DIOXIDE                                      | -   | F   | N N N N                             | N                                                    |             |
| 051   | TOLAZAMIDE                                           | ?   | F   | N N N N                             | N                                                    |             |
| 031   | TOLBITAMIDE                                          | -   | F   | N N N N                             | N                                                    |             |
| 371   | TOLUENE                                              | -   | I   | 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   | TRICHLOROFLUOROETHANE                                 | -   | G   | IS IS IS                             | N                                                    |             |
| 139   | TRIPHENYLTHIOXIDE                                    | -   | F   | N N N N                             | N                                                    |             |
| 011   | TRISODIUM ETHYLENEDIAMINEETETRAACETATE TRIHYDROCHLORIDE | -   | F   | N N N N                             | N                                                    |             |
| 071   | L-Tryptophan                                         | -   | I   | NE NE NE                             | N                                                    |             |
| 375   | VINYL TOLUENENE                                       | -   | I   | NE NE NE                             | N                                                    |             |
| 327   | XYLENE (MIXED)                                       | -   | G   | NE NE NE                             | N                                                    |             |

Number of Chemicals = 128

|                  | TOTALS | MR* | FR | MM | FM | Other sites |
|------------------|--------|-----|----|----|----|-------------|
|                  | 115    | 115 | 117| 118|    |             |

Between 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 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 (acryline); 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 1894 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 foreestomach 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-

| Study result | By experiment | By chemical |
|--------------|---------------|-------------|
|               | Rats          | Mice        |          |
|               | Male | Female | Male | Female | Total | Male | Female | Overall |
| Positive      | 127  | 107   | 102  | 125    | 459   | 146  | 137    | 198     |
| Equivocal     | 41   | 36    | 35   | 29     | 132   | 48   | 35     | 83      |
| No evidence   | 183  | 211   | 204  | 205    | 803   | 162  | 178    | 128     |
| Totals        | 351  | 354   | 341  | 343    | 1394  | 356  | 350    | 379     |
Table 3. Carcinogenicity results for 313 chemical studies in rodents. *

| Proportion of positive studies | Rats | Mice | Number of studies with these results |
|-------------------------------|------|------|-------------------------------------|
|                               | Male | Female | Male | Female |                                  |
| 4/4                           | +    | +     | +    | +     | 43                                  |
| 3/4                           | +    | +     | +    | -     | 1                                  |
|                               | +    | +     | -    | +     | 11                                 |
|                               | +    | -     | +    | +     | 7                                  |
|                               | -    | +     | -    | +     | 6                                  |
| Subtotals                     | 25   | 8.0                                           |
| 2/4                           | +    | -     | +    | -     | 19                                  |
|                               | +    | -     | -    | -     | 2                                  |
|                               | +    | -     | +    | -     | 7                                  |
|                               | -    | +     | -    | +     | 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

*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. *

| Comparison                        | Observed response | % Concordant (++ or --) responses |
|-----------------------------------|-------------------|----------------------------------|
| Male rats vs. female rats         | + +               | 84.5 (295/349)                   |
| Male rats vs. male mice           | + -               | 70.3 (223/317)                   |
| Male rats vs. female mice         | + +               | 74.5 (239/321)                   |
| Female rats vs. male mice         | + +               | 74.8 (239/318)                   |
| Female rats vs. female mice       | + -               | 76.8 (248/322)                   |
| Male mice vs. female mice         | + +               | 86.7 (294/339)                   |
| Rats vs. mice                     | + +               | 74.4 (233/313)                   |

*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.

Carcinogenic 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.

| Site                        | Male POS | Male EE | Female POS | Female EE | Male POS | Male EE | Female POS | Female EE | Totals POS | Totals EE | Totals 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         | 0         | 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        | 22            |
| Glanular 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         | 8        | 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/ovary                | 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        |

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

** 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.

| Organs/systems       | Chemicals | % of 379 chemicals | Rats | Mice | % of 1394 experiments |
|----------------------|-----------|---------------------|------|------|-----------------------|
| 1. Liver             | 104       | 27%                 | Male | Female | 58 | 75 | 203 | 15%          |
| 2. Lung              | 30        | 8%                  | Male | Female | 18 | 21 | 51 | 4%           |
| 3. Hematopoietic system | 29     | 8%                  | Male | Female | 8 | 13 | 43 | 3%           |
| 4. Mammary gland     | 27        | 7%                  | Male | Female | 0 | 9  | 34 | 2%           |
| 5. Forestomach       | 23        | 6%                  | Male | Female | 15 | 16 | 57 | 4%           |
| 6. Thyroid gland     | 19        | 5%                  | Male | Female | 6 | 8  | 41 | 3%           |
| 7. Zymbal gland      | 18        | 5%                  | Male | Female | 1 | 2  | 34 | 2%           |
| 8. Urinary bladder   | 16        | 4%                  | Male | Female | 3 | 3  | 26 | 2%           |
| 9. Skin              | 15        | 4%                  | Male | Female | 3 | 2  | 26 | 2%           |
| 10. Circulatory system | 13       | 3%                  | Male | Female | 8 | 9  | 23 | 2%           |
| 11. Adrenal gland    | 13        | 3%                  | Male | Female | 5 | 4  | 17 | 1%           |

Totals | 161 | 149 | 129 | 170 |
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

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

| Site            | Male rats | Female rats | Composite sites | Rats | Unique chemicals |
|-----------------|-----------|-------------|----------------|------|------------------|
| Liver           | 38        | 32          | Liver<sup>a</sup> | 38   | 32               | 44              |
| Kidney          | 25        | 22          | Kidney<sup>a</sup> | 25   | 9                | 28              |
| Zymbal gland    | 16        | 15          | Mammary gland   | 3    | 22               | 22              |
| Thyroid gland   | 14        | 13          | Zymbal gland<sup>a</sup> | 16   | 15               | 18              |
| Forestomach     | 14        | 11          | Thyroid gland<sup>a</sup> | 14   | 13               | 17              |
| Thyroid gland   | 14        | 10          | Hematopoietic system<sup>a</sup> | 12   | 10               | 17              |
| Skin            | 14        | 10          | Forestomach<sup>a</sup> | 15   | 11               | 15              |
| Intestines      | 9         | 9           | Skin           | 14   | 7                | 15              |
| Nasal cavity    | 8         | 8           | Urinary bladder | 10   | 14               | 14              |

<sup>a</sup> 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.

| Site            | Male mice | Female mice | Composite sites | Mice | Unique chemicals |
|-----------------|-----------|-------------|----------------|------|------------------|
| Liver           | 58        | 75          | Liver<sup>a</sup> | 58   | 75               | 86              |
| Lung            | 18        | 21          | Lung<sup>a</sup> | 18   | 21               | 23              |
| Forestomach     | 15        | 16          | Forestomach<sup>a</sup> | 15   | 16               | 17              |
| Hematopoietic system | 8    | 13          | Hematopoietic system<sup>a</sup> | 8    | 13               | 15              |
| Circulatory system | 8    | 9           | Circulatory system<sup>a</sup> | 8    | 9                | 11              |
| Thyroid gland   | 6         | 9           | Mammary gland   | 0    | 9                | 9               |
| Harderian gland | 5         | 8           | Thyroid gland<sup>a</sup> | 6    | 8                | 9               |
| Adrenal gland   | 5         | 8           | Ovary           | 0    | 8                | 8               |
| Kidney          | 4         | 7           | Ovary           | 5    | 6                | 7               |
| Five sites<sup>b</sup> | 3     | 6           | Uterus/cervix   | 0    | 7                | 7               |

<sup>a</sup> Occurs in top 10 in both male and female mice.

<sup>b</sup> Heart, nasal cavity, preputial gland, skin, urinary bladder.
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).*

| Site                                      | Males and females | Rate | Males          | Rate | Females        | 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

| Site                                      | Males and females | Rate | Males          | Rate | Females        | 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 |

*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
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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 (foregut, 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, adenosomas 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 female rat, 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 [hemangiom-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 biological 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 irrelevant 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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