EXPEDITED CANCER POTENCY VALUES AND PROPOSED REGULATORY LEVELS FOR CERTAIN PROPOSITION 65 CARCINOGENS

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY

April 1992

OEHHA

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

Reproductive and Cancer Hazard Assessment Section

TABLE OF CONTENTS

Introduction 1

Methodology 1

Potency Values for Proposition 65 Carcinogens 3

Expedited Potencies Compared with Conventional Estimates 4

Conclusion 5

References 7

Figures

Figure 1: Ratio of Expedited to Conventional Potency Estimates 9

Tables

Table 1: Expedited No Significant Risk Levels for 140 Proposition 65 Carcinogens 10

Table 2: Expedited Cancer Potency Values for 140 Proposition 65 Carcinogens 13

Table 3: Ratio of Expedited to Conventional Potency Values 16

Table 4: Outliers - Expedited Potencies Differing by More than a Factor of 10 from DHS, Cal/EPA, or US EPA Potency Values 19

Appendices

Appendix 1: Data Sets Serving as Basis for Potency Derivations for 140 Proposition 65 Chemicals 21

Appendix 2: Example of Potency Derivation Using the Expedited Procedure 32

Appendix 3: Potency Derivation and Data Set Selection 39

INTRODUCTION

This report presents methodology for the derivation of cancer potency values using an expedited procedure, and provides potency estimates and regulatory values ("No Significant Risk Levels" [NSRLs]) for a number of agents listed as carcinogens under Proposition 65 (California Health and Safety Code 25249.5 *et seq.*). Previous reports and presentations on this topic (CDHS, 1990a,b; Cal/EPA/OEHHA, 1991a,b; Zeise et al., 1991) have received extensive discussion and comment. This version is the final result of those prior activities.

We begin this report by presenting the methodology for the expedited potency procedure. This is followed by a brief discussion of the data base serving as the basis for potency derivation and presentation of the values derived for Proposition 65 carcinogens for which regulatory values have not yet been published. For agents with NSRLs already in regulation, potencies were also derived using the expedited procedure. To evaluate the accuracy of the expedited method, these expedited values are compared to values previously developed by regulatory agencies using standard as well as non-default methodologies.

Appendices include information on data sets used in the analysis, a detailed example of potency estimation by the expedited approach, and a discussion of the derivation of each expedited value.

METHODOLOGY

To derive expedited potency values, default procedures specified in the administrative regulations for Proposition 65 (Title 22 California Code of Regulations [CCR] 12703) are applied to data sets selected from the extensive tabulations of Gold et al. (1984, 1986, 1987, 1989, 1990). The usual practice by regulatory agencies is to begin the assessment with a full literature search to locate all data on the carcinogenicity and dose response characteristics of the compound. This is followed by an evaluation of the pharmacokinetic and mechanistic (e.g., genotoxicity) data, and a dose response evaluation of all adequate bioassays. Occasionally the data support a pharmacokinetic analysis in the derivation of target dose estimates, or a dose response model different from the default. The expedited procedure used in this document differs from this usual practice in two ways. First, it relies on cancer dose response data evaluated and extracted from the original literature by Gold et al. Second, under the expedited procedure the choice of the multistage model is automatic, and pharmacokinetic adjustments are not employed.

The methods for expediting potency estimation incorporate the following assumptions:

- The dose response relationship for carcinogenic effects in the most sensitive species tested is representative of that in humans.
- Observed experimental results can be extrapolated across species by use of the interspecies factor based on "surface area scaling."
- The dose to the tissue giving rise to a tumor is assumed to be proportional to the administered dose.
- The multistage polynomial can be used to extrapolate potency outside the range of experimental observations to yield estimates of "low" dose potency.
- Cancer hazard increases with the third power of age.

Further details on the methods of expedited potency derivation, including criteria for selecting bioassay data sets from the Gold et al. data base and default procedures for dose response evaluation, are given below.

Data Selection: Gold et al. (1984, 1986, 1987, 1989, 1990) have created the Carcinogenic Potency Database (CPDB) containing the results of more than 4000 chronic laboratory animal experiments on 1050 chemicals by combining published literature with the results of Federal chemical testing programs. Included in their data set tabulations are estimates of average doses used in the bioassay, resulting tumor incidences for each of the dose levels employed for sites where significant responses were observed, dosing period, length of study and histopathology. Dose calculations follow procedures similar to those of regulatory agencies; details on methods used are given in Gold et al. (1984). We reviewed the quality assurance, literature review, and control procedures used in compiling the data and found them to be sufficient for use in an expedited procedure.

Cancer potency estimates are derived by applying the mathematical approach described in the section below to dose response data in the Gold et al. database. The following criteria are used for data selection.

1. Data sets with statistically significant increases in cancer incidence with dose ($p \leq 0.05$) are used. (If the authors of the bioassay report consider a statistically significant result to be unrelated to the exposure to the carcinogen, the associated data set is not used.)

2. Data sets are not selected if the endpoint is specified as "all tumor-bearing animals" or results are from a combination of unrelated tissues and tumors.

3. When several studies are available, and one study stands out as being of higher quality due to numbers of dose groups, magnitude of the dose applied, duration of study, or other factors, the higher quality study is chosen as the basis for potency calculation if study results are consistent with those of the other bioassays listed.

4. When there are multiple studies of similar quality in the sensitive species, the geometric mean of potencies derived from these studies is taken. If the same experimentalists tested two sexes of the same species/strain under the same laboratory conditions, and no other adequate studies are available for that species, the data set for the more sensitive sex is selected.

5. Potency is derived from data sets that tabulate malignant tumors, combined malignant and benign tumors, or tumors that would have likely progressed to malignancy.

Mathematical Model: Cancer potency is defined as the slope of the dose response curve at low doses. Following the default approach, this slope is estimated from the dose response data collected at high doses and assumed to hold at very low doses. The Crump linearized multistage polynomial (Crump et al., 1977) is fit to animal bioassay data:

$$\text{Probability of cancer} = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + \ldots)] \qquad (1)$$

Cancer potency is estimated from the upper 95% confidence bound on the linear coefficient q_1, which will be termed $q_1(95)$.

For a given chemical, the model is fit to a number of data sets. As discussed in the section above, the default is to select the data for the most sensitive target organ in the most

sensitive species and sex, unless data indicate that this is inappropriate. Deviations from this default occur, for example, when there are several bioassays or large differences exist between potency values calculated from available data sets.

Standard bioassays on mice and rats last approximately two years. In standard risk assessments, this is the assumed lifespan for these species. Animals in experiments of shorter duration are at a lower risk of developing tumors than those in the standard bioassay; thus potency is underestimated unless an adjustment for experimental duration is made. In estimating potency, short duration of an experiment is taken into account by multiplying $q_1(95)$ by a correction factor equal to the cube of the ratio of the assumed standard lifespan of the animal to the duration of the experiment (T_e). This assumes that the cancer hazard would have increased with the third power of the age of the animals had they lived longer:

$$q_{animal} = q_1(95) \cdot (104 \text{ weeks}/T_e)^3 \qquad (2)$$

In some cases survival in the bioassay is inadequate, and the number of initial animals subject to late occurring tumors is significantly reduced. In such situations, the above described procedure can, at times, significantly underestimate potency. A time-dependent model fit to individual animal data (i.e., the data set with the tumor status and time of death for each animal under study) may provide better potency estimates. When Gold et al. indicates that survival is poor for a selected data set, a time-dependent analysis is attempted if the required data is available in the Tox_Risk (Crump et al., 1991) data base. The Weibull multistage model (Weibull-in-time; multistage-in-dose) is fit to the individual animal data.

To estimate human cancer potency, q_{animal} values derived from bioassay data are multiplied by an interspecies scaling factor (K; the ratio of human body weight (bw_h) to test animal body weight (bw_a), taken to the 1/3 power; see Anderson et al. (1983) for details):

$$K = (bw_h/bw_a)^{1/3} \qquad (3)$$

Thus,

$$\text{Cancer potency} = q_{human} = K \cdot q_{animal} \qquad (4)$$

From these potency values, exposures associated with a given level of cancer risk can be derived. For example, the no significant risk level for Proposition 65 is the intake associated with a lifetime cancer risk of 10^{-5} or lower for a 70-kg adult. This level, in units of μg/day, is calculated according to the following equation:

$$I = \frac{10^{-5} \times 70 \text{ kg}}{q_{human}} \times \frac{1000 \ \mu g}{mg} \qquad (5)$$

where q_{human} is given in units of $(mg/kg\text{-}day)^{-1}$.

POTENCY VALUES FOR PROPOSITION 65 CARCINOGENS

Potency values for 140 Proposition 65 carcinogens are calculated following the procedures given above and details on their derivation are presented in Appendices 2 and 3. Intake levels associated with no significant cancer risk ($< 10^{-5}$) derived from these values following Equation 5 are given in Table 1. Table 2 lists the potency values. Appendix 1 includes: the CAS number of the chemical; the species, sex, tumor type and site, and duration of the experiment serving as the basis of potency estimation; estimates of the human potency; and the intake level (micrograms per day) associated with a 10^{-5} risk of cancer. Further details

on the potency calculation are given in the glossary to Appendix 1. Appendix 2 provides a detailed example of the derivation of a potency value using the expedited procedure. Finally, Appendix 3 outlines the rationale for the selection of the data set(s) serving as the basis for the potency calculation for individual agents.

Of the 140 Proposition 65 carcinogens for which expedited potency values are presented, the following are identified by the International Agency for Research on Cancer (1987) as known human carcinogens: 4-aminobiphenyl, azathioprine, chlorambucil, cyclophosphamide, diethylstilbestrol, melphalan, and 2-naphthylamine. In addition, IARC (1987) has determined that the following have limited evidence of human carcinogenicity: dimethylcarbamyl chloride, 4,4'-methylene bis(2-chloroaniline), N-methyl-N'-nitro-N-nitrosoguanidine, phenacetin, procarbazine hydrochloride, styrene oxide, tris(1-aziridinyl)phosphine sulfide (thiotepa), and tris(2,3-dibromopropyl) phosphate. Any revision of the potency estimates for these chemicals should consider available epidemiological data.

EXPEDITED POTENCIES COMPARED WITH CONVENTIONAL ESTIMATES

To assess the accuracy of our accelerated method of estimating potencies, we derived expedited potencies for chemicals already addressed by regulatory agencies. These estimates are compared with a set of seventy-eight conventional potency estimates on seventy-five agents derived by regulatory agencies (CDHS, Cal/EPA and US EPA) For three of the seventy-five compounds both ingestion and inhalation numbers are available. Most of these potency estimates have been used to establish regulatory "No Significant Risk Levels" to implement Proposition 65 in California. This comparison set includes *de novo* cancer potency assessments by CDHS and Cal/EPA, potencies derived by US EPA and adopted by Cal/EPA/OEHHA, and three additional US EPA potencies. Table 3 presents the comparison, listing the conventional and expedited potency estimates and the ratio of the two values for each chemical.

Distributional Comparisons

The concordance between the expedited and conventional results is excellent, particularly considering the substantially different resources and time required by the two approaches. Figure 1 plots the frequency distribution of the ratio of the expedited to conventional potencies and Table 4 lists the ratios for each of the chemicals studied. Ninety percent of the expedited potency estimates are within a factor of ten of the conventional estimates. By taking the logarithm of these ratios, the distribution can be further characterized: the geometric mean of the ratios of expedited to conventional estimates is 1.20, with one standard deviation corresponding to a factor of four.

Discrepancies/Outliers

Expedited potency estimates differ from conventional potency estimates by more than a factor of ten for 9% (seven out of seventy-eight) of the compounds studied. Of these, two differ by more than a factor of twenty-five (N-nitroso-N-methylurea, benzidine). Factors which could account for differences of ten or more are summarized in Table 4 and are described below.

Most Apparently Sensitive Study not Included by Regulatory Agency: For epichlorohydrin, the most sensitive study which was the basis for the expedited potency was excluded by CDHS (1988a) and US EPA (1984) in conventional analyses. Epidemiologic data indicated that the potency derived from this animal bioassay overpredicted human potency. In addition, there were technical reasons for discounting this study (i.e., the occurrence of "hair

balls" in the forestomach of treated animals which confounded the finding of forestomach tumors). Because the epidemiologic data was not sufficient for a full dose response evaluation, a second animal bioassay was selected by CDHS and US EPA that predicted a potency in accordance with the human data.

Best Data Set Not Available in Gold et al.: 1) For 1,3-butadiene, the best data set for dose response evaluation was not available in Gold et al. The expedited potency is based on an NTP high dose bioassay in male and female mice. A recent low, multiple dose study, not yet published in final form by the NTP, served as the basis of the Cal/EPA/OEHHA (1991c) potency analyses. The low multiple dose study enabled the exploration of the dose response for late appearing tumors, the occurrence of which was obscured by mortality in the high dose study. Extending the expedited procedure to include a full mortality analysis might have resulted in a smaller difference between the expedited and draft regulatory value. Nonetheless, the lack of the most recent bioassay in the Gold et al. database was the predominant reason for the discrepancy. 2) For N-nitroso-N-methylurea (NMU), only two studies of the numerous studies available for this compound met the criteria for inclusion in the Gold et al. data base, and the study selected by CDHS was not included in the Gold et al. data base. The selection of any particular study for NMU is a compromise, because all are far from ideal. CDHS (1988b) chose a relatively large chronic study via subcutaneous injection; studies by this route were not tabulated by Gold et al.

Non-Default Assessment: 1) In the case of formaldehyde, a pharmacokinetic and mechanistic analysis resulted in a proposed potency (Cal/EPA/OEHHA, 1991d) approximately one order of magnitude less than that derived using the expedited algorithm. The expedited procedure does not provide for pharmacokinetic and mechanistic analyses. Had we compared the expedited value with the one previously used by regulatory agencies (US EPA, 1987), the difference would have been only a factor of five. 2) For the ethylene dibromide inhalation potency, both the CDHS (1988c) and the expedited potency value were derived from dose response data for nasal tumors in male rats, but the expedited value is significantly larger than that derived by CDHS. The CDHS analysis used data for malignant tumors alone; the expedited used malignant and benign, in accordance with current guidelines for dose response evaluation (CDHS, 1985). Had CDHS used the combined data for benign and malignant tumors as the basis of the potency derivation, ethylene dibromide would not have been identified as an outlier.

Interspecies Differences in Carcinogenic Potency: Substantial differences in carcinogenic response between humans and experimental animals have been noted for two of the outliers: aflatoxin and benzidine. The significantly greater carcinogenic activity of benzidine in the human bladder in contrast to sites associated with carcinogenesis in laboratory animals has been attributed to pharmacokinetic differences (CDHS, 1988d). Aflatoxin produces liver cancer in numerous species, including humans, non-human primates, trout, hamsters, rats and mice. However, rats, the species most sensitive to aflatoxin carcinogenesis, appear to be significantly more sensitive than humans or the other species tested (CDHS, 1990c). The expedited potency value for aflatoxin derived from rat data is a factor of 20 greater than the value derived from human epidemiologic data.

CONCLUSION

One hundred forty potency values and associated Proposition 65 "No Significant Risk Levels" have been derived for previously unassessed agents and are presented here. The comparisons of expedited and conventional potency estimates indicate that reliable potency values can be derived using the expedited procedure. We recognize that more extensive analyses may result in improved potency estimates and that some of the values presented here

may require revision. Differences between estimates of a factor of four or less may merely be reflective of the inherent uncertainty in potency evaluation, rather than indicative that one value is more accurate. Therefore, if a reanalysis produces a value within a factor of four of the current expedited potency, we do not anticipate changing the No Significant Risk Level. Public health or scientific considerations, however, may necessitate a more detailed analysis for a particular chemical and a change in the potency value.

REFERENCES

Anderson EL and the US Environmental Protection Agency Carcinogen Assessment Group (1983). Quantitative Approaches in Use to Assess Cancer Risk. *Risk Analysis* 3: 277-295.

California Environmental Protection Agency, Office of Environmental Health Hazard Assessment (Cal/EPA/OEHHA, 1991a). *Expedited Cancer Potency Values and Proposed Regulatory Levels for 138 Proposition 65 Carcinogens.* Reproductive and Cancer Hazard Assessment Section, OEHHA, Berkeley, CA, August 1991.

California Environmental Protection Agency, Office of Environmental Health Hazard Assessment (Cal/EPA/OEHHA, 1991b). Presentation at the April 1991 Meeting of the Proposition 65 Scientific Advisory Panel by the Reproductive and Cancer Hazard Assessment Section, OEHHA. University of California, Davis, CA.

California Environmental Protection Agency, Office of Environmental Health Hazard Assessment (Cal/EPA/OEHHA, 1991c). *Health Effects of 1,3-Butadiene.* Air Toxicology and Epidemiology Section, OEHHA, Berkeley, CA.

California Environmental Protection Agency, Office of Environmental Health Hazard Assessment, Air Toxicology and Epidemiology Section (Cal/EPA/OEHHA, 1991d). *Cancer Risk Assessment for Airborne Formaldehyde.* Air Toxicology and Epidemiology Section, OEHHA, Berkeley, CA.

California Department of Health Services (CDHS, 1990a). *Expedited Method for Estimating Carcinogenic Potency: Use of Tabulated TD50 Values of Gold et al.* Reproductive and Cancer Hazard Assessment Section, CDHS, Berkeley, CA.

California Department of Health Services (CDHS, 1990b). Presentation at the August 1990 Meeting of the Proposition 65 Scientific Advisory Panel by the Reproductive and Cancer Hazard Assessment Section, CDHS. University of California, Davis, CA.

California Department of Health Services (CDHS, 1990c). *Risk Specific Intake Levels for the Proposition 65 Carcinogen: Aflatoxin.* Reproductive and Cancer Hazard Assessment Section, CDHS, Berkeley, CA.

California Department of Health Services (CDHS, 1988a). *Risk Specific Intake Levels for the Proposition 65 Carcinogen: Epichlorohydrin.* Reproductive and Cancer Hazard Assessment Section, CDHS, Berkeley, CA.

California Department of Health Services (CDHS, 1988b). *Risk Specific Intake Levels for the Proposition 65 Carcinogen: N-Nitroso-N-Methylurea.* Reproductive and Cancer Hazard Assessment Section, CDHS, Berkeley, CA.

California Department of Health Services (CDHS, 1988c). *Risk Specific Intake Levels for the Proposition 65 Carcinogen: Ethylene Dibromide.* Reproductive and Cancer Hazard Assessment Section, CDHS, Berkeley, CA.

California Department of Health Services (CDHS, 1988d). *Risk Specific Intake Levels for the Proposition 65 Carcinogen: Benzidine.* Reproductive and Cancer Hazard Assessment Section, CDHS, Berkeley, CA.

California Department of Health Services (CDHS, 1985). *Guidelines for Chemical*

Carcinogen Risk Assessment and Their Scientific Rationale. CDHS, Health and Welfare Agency, Sacramento, CA.

Crump KS, Guess HA, and Deal LL (1987). Confidence Intervals and Test of Hypotheses Concerning Dose Response Relations Inferred from Animal Carcinogenicity Data. *Biometrics* 33: 437-451.

Crump KS, Howe RB, Van Landingham C, and Fuller WG (1991). **TOX_RISK** Version 3. **TOX**icology **RISK** Assessment Program. KS Crump Division, Clement International Corporation, 1201 Gaines Street, Ruston, Louisiana 71270.

Gold L, Sawyer C, Magaw R, Backman G, de Veciana M, Levinson R, Hooper N, Havender W, Bernstein L, Peto R, Pike M, and Ames B (1984). A Carcinogenic Potency Database of the standardized results of animal bioassays. *Environmental Health Perspectives* 58: 9-319.

Gold L, de Veciana M, Backman G, Magaw R, Lopipero P, Smith M, Blumenthal M, Levinson R, Bernstein L, Ames B (1986). Chronological Supplement to the Carcinogenic Potency Database: Standardized results of animal bioassays published through December 1982. *Environmental Health Perspectives* 67: 161-200.

Gold L, Slone T, Backman G, Magaw R, Da Costa M, Ames B (1987). Second chronological supplement to the Carcinogenic Potency Database: Standardized results of animal bioassays published through December 1984 and by the National Toxicology Program through May 1986. *Environmental Health Perspectives* 74: 237-329.

Gold L, Slone T, Bernstein L (1989). Summary of Carcinogenic Potency and Positivity for 492 Rodent Carcinogens in the Carcinogenic Potency Database. *Environmental Health Perspectives* 79: 259-272.

Gold L, Slone T, Backman G, Eisenberg S, Da Costa M, Wong M, Manley N, and Ames B (1990). Third chronological supplement to the Carcinogenic Potency Database: Standardized results of animal bioassays published through December 1986 and by the National Toxicology Program through June 1987. *Environmental Health Perspectives* 84: 215-285.

International Agency for Research on Cancer (IARC, 1987). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans.* Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42. Supplement 7. IARC, Lyon, France.

United States Environmental Protection Agency (US EPA, 1987). *Assessment of Health Risks to Garment Workers and Certain Home Residents from Exposure to Formaldehyde.* EPA-560/1987.1. Office of Pesticides and Toxic Substances, Washington D.C.

United States Environmental Protection Agency (US EPA, 1984). *Health Assessment Document for Epichlorohydrin.* EPA-600/8-83-032f. Office of Health and Environmental Assessment, Washington DC.

Zeise L, Cranor C, Hennig M, Hoover S, Pease W, and Book S (1991). *Expedited procedures for establishing carcinogenic potency values for regulatory purposes.* Presented at the December 1991 Society of Risk Analysis Annual Meeting, Baltimore, MD.

FIGURE 1: RATIO OF POTENCY ESTIMATES
Expedited Potency/Conventional Potency

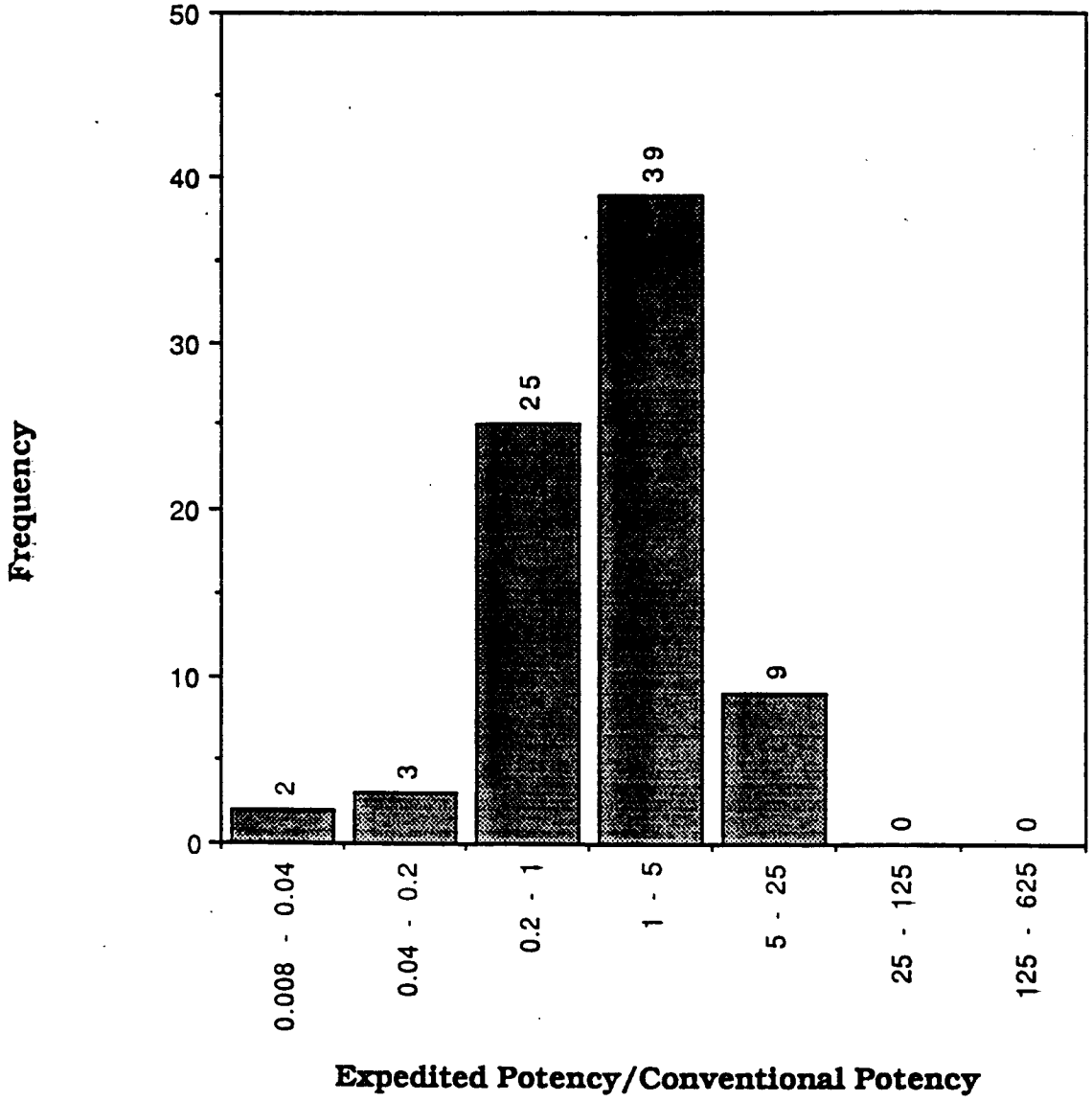

TABLE 1: NO SIGNIFICANT RISK LEVELS DERIVED FROM EXPEDITED POTENCIES FOR PROPOSITION 65 CARCINOGENS

	CHEMICAL	INTAKE NSRL (µg/day)
1	A-alpha-C (2-Amino-9H-pyrido[2,3-b]indole)	2
2	Acetamide	10
3	2-Acetylaminofluorene	0.2
4	Actinomycin D	0.00008
5	AF-2;[2-(2-furyl)-3(5-nitro-2-furyl)]acrylamide	3
6	2-Aminoanthraquinone	20
7	o-Aminoazotoluene	0.2
8	4-Aminobiphenyl (4-aminodiphenyl)	0.03
9	3-Amino-9-ethylcarbazole hydrochloride	9
10	1-Amino-2-methylanthraquinone	5
11	2-Amino-5-(5-nitro-2-furyl)-1,3,4-thiadiazole	0.04
12	Amitrole	0.7
13	o-Anisidine	5
14	o-Anisidine hydrochloride	7
15	Aramite	20
16	Auramine	0.8
17	Azaserine	0.06
18	Azathioprine	0.4
19	Benzyl violet 4B	30
20	beta-Butyrolactone	0.7
21	Captafol	5
22	Captan	300
23	Chlorambucil	0.002
24	Chlordecone (Kepone)	0.04
25	Chlorendic acid	8
26	Chlorinated paraffins (Average chain length, C12: approximately 60 percent chlorine by weight)	8
27	Chlorodibromomethane	7
28	Chloromethyl methyl ether (technical grade)	0.3
29	3-Chloro-2-methylpropene	5
30	4-Chloro-ortho-phenylenediamine	40
31	Chlorothalonil	200
32	p-Chloro-o-toluidine	3
33	Chlorozotocin	0.003
34	C. I. Basic Red 9 monohydrochloride	3
35	Cinnamyl anthranilate	200
36	p-Cresidine	5
37	Cupferron	3
38	Cyclophosphamide (anhydrous)	1
39	Cyclophosphamide (hydrated)	1
40	D&C Red No. 9	100
41	Dacarbazine	0.01
42	Daminozide	40
43	Dantron (Chrysazin; 1,8-Dihydroxyanthraquinone)	9
44	2,4-Diaminoanisole	30
45	2,4-Diaminoanisole sulfate	50
46	4,4'-Diaminodiphenyl ether (4,4'-Oxydianiline)	5
47	2,4-Diaminotoluene	0.2
48	Dibenz[a,h]anthracene	0.2
49	1,1-Dichloroethane	100

TABLE 1: NO SIGNIFICANT RISK LEVELS DERIVED FROM EXPEDITED POTENCIES FOR PROPOSITION 65 CARCINOGENS

	CHEMICAL	INTAKE NSRL (µg/day)
50	Diethylstilbestrol	0.002
51	Diglycidyl resorcinol ether (DGRE)	0.4
52	Dihydrosafrole	20
53	4-Dimethylaminoazobenzene	0.2
54	trans-2[(Dimethylamino)methylimino]-5-[2-(5-nitro-2- furyl)vinyl]-1,3,4-oxadiazole	2
55	7,12-Dimethylbenz(a)anthracene	0.003
56	Dimethylcarbamyl chloride	0.05
57	1,2-Dimethylhydrazine	0.001
58	Dimethylvinylchloride	20
59	Direct Black 38 (technical grade)	0.09
60	Direct Blue 6 (technical grade)	0.09
61	Direct Brown 95 (technical grade)	0.1
62	Disperse Blue 1	200
63	Estradiol 17B	0.02
64	Ethyl-4,4'-dichlorobenzilate (chlorobenzilate)	7
65	Ethylene thiourea	20
66	Ethyleneimine	0.01
67	2-(2-Formylhydrazino)-4-(5-nitro-2-furyl)thiazole	0.3
68	Glu-P-1 (2-Amino-6-methyldipyrido [1,2-a:3' ,2' -d]imidazole)	0.1
69	Glu-P-2 (2-Aminodipyrido[1,2-a:3',2'-d]imidazole)	0.5
70	Gyromitrin (Acetaldehyde methylformylhydrazone)	0.07
71	HC Blue 1	10
72	Hexachloroethane	20
73	Hydrazobenzene (1,2-Diphenylhydrazine)	0.8
74	IQ (2-Amino-3-methylimidazo[4,5-f]quinoline)	0.5
75	Lasiocarpine	0.09
76	Lead acetate	3
77	Lead subacetate	20
78	Me-A-alpha-C (2-Amino-3-methyl-9H-pyrido[2,3-b]indole)	0.6
79	Melphalan	0.005
80	3-Methylcholanthrene	0.03
81	4,4'-Methylene bis(2-chloroaniline)	0.5
82	4,4'-Methylene bis(2-methylaniline)	0.8
83	4,4'-Methylenedianiline	0.4
84	4,4'-Methylenedianiline dihydrochloride	0.6
85	Methyl methanesulfonate	7
86	2-Methyl-1-nitroanthraquinone (of uncertain purity)	0.2
87	N-Methyl-N'-nitro-N-nitrosoguanidine	0.08
88	Methylthiouracil	2
89	Michler's ketone	0.8
90	Mirex	0.04
91	Mitomycin C	0.00009
92	Monocrotaline	0.07
93	2-Naphthylamine	0.4
94	Nitrilotriacetic acid	100
95	Nitrilotriacetic acid, trisodium salt monohydrate	70
96	5-Nitroacenaphthene	6

TABLE 1: NO SIGNIFICANT RISK LEVELS DERIVED FROM EXPEDITED POTENCIES FOR PROPOSITION 65 CARCINOGENS

	CHEMICAL	INTAKE NSRL (µg/day)
97	5-Nitro-o-anisidine	10
98	Nitrofen (technical grade)	9
99	Nitrofurazone	0.5
100	1-[(5-Nitrofurfurylidene)-amino]-2-imidazolidinone	0.4
101	N-[4-(5-Nitro-2-furyl)-2-thiazolyl]acetamide	0.5
102	p-Nitrosodiphenylamine	30
103	N-Nitroso-N-methylurethane	0.006
104	N-Nitrosomorpholine	0.1
105	N-Nitrosonornicotine	0.5
106	N-Nitrosopiperidine	0.07
107	Phenacetin	300
108	Phenazopyridine	4
109	Phenazopyridine hydrochloride	5
110	Phenesterin	0.005
111	Phenobarbital	2
112	Phenoxybenzamine	0.2
113	Phenoxybenzamine hydrochloride	0.3
114	o-Phenylphenate, sodium	200
115	Ponceau MX (D&C Red No. 5)	200
116	Ponceau 3R (FD&C Red No. 1)	40
117	Potassium bromate	1
118	Procarbazine	0.05
119	Procarbazine hydrochloride	0.06
120	1,3-Propane sultone	0.3
121	beta-Propiolactone	0.05
122	Propylthiouracil	0.7
123	Reserpine	0.06
124	Safrole	3
125	Sterigmatocystin	0.02
126	Streptozotocin	0.006
127	Styrene oxide	4
128	Sulfallate	4
129	1,1,2,2-Tetrachloroethane	3
130	Thioacetamide	0.1
131	4,4'-Thiodianiline	0.05
132	Thiourea	10
133	Toluene diisocyanate	20
134	o-Toluidine	4
135	o-Toluidine hydrochloride	5
136	Tris(1-aziridinyl)phosphine sulfide (Thiotepa)	0.06
137	Tris(2,3-dibromopropyl)phosphate	0.3
138	Trp-P-1 (Tryptophan-P-1)	0.03
139	Trp-P-2 (Tryptophan-P-2)	0.2
140	Vinyl trichloride (1,1,2-Trichloroethane)	10

TABLE 2: HUMAN POTENCY ESTIMATES DERIVED FROM EXPEDITED POTENCIES FOR PROPOSITION 65 CARCINOGENS

	CHEMICAL	HUMAN POTENCY (mg/kg-day)-1
1	A-alpha-C (2-Amino-9H-pyrido[2,3-b]indole)	0.40
2	Acetamide	0.070
3	2-Acetylaminofluorene	3.8
4	Actinomycin D	8700
5	AF-2;[2-(2-furyl)-3(5-nitro-2-furyl)]acrylamide	0.24
6	2-Aminoanthraquinone	0.033
7	o-Aminoazotoluene	3.8
8	4-Aminobiphenyl (4-aminodiphenyl)	21
9	3-Amino-9-ethylcarbazole hydrochloride	0.078
10	1-Amino-2-methylanthraquinone	0.15
11	2-Amino-5-(5-nitro-2-furyl)-1,3,4-thiadiazole	16
12	Amitrole	0.94
13	o-Anisidine	0.14
14	o-Anisidine hydrochloride	0.11
15	Aramite	0.030
16	Auramine	0.88
17	Azaserine	11
18	Azathioprine	1.8
19	Benzyl violet 4B	0.020
20	beta-Butyrolactone	1.0
21	Captafol	0.15
22	Captan	0.0023
23	Chlorambucil	440
24	Chlordecone (Kepone)	16
25	Chlorendic acid	0.091
26	Chlorinated paraffins (Average chain length, C12: approximately 60 percent chlorine by weight)	0.089
27	Chlorodibromomethane	0.094
28	Chloromethyl methyl ether (technical grade)	2.4
29	3-Chloro-2-methylpropene	0.14
30	4-Chloro-ortho-phenylenediamine	0.016
31	Chlorothalonil	0.0031
32	p-Chloro-o-toluidine	0.27
33	Chlorozotocin	240
34	C. I. Basic Red 9 monohydrochloride	0.25
35	Cinnamyl anthranilate	0.0046
36	p-Cresidine	0.15
37	Cupferron	0.22
38	Cyclophosphamide (anhydrous)	0.61
39	Cyclophosphamide (hydrated)	0.57
40	D&C Red No. 9	0.0053
41	Dacarbazine	49
42	Daminozide	0.018
43	Dantron (Chrysazin; 1,8-Dihydroxyanthraquinone)	0.076
44	2,4-Diaminoanisole	0.023
45	2,4-Diaminoanisole sulfate	0.013
46	4,4'-Diaminodiphenyl ether (4,4'-Oxydianiline)	0.14
47	2,4-Diaminotoluene	4.0
48	Dibenz[a,h]anthracene	4.1
49	1,1-Dichloroethane	0.0057

TABLE 2: HUMAN POTENCY ESTIMATES DERIVED FROM EXPEDITED POTENCIES FOR PROPOSITION 65 CARCINOGENS

	CHEMICAL	HUMAN POTENCY (mg/kg-day)-1
50	Diethylstilbestrol	350
51	Diglycidyl resorcinol ether (DGRE)	1.7
52	Dihydrosafrole	0.044
53	4-Dimethylaminoazobenzene	4.6
54	trans-2[(Dimethylamino)methylimino]-5-[2-(5-nitro-2- furyl)vinyl]-1,3,4-oxadiazole	0.44
55	7,12-Dimethylbenz(a)anthracene	250
56	Dimethylcarbamyl chloride	13
57	1,2-Dimethylhydrazine	550
58	Dimethylvinylchloride	0.045
59	Direct Black 38 (technical grade)	7.4
60	Direct Blue 6 (technical grade)	7.4
61	Direct Brown 95 (technical grade)	6.7
62	Disperse Blue 1	0.0045
63	Estradiol 17B	39
64	Ethyl-4,4'-dichlorobenzilate (chlorobenzilate)	0.11
65	Ethylene thiourea	0.045
66	Ethyleneimine	65
67	2-(2-Formylhydrazino)-4-(5-nitro-2-furyl)thiazole	2.3
68	Glu-P-1 (2-Amino-6-methyldipyrido [1,2-a:3' ,2' -d]imidazole)	4.8
69	Glu-P-2 (2-Aminodipyrido[1,2-a:3',2'-d]imidazole)	1.4
70	Gyromitrin (Acetaldehyde methylformylhydrazone)	10
71	HC Blue 1	0.051
72	Hexachloroethane	0.039
73	Hydrazobenzene (1,2-Diphenylhydrazine)	0.87
74	IQ (2-Amino-3-methylimidazo[4,5-f]quinoline)	1.4
75	Lasiocarpine	7.8
76	Lead acetate	0.28
77	Lead subacetate	0.038
78	Me-A-alpha-C (2-Amino-3-methyl-9H-pyrido[2,3-b]indole)	1.2
79	Melphalan	130
80	3-Methylcholanthrene	22
81	4,4'-Methylene bis(2-chloroaniline)	1.5
82	4,4'-Methylene bis(2-methylaniline)	0.92
83	4,4'-Methylenedianiline	1.6
84	4,4'-Methylenedianiline dihydrochloride	1.2
85	Methyl methanesulfonate	0.099
86	2-Methyl-1-nitroanthraquinone (of uncertain purity)	4.3
87	N-Methyl-N'-nitro-N-nitrosoguanidine	8.3
88	Methylthiouracil	0.40
89	Michler's ketone	0.86
90	Mirex	18
91	Mitomycin C	8200
92	Monocrotaline	10
93	2-Naphthylamine	1.8
94	Nitrilotriacetic acid	0.0053
95	Nitrilotriacetic acid, trisodium salt monohydrate	0.010
96	5-Nitroacenaphthene	0.13

TABLE 2: HUMAN POTENCY ESTIMATES DERIVED FROM EXPEDITED POTENCIES FOR PROPOSITION 65 CARCINOGENS

	CHEMICAL	HUMAN POTENCY (mg/kg-day)-1
97	5-Nitro-o-anisidine	0.049
98	Nitrofen (technical grade)	0.082
99	Nitrofurazone	1.3
100	1-[(5-Nitrofurfurylidene)-amino]-2-imidazolidinone	1.8
101	N-[4-(5-Nitro-2-furyl)-2-thiazolyl]acetamide	1.5
102	p-Nitrosodiphenylamine	0.022
103	N-Nitroso-N-methylurethane	110
104	N-Nitrosomorpholine	6.7
105	N-Nitrosonornicotine	1.4
106	N-Nitrosopiperidine	9.4
107	Phenacetin	0.0022
108	Phenazopyridine	0.17
109	Phenazopyridine hydrochloride	0.15
110	Phenesterin	150
111	Phenobarbital	0.46
112	Phenoxybenzamine	3.1
113	Phenoxybenzamine hydrochloride	2.7
114	o-Phenylphenate, sodium	0.0030
115	Ponceau MX (D&C Red No. 5)	0.0045
116	Ponceau 3R (FD&C Red No. 1)	0.016
117	Potassium bromate	0.49
118	Procarbazine	14
119	Procarbazine hydrochloride	12
120	1,3-Propane sultone	2.4
121	beta-Propiolactone	14
122	Propylthiouracil	1.0
123	Reserpine	11
124	Safrole	0.22
125	Sterigmatocystin	35
126	Streptozotocin	110
127	Styrene oxide	0.16
128	Sulfallate	0.19
129	1,1,2,2-Tetrachloroethane	0.27
130	Thioacetamide	6.1
131	4,4'-Thiodianiline	15
132	Thiourea	0.072
133	Toluene diisocyanate	0.039
134	o-Toluidine	0.18
135	o-Toluidine hydrochloride	0.13
136	Tris(1-aziridinyl)phosphine sulfide (Thiotepa)	12
137	Tris(2,3-dibromopropyl)phosphate	2.3
138	Trp-P-1 (Tryptophan-P-1)	26
139	Trp-P-2 (Tryptophan-P-2)	3.2
140	Vinyl trichloride (1,1,2-Trichloroethane)	0.072

TABLE 3: RATIO OF EXPEDITED TO CONVENTIONAL POTENCY VALUES

CHEMICAL †	CAS #	EXPEDITED HUMAN POTENCY (mg/kg-day)-1	CONVENTIONAL HUMAN POTENCY (mg/kg-day)-1	RATIO OF EXPEDITED POTENCY TO CONVENTIONAL POTENCY
Benzidine [and its salts]	92-87-5	4.7	500	0.00940
N-Nitroso-N-methylurea	684-93-5	1.6	124	0.01
1,3-Butadiene	106-99-0	0.12	1.8	0.07
Ochratoxin A*	303-47-9	2.9	20	0.15
2,4,6-Trichlorophenol	88-06-2	0.013	0.07	0.19
Polybrominated biphenyls	N/A	6.5	30	0.22
Ethylene oxide (inhalation)	75-21-8	0.088	0.35	0.25
Bromodichloromethane	75-27-4	0.035	0.13	0.27
1,4-Dioxane	123-91-1	0.0076	0.027	0.28
Metronidazole*	443-48-1	0.051	0.18	0.28
Acrylonitrile	107-13-1	0.39	1.0	0.39
2,3,7,8-Tetrachlorodibenzo-para-dioxin (TCDD)*	1746-01-6	61000	130000	0.47
Propylene oxide (inhalation)*	75-56-9	0.0058	0.012	0.48
N-Nitrosodiphenylamine	86-30-6	0.0047	0.009	0.52
p-Dichlorobenzene	106-46-7	0.022	0.04	0.55
Acrylamide	79-06-1	2.6	4.5	0.58
gamma-HCH (Lindane)	58-89-9	0.64	1.1	0.58
beta-HCH	319-85-7	0.90	1.5	0.60
Ethylene dibromide (oral)	106-93-4	2.3	3.6	0.64
Bis(2-chloroethyl)ether	111-44-4	1.6	2.5	0.64
Polychlorinated biphenyls (containing 60 or more percent chlorine by molecular weight)	N/A	5.0	7.7	0.65
Carbon tetrachloride	56-23-5	0.12	0.18	0.67
Hydrazine sulfate	10034-93-2	2.1	3	0.70
N-Nitrosodiethanolamine	1116-54-7	2.1	2.8	0.75
Propylene oxide (oral)	75-56-9	0.19	0.24	0.79
Benzyl chloride	100-44-7	0.17	0.2	0.85
Urethane (Ethyl carbamate)	51-79-6	0.88	1	0.88
Dieldrin	60-57-1	15	16	0.94
Hexachlorobenzene	118-74-1	1.7	1.8	0.94

TABLE 3: RATIO OF EXPEDITED TO CONVENTIONAL POTENCY VALUES

CHEMICAL †	CAS #	EXPEDITED HUMAN POTENCY (mg/kg-day)-1	CONVENTIONAL HUMAN POTENCY (mg/kg-day)-1	RATIO OF EXPEDITED POTENCY TO CONVENTIONAL POTENCY
Allyl chloride	107-05-1	0.020	0.021	0.95
Benzo[a]pyrene	50-32-8	11.5	11.5	1.00
Aldrin	309-00-2	18	17	1.06
Heptachlor	76-44-8	4.9	4.5	1.09
1,3-Dichloropropene*	542-75-6	0.20	0.18	1.11
1,2-Dichloropropane*	78-87-5	0.074	0.063	1.17
Tetrachloroethylene (Perchloroethylene) (oral)	127-18-4	0.062	0.051	1.22
Selenium sulfide*	7446-34-6	0.094	0.077	1.22
Vinyl trichloride**	79-00-5	0.072	0.057	1.26
Trichloroethylene (oral)*	79-01-6	0.019	0.015	1.27
1,2-Dibromo-3-chloropropane (DBCP)	96-12-8	9.0	7	1.29
1,1,2,2-Tetrachloroethane**	79-34-5	0.27	0.2	1.35
alpha-HCH	319-84-6	3.7	2.7	1.37
Chlordane	57-74-9	1.8	1.3	1.38
4,4'-Methylene bis(N,N-dimethyl)benzenamine	101-61-1	0.066	0.046	1.43
2,4-Dinitrotoluene	121-14-2	0.45	0.31	1.45
Ethylene dichloride (1,2-Dichloroethane)	107-06-2	0.11	0.07	1.57
Vinyl bromide*	593-60-2	0.47	0.29	1.62
Hydrazine	302-01-2	28	17	1.65
Benzene	71-43-2	0.17	0.1	1.70
N-Nitroso-N-ethylurea	759-73-9	50	27	1.85
DDE (Dichlorodiphenyldichloroethylene)	72-55-9	0.64	0.34	1.88
Trichloroethylene (inhalation)*	79-01-6	0.019	0.01	1.90
Dichloromethane (Methylene chloride)*	75-09-2	0.0069	0.0035	1.97
Butylated hydroxyanisole	25013-16-5	0.00040	0.0002	2.00
Di(2-ethylhexyl)phthalate	117-81-7	0.017	0.0084	2.02
Tetrachloroethylene (Perchloroethylene) (inhalation)*	127-18-4	0.062	0.028	2.21
Vinyl chloride*	75-01-4	0.61	0.27	2.26
Toxaphene (Polychorinated camphenes)	8001-35-2	2.8	1.2	2.33
N-Nitrosopyrrolidine	930-55-2	5.0	2.1	2.38

TABLE 3: RATIO OF EXPEDITED TO CONVENTIONAL POTENCY VALUES

CHEMICAL †	CAS #	EXPEDITED HUMAN POTENCY (mg/kg-day)-1	CONVENTIONAL HUMAN POTENCY (mg/kg-day)-1	RATIO OF EXPEDITED POTENCY TO CONVENTIONAL POTENCY
DDD (Dichlorodiphenyldichloroethane)	72-54-8	0.60	0.24	2.50
Bis(chloromethyl)ether	542-88-1	120	46	2.61
N-Nitrosodi-n-butylamine	924-16-3	29	10.8	2.69
Hexachloroethane**	67-72-1	0.039	0.014	2.79
Chloroform (oral)	67-66-3	0.10	0.031	3.23
Hexachlorodibenzodioxin (HCDDs)*	34465-46-8	11000	3300	3.33
Azobenzene	103-33-3	0.44	0.11	4.00
Acetaldehyde	75-07-0	0.032	0.0077	4.16
DDT (Dichlorodiphenyltrichloroethane)	50-29-3	1.5	0.34	4.41
1,1-Dimethylhydrazine*	57-14-7	9.8	2.2	4.45
3,3'-Dichlorobenzidine	91-94-1	6.1	1.2	5.08
N-Nitrosodimethylamine	62-75-9	99	16	6.19
N-Nitrosodiethylamine	55-18-5	230	36	6.39
Aniline	62-53-3	0.043	0.0057	7.54
N-Nitrosodi-n-propylamine	621-64-7	66	7	9.43
Ethylene dibromide (inhalation)	106-93-4	2.6	0.25	10.40
Epichlorohydrin	106-89-8	0.95	0.08	11.88
Formaldehyde (gas)*	50-00-0	0.23	0.0175	13.14
Aflatoxins*	N/A	930	46	20

† For all chemicals not marked by a single or double asterisk, the conventional potencies serve as the basis for NSRL regulations under Proposition 65.

* Conventional potency is at the proposed or draft stage; this potency does not yet form the basis of a promulgated Proposition 65 NSRL regulation.

** Conventional potency is an EPA value. This potency does not form the basis of a promulgated Proposition 65 NSRL regulation.

TABLE 4: OUTLIERS - EXPEDITED POTENCIES DIFFERING BY MORE THAN FACTOR OF 10 FROM CDHS, CAL/EPA, OR US EPA POTENCY VALUES

Chemical	Expedited:Conventional Ratio	Comments
Aflatoxin B_1	20	The expedited value is derived from the most sensitive of several rat bioassays; the CDHS estimate is based on human data. Rats appear to be more sensitive than other species, including humans and primates.
Benzidine	0.0094	The CDHS estimate is based on human data. Humans are demonstrably more sensitive than experimental animals, probably due to pharmacokinetic differences.
1,3-Butadiene	0.07	The expedited potency is based on an NTP high dose bioassay in male and female mice. A recent low, multiple dose study, not yet published in formal final report, served as the basis of the Cal/EPA/OEHHA potency analyses. This study has not yet been included in the Gold et al. data base. The low multiple dose study enabled the exploration of the dose response for late appearing tumors, the occurrence of which was obscured by mortality in the high dose study.
Epichlorohydrin	11.9	The expedited value is derived from the gavage study. Human data indicate that the gavage study may result in an overestimate. CDHS derived a potency estimate from the drinking water study. The results from the inhalation study are consistent with drinking water study.
Ethylene dibromide (inhalation)	10.4	CDHS estimated potency from dose response data for malignant nasal tumors in male rats treated via inhalation. The expedited potency is based on the same target site, species and sex, but includes benign and malignant tumors. Following CDHS guidelines, malignant and benign tumors at the sensitive site should be combined.

TABLE 4: OUTLIERS - EXPEDITED POTENCIES DIFFERING BY MORE THAN FACTOR OF 10 FROM CDHS, CAL/EPA, OR US EPA POTENCY VALUES (Continued)

Chemical	Expedited:Conventional Ratio	Comments
N-Nitroso-N-methylurea	0.01	NMU is a carcinogen used in the past to investigate mechanism of action of carcinogens. Although numerous studies are available on this compound, only two oral (feed) studies in primates meet the criteria of Gold et al. One is of relatively short duration in a small number of primates; the second study, which served as the basis of the expedited value, used slightly more animals and was of longer duration. The CDHS value is based on the only relatively large chronic study found in the literature. It was performed via subcutaneous injection.
Formaldehyde	13.1	The conventional value is a draft value based on pharmacokinetic and mechanistic analysis of dose-response data and carcinogenesis information. The current conventional value for formaldehyde is a factor of 5.1 smaller than the expedited value. The expedited procedure does not allow for a pharmacokinetic and mechanistic analysis.

APPENDIX 1: DATA SETS SERVING AS BASIS FOR POTENCY DERIVATIONS FOR 140 PROPOSITION 65 CARCINOGENS

This table includes the CAS number of the chemical, the relevant line number which identifies the data set in the Gold et al. database, the species and sex of the experimental animals used in the study chosen for potency estimation, the length of the experiment, the human potency, and the Proposition 65 no significant risk level. For a detailed explanation of the information in each column, see the glossary which follows the table. Note that the line numbers presented are specific to the 1990 compilation of the Gold et al. database, which merged data from four papers (Gold et al., 1984; 1986; 1987; 1990). References for the original bioassay reports are given in Appendix 3.

APPENDIX 1: DATASETS SERVING AS BASIS FOR POTENCY DERIVATIONS FOR 140 PROPOSITION 65 CARCINOGENS

	A	B	C	D	E	F	G	H
	CHEMICAL	CAS	LINE NO.	SPECIES	SITE	EXPT	HUMAN	INTAKE
		NUMBER	FROM	&	&	LENGTH	POTENCY	NSRL
			GOLD et al.	SEX	HSTP	(wks)	(mg/kg-d)-1	(µg/day)
1	A-alpha-C (2-Amino-9H-pyrido[2,3-b]indole)	26148-68-5	261	M, f	liv-mix	97	0.40	2
2	Acetamide	60-35-5	10√	R, m	liv-hpc	69	0.070	10
3	2-Acetylaminofluorene	53-96-3	85	R, m	liv-hpc	104	3.8	0.2
4	Actinomycin D	50-76-0	114	R, m	per-sar	78	8700	0.00008
5	AF-2;[2-(2-furyl)-3(5-nitro-2-furyl)]acrylamide	3688-53-7	geo-mean	R, f	mgl-mix	104	0.24	3
6	2-Aminoanthraquinone	117-79-3	266†	R, m	liv-MXA	109	0.033	20
7	ortho-Aminoazotoluene	97-56-3	268√	R, f	liv-mix	63	3.8	0.2
8	4-Aminobiphenyl (4-aminodiphenyl)	92-67-1	272	M, f	liv-mix	70	21	0.03
9	3-Amino-9-ethylcarbazole hydrochloride	6109-97-3	219a•	R, m	liv-MXA	109	0.078	9
10	1-Amino-2-methylanthraquinone	82-28-0	233a†	R, m	liv-MXA	104	0.15	5
11	2-Amino-5-(5-nitro-2-furyl)-1,3,4-thiadiazole	712-68-5	244	R, f	mgl-mix	66	16	0.04
12	Amitrole	61-82-5	292	R, f	thy-ben	165	0.94	0.7
13	ortho-Anisidine	90-04-0	331a√†*	R, m	ubl-MXA	104	0.14	5
14	ortho-Anisidine hydrochloride	134-29-2	331a√†	R, m	ubl-MXA	104	0.11	7
15	Aramite	140-57-8	geo-mean√	R, b	liv-__	104	0.030	20
16	Auramine	492-80-8	403	R, m	liv-hpt	126	0.88	0.8
17	Azaserine	115-02-6	408	R, b	pae-car	78	11	0.06
18	Azathioprine	446-86-6	410	R, f	edu-sqc	52	1.8	0.4
19	Benzyl violet 4B	1694-09-3	4013	R, f	mgl-car	52	0.020	30
20	beta-Butyrolactone	3068-88-0	637	R, f	for-sqc	70	1.0	0.7
21	Captafol	2425-06-1	663^	M, f	liv-mix	104	0.15	5
22	Captan	133-06-2	669	M, m	duo-adm	90	0.0023	300
23	Chlorambucil	305-03-3	721†	M, f	lun-mix	78	440	0.002
24	Chlordecone (Kepone)	143-50-0	2133	M, m	liv-hpc	89	16	0.04
25	Chlorendic acid	115-28-6	744b	R, m	liv-MXA	104	0.091	8
26	Chlorinated paraffins (Average chain length, C12:	108171-26-2	745a	M, f	liv-MXA	104	0.089	8
	approximately 60 percent chlorine by weight)							
27	Chlorodibromomethane	124-48-1	839	M, f	liv-MXA	109	0.094	7
28	Chloromethyl methyl ether (technical grade)	107-30-2	872	R, m	mix-mix	122	2.4	0.3
29	3-Chloro-2-methylpropene	563-47-3	769	M, m	for-MXA	104	0.14	5
30	4-Chloro-ortho-phenylenediamine	95-83-0	789a	R, m	ubl-MXA	104	0.016	40
31	Chlorothalonil	1897-45-6	907	R, m	kid-MXA	109	0.0031	200
32	p-Chloro-o-toluidine	95-69-2	geo-mean*§	M	geo-mean	104	0.27	3
33	Chlorozotocin	54749-90-5	909√†	R, m	pec-mix	100	240	0.003
34	C. I. Basic Red 9 monohydrochloride	569-61-9	3402	M, f	liv-MXA	104	0.25	3
35	Cinnamyl anthranilate	87-29-6	933	M, f	liv-MXA	104	0.0046	200

APPENDIX 1: DATASETS SERVING AS BASIS FOR POTENCY DERIVATIONS FOR 140 PROPOSITION 65 CARCINOGENS

	A	B	C	D	E	F	G	H
	CHEMICAL	CAS	LINE NO.	SPECIES	SITE	EXPT	HUMAN	INTAKE
		NUMBER	FROM	&	&	LENGTH	POTENCY	NSRL
			GOLD et al.	SEX	HSTP	(wks)	(mg/kg-d)-1	(µg/day)
36	para-Cresidine	120-71-8	970§	M, f	ubi-MXA	97	0.15	5
37	Cupferron	135-20-6	978a†	R, m	__-hes	104	0.22	3
38	Cyclophosphamide (anhydrous)	50-18-0	1018*	R, b	ubl-tcc	156	0.61	1
39	Cyclophosphamide (hydrated)	6055-19-2	1018	R, b	ubl-tcc	156	0.57	1
40	D&C Red No. 9	5160-02-1	3343a	R, m	spl-MXA	104	0.0053	100
41	Dacarbazine	4342-03-4	1026	M, f	lun-mix	61	49	0.01
42	Daminozide	1596-84-5	1032	M, m	blv-mix	81	0.018	40
43	Dantron (Chrysazin; 1,8-Dihydroxyanthraquinone)	117-10-2	931	M, m	liv-hpc	77	0.076	9
44	2,4-Diaminoanisole	615-05-4	1138a*	R, m	thy-MXA	109	0.023	30
45	2,4-Diaminoanisole sulfate	39156-41-7	1138a	R, m	thy-MXA	109	0.013	50
46	4,4'-Diaminodiphenyl ether (4,4'-Oxydianiline)	101-80-4	2921a†	R, m	liv-MXA	104	0.14	5
47	2,4-Diaminotoluene	95-80-7	see note¿§	R, f	mgl-MXA	104	4.0	0.2
48	Dibenz[a,h]anthracene	53-70-3	1165	M, m	lun-alc	60	4.1	0.2
49	1,1-Dichloroethane	75-34-3	1266a§	R, f	mgl-adc	113	0.0057	100
50	Diethylstilbestrol	56-53-1	geo-mean	M	mgl-__	104	350	0.002
51	Diglycidyl resorcinol ether (DGRE)	101-90-6	1412	R, m	for-MXB	104	1.7	0.4
52	Dihydrosafrole	94-58-6	1419†	R, b	eso-mix	104	0.044	20
53	4-Dimethylaminoazobenzene	60-11-7	1441	R, f	liv-hpt	56	4.6	0.2
54	trans-2[(Dimethylamino)methylimino]-5-[2-(5-nitro-2-furyl)vinyl]-1,3,4-oxadiazole	55738-54-0	1457	R, f	mgl-adc	66	0.44	2
55	7,12-Dimethylbenz(a)anthracene	57-97-6	1466	M, f	mei-ane	60	250	0.003
56	Dimethylcarbamyl chloride	79-44-7	1467	H, m	nas-sqc	113	13	0.05
57	1,2-Dimethylhydrazine	540-73-8	1483*	M, m	blv-ang	52	550	0.001
58	Dimethylvinylchloride	513-37-1	1487†	M, f	for-MXA	104	0.045	20
59	Direct Black 38 (technical grade)	1937-37-7	547†	R, m	liv-MXA	13	7.4	0.09
60	Direct Blue 6 (technical grade)	2602-46-2	549†	R, m	liv-MXA	13	7.4	0.09
61	Direct Brown 95 (technical grade)	16071-86-6	579†	R, f	liv-MXA	13	6.7	0.1
62	Disperse Blue 1	2475-45-8	553	R, m	ubl-MXB	104	0.0045	200
63	Estradiol 17B	50-28-2	1628	M, f	mgl-adc	52	39	0.02
64	Ethyl-4,4'-dichlorobenzilate (chlorobenzilate)	510-15-6	geo-mean	M	liv-__	104	0.11	7
65	Ethylene thiourea	96-45-7	1724a	R, b	thy-mix	104	0.045	20
66	Ethyleneimine	151-56-4	geo-mean	M	lun & liv	104	65	0.01
67	2-(2-Formylhydrazino)-4-(5-nitro-2-furyl)thiazole	3570-75-0	1815	R, f	mgl-adc	75	2.3	0.3
68	Glu-P-1 (2-Amino-6-methyldipyrido[1,2-a:3',2'-d]imidazole)	67730-11-4	234	M, f	liv-mix	67	4.8	0.1
69	Glu-P-2 (2-Aminodipyrido[1,2-a:3',2'-d]imidazole)	67730-10-3	279	M, f	liv-mix	82	1.4	0.5

APPENDIX 1: DATASETS SERVING AS BASIS FOR POTENCY DERIVATIONS FOR 140 PROPOSITION 65 CARCINOGENS

	A	B	C	D	E	F	G	H
	CHEMICAL	CAS	LINE NO.	SPECIES	SITE	EXPT	HUMAN	INTAKE
		NUMBER	FROM	&	&	LENGTH	POTENCY	NSRL
			GOLD et al.	SEX	HSTP	(wks)	(mg/kg-d)-1	(µg/day)
70	Gyromitrin (Acetaldehyde methylformylhydrazone)	16568-02-8	6 √	M, m	pre-mix	79	10	0.07
71	HC Blue 1	2784-94-3	560	M, f	liv-MXA	104	0.051	10
72	Hexachloroethane	67-72-1	1921†	M, f	liv-hpc	90	0.039	20
73	Hydrazobenzene (1,2-Diphenylhydrazine)	122-66-7	1987a	R, m	liv-MXA	109	0.87	0.8
74	IQ (2-Amino-3-methylimidazo[4,5-f]quinoline)	76180-96-6	241	R, m	zym-sqc	104	1.4	0.5
75	Lasiocarpine	303-34-4	2138§	R, m	liv-MXB	104	7.8	0.09
76	Lead acetate	301-04-2	2147	R, m	kid-tcc	76	0.28	3
77	Lead subacetate	1335-32-6	geo-mean	R	kid-mix	104	0.038	20
78	Me-A-alpha-C (2-Amino-3-methyl-9H-pyrido[2,3-b]indole)	68006-83-7	225	M, m	blv-hms	73	1.2	0.6
79	Melphalan	148-82-3	2222	R, m	per-mix	67	130	0.005
80	3-Methylcholanthrene	56-49-5	geo-mean	R, f	mam & mgl	104	22	0.03
81	4,4'-Methylene bis(2-chloroaniline)	101-14-4	2369	D, f	ubl-ptc	468	1.5	0.5
82	4,4'-Methylene bis(2-methylaniline)	838-88-0	2381	R, f	liv-hpc	82	0.92	0.8
83	4,4'-Methylenedianiline	101-77-9	2401†*	M, m	liv-MXA	104	1.6	0.4
84	4,4'-Methylenedianiline dihydrochloride	13552-44-8	2401†	M, m	liv-MXA	104	1.2	0.6
85	Methyl methanesulfonate	66-27-3	2312a	M, m	thm-lym	104	0.099	7
86	2-Methyl-1-nitroanthraquinone (of uncertain purity)	129-15-7	2332	M, m	sub-hes	46	4.3	0.2
87	N-Methyl-N'-nitro-N-nitrosoguanidine	70-25-7	geo-mean	R, m	stg & git	104	8.3	0.08
88	Methylthiouracil	56-04-2	2422	H, f	thy-mix	52	0.40	2
89	Michler's ketone	90-94-8	2442	R, f	liv-MXA	109	0.86	0.8
90	Mirex	2385-85-5	geo-mean	M	liv-	104	18	0.04
91	Mitomycin C	50-07-7	2450	R, f	per-sar	78	8200	0.00009
92	Monocrotaline	315-22-0	2461	R, m	liv-hpc	71	10	0.07
93	2-Naphthylamine	91-59-8	2493	P, f	ubl-mix	260	1.8	0.4
94	Nitrilotriacetic acid	139-13-9	2534f	R, f	liv-MXB	99	0.0053	100
95	Nitrilotriacetic acid, trisodium salt monohydrate	18662-53-8	geo-mean	R	geo-mean	104	0.010	70
96	5-Nitroacenaphthene	602-87-9	2636b	R, f	eac-MXA	100	0.13	6
97	5-Nitro-o-anisidine	99-59-2	2573a	R, m	ski-MXA	109	0.049	10
98	Nitrofen (technical grade)	1836-75-5	geo-mean	M	liv-	104	0.082	9
99	Nitrofurazone	59-87-0	2576	R, f	mam-tum	66	1.3	0.5
100	1-[(5-Nitrofurfurylidene)-amino]-2-imidazolidinone	555-84-0	2663a	R, f	mgl-adc	66	1.8	0.4
101	N-[4-(5-Nitro-2-furyl)-2-thiazolyl]acetamide	531-82-8	2589	H, m	ubl-mix	70	1.5	0.5
102	p-Nitrosodiphenylamine	156-10-5	2810	R, m	liv-MXA	104	0.022	30
103	N-Nitroso-N-methylurethane	615-53-2	2726a	H, b	eso-epc	73	110	0.006
104	N-Nitrosomorpholine	59-89-2	2843^	H, f	res-mix	104	6.7	0.1

APPENDIX 1: DATASETS SERVING AS BASIS FOR POTENCY DERIVATIONS FOR 140 PROPOSITION 65 CARCINOGENS

	A	B	C	D	E	F	G	H
	CHEMICAL	CAS	LINE NO.	SPECIES	SITE	EXPT	HUMAN	INTAKE
		NUMBER	FROM	&	&	LENGTH	POTENCY	NSRL
			GOLD et al.	SEX	HSTP	(wks)	(mg/kg-d)-1	(µg/day)
105	N-Nitrosonornicotine	16543-55-8	2846	H, m	res-pam	96	1.4	0.5
106	N-Nitrosopiperidine	100-75-4	2861†	R, b	liv-mix	143	9.4	0.07
107	Phenacetin	62-44-2	2981b	R, m	nas-adc	104	0.0022	300
108	Phenazopyridine	94-78-0	2984*	M, f	liv-MXA	104	0.17	4
109	Phenazopyridine hydrochloride	136-40-3	2984	M, f	liv-MXA	104	0.15	5
110	Phenesterin	3546-10-9	2988a§	M, f	lun-MXA	83	150	0.005
111	Phenobarbital	50-06-6	3011	M, m	liv-esn	65	0.46	2
112	Phenoxybenzamine	59-96-1	3043*√	R, m	per-srn	83	3.1	0.2
113	Phenoxybenzamine hydrochloride	63-92-3	3043√	R, m	per-srn	83	2.7	0.3
114	o-Phenylphenate, sodium	132-27-4	3110†	R, m	unt-mix	91	0.0030	200
115	Ponceau MX (D&C Red No. 5)	3761-53-3	3335	R, f	liv-nod	104	0.0045	200
116	Ponceau 3R (FD&C Red No. 1)	3564-09-8	geo-mean	R	liv & bil	104	0.016	40
117	Potassium bromate	7758-01-2	572	R, m	kid-mix	112	0.49	1
118	Procarbazine	671-16-9	geo-mean*√	M	lun & ute	104	14	0.05
119	Procarbazine hydrochloride	366-70-1	geo-mean√	M	lun & ute	104	12	0.06
120	1,3-Propane sultone	1120-71-4	3234√	R, m	crb-mag	60	2.4	0.3
121	beta-Propiolactone	57-57-8	3240	M, m	for-tum	83	14	0.05
122	Propylthiouracil	51-52-5	3279√	R, m	thy-ade	52	1.0	0.7
123	Reserpine	50-55-5	3381	R, m	adr-MXA	104	11	0.06
124	Safrole	94-59-7	geo-mean	M	liv-__	104	0.22	3
125	Sterigmatocystin	10048-13-2	geo-mean√	R	liv-__	104	35	0.02
126	Streptozotocin	18883-66-4	3530†	M, f	lun-mix	78	110	0.006
127	Styrene oxide	96-09-3	3549	R, m	for-mix	109	0.16	4
128	Sulfallate	95-06-7	3555	R, f	mgl-acn	104	0.19	4
129	1,1,2,2-Tetrachloroethane	79-34-5	3612	M, f	liv-hpc	92	0.27	3
130	Thioacetamide	62-55-5	3684	M, f	liv-hpt	65	6.1	0.1
131	4,4'-Thiodianiline	139-65-1	3692a§	R, f	ute-acn	104	15	0.05
132	Thiourea	62-56-6	3709	R, m	aur-epc	113	0.072	10
133	Toluene diisocyanate	26471-62-5	3751b	R, m	sub-MXA	109	0.039	20
134	ortho-Toluidine	95-53-4	geo-mean*§	R, m	sub & ski	104	0.18	4
135	ortho-Toluidine hydrochloride	636-21-5	geo-mean§	R, m	sub & ski	104	0.13	5
136	Tris(1-aziridinyl)phosphine sulfide (Thiotepa)	52-24-4	geo-mean√	R	geo-mean	104	12	0.06
137	Tris(2,3-dibromopropyl)phosphate	126-72-7	3904†	R, m	kid-tla	104	2.3	0.3
138	Trp-P-1 (Tryptophan-P-1)	62450-06-0	208*	R, f	liv-hpc	52	26	0.03
139	Trp-P-2 (Tryptophan-P-2)	62450-07-1	226*	M, f	liv-hpc	88	3.2	0.2
140	Vinyl trichloride (1,1,2-Trichloroethane)	79-00-5	3802	M, f	liv-hpc	90	0.072	10

Glossary

Column A: Proposition 65 chemicals which are in the three volume set -- Combined Plot of the Carcinogenic Potency Database: Merged data from four papers, obtained from L.S. Gold, Cell and Molecular Biology, Lawrence Berkeley Laboratory, Berkeley, CA 94720.

Column B: Chemical Abstracts Services (CAS) registry number.

Column C: Line number for the experiment and chemical in the Combined Plot of the Carcinogenic Potency Database.

† Dropped the high dose group due to non-linearity; this was determined by running the computer program TOX_RISK (Crump et al., 1991). If the p-value based on the chi-square goodness-of-fit test, provided in the TOX_RISK program, is less than or equal to 0.05, non-linearity is indicated. Following the US EPA (Anderson, 1983), the high dose group was excluded from the analysis to correct for the poor fit.

^ Dropped the middle and high dose groups due to non-linearity (see explanation of † above).

* Potency derived using a molecular weight conversion. This conversion was used to calculate the potency of a chemical from the potency of its hydrate, hydrochloride, dihydrochloride, monoacetate, or sulfate as in the following example:

$$q_h \text{ (anhydrous)} = q_h \text{ (hydrate)} \quad X \quad \frac{\text{M.W.(hydrate)}}{\text{M.W.(anhydrous)}}$$

where q_h is the human potency and M.W. is the molecular weight. This conversion assumes that intake of the equivalent moles of the two forms of the chemical (e.g. the anhydrous form and hydrate; or the salt and the base) results in equivalent concentrations of the active species *in vivo*. For this document, the conversion was not applied to inorganic compounds.

✓ Decreased survival according to Gold et al.; potency may be an underestimate.

§ Decreased survival according to Gold et al.; time-to-tumor analysis performed using Tox_Risk (Crump et al., 1991).

• Included in the potency analysis all dose groups as given in the NCI technical report; Gold et al. listed only the high dose group.

¿ Gold et al. did not include the data for the combined incidence of mammary gland tumors of all types, which were tabulated and noted as biologically significant by the NCI. The individual animal data for the time-to-tumor analysis were obtained from Tox_Risk (Crump et al., 1991).

Geo-mean: The geometric mean is the nth root of the product of the human potencies (q_{human}) for the relevant studies.

$$\text{geo-mean} = [(q_{human})_1 \text{ X } (q_{human})_2 \text{ X } .... \text{ X } (q_{human})_n]^{1/n}$$

The human potencies for the different studies are weighted equally in the calculation. The following is a list of the chemicals for which geometric means were derived and the particular line numbers from the Combined Plot of the Carcinogenic Potency Database used in the calculations.

AF-2; [2-(2-furyl)-3(5-nitro-2-furyl)]acrylamide: 128, 129
Aramite: 349,m350✓,m356
p-Chloro-o-toluidine: 802†, 803§, 804†, 806a
Diethylstilbestrol: 1384, 1385†, 1386, 1387†, 1388
Ethyl-4,4'-dichlorobenzilate: 830, 832†, 833, 835
Ethyleneimine: 1710, 1711, 1713
Lead subacetate: 2152, 2153, 2154, 2155, 2156
3-Methylcholanthrene: 2358, 2359, 2360, 2361, 2362, 2363, 2364, 2366, 2367, 2368
N-Methyl-N'-nitro-N-nitrosoguanidine: 2316, 2317, 2321
Mirex: 2444, 2445, 2446, 2447
Nitrilotriacetic acid, trisodium salt monohydrate: 2540, 2542, 2544, 2545
Nitrofen, technical grade: 2646, 2647†, 2649, 2650
Ponceau 3R: 3348, 3349, 3350, 3351^, 3352, 3353, 3354, 3355
Procarbazine & Procarbazine hydrochloride: 3213a†✓, 3215a†✓, 3217, 3218
Safrole: 3445, 3446,m3447, 3449, 3450,m3451, 3453, 3454, 3455, 3456, 3457, 3458
Sterigmatocystin: 3525, 3526, 3527, 3528†✓, 3529
o-Toluidine & o-Toluidine hydrochloride: 3768a§, 3769, 3770
Tris(1-aziridinyl)phospine sulfide (Thiotepa): 3679b✓, 3681a✓

Column D: Species and sex in the experiments selected for potency calculation (body weights from Gold et al., 1984, unless otherwise specified).

D,f:	Dog, female - 16 kg body weight
H,m:	Hamster, male - 0.125 kg body weight
H,f:	Hamster, female - 0.11 kg body weight
H,b:	Hamster, both sexes - 0.1175 kg body weight
P,f:	Monkey, (rhesus), female - 8 kg body weight (US EPA, 1988)
M,m:	Mouse, male - 0.03 kg body weight
M,f:	Mouse, female - 0.025 kg body weight
R,m:	Rat, male - 0.5 kg body weight
R,f:	Rat, female - 0.35 kg body weight
R,b:	Rat, both sexes - 0.425 kg body weight
R :	Geometric mean; experiments used included male, female and/or sexes combined. For the animal potency value, potencies from individual studies were normalized to male rats using a surface area correction.
M :	Geometric mean; experiments used included male, female and/or sexes combined. For the animal potency value, potencies from individual studies were normalized to male mice using a surface area correction.

Column E: Site and histopathology for dose response data used in the potency calculation, as indicated in the Combined Plot of the Carcinogenic Potency Database.

__-hes:	All target sites; hemangiosarcoma.
adr-MXA:	Adrenal gland; more than one tumor type; combined by NCI/NTP.
aur-epc:	Auricular region; epidermoid carcinoma.
blv-ang:	Blood vessels; angiosarcoma.
blv-hms:	Blood vessels; hemangioendothelial sarcoma
blv-mix:	Blood vessels; more than one tumor type; tumor types specified in published experiment.
crb-mag:	Cerebrum; malignant glioma.
duo-adm:	Duodenum; adenomatous polyp, NOS or adenocarcinoma in adenomatous polyp.
eac-MXA:	Ear canal; more than one tumor type, combined by NCI/NTP.
edu-sqc:	Ear duct; squamous cell carcinoma.
eso-epc:	Esophagus; epidermoid carcinoma.
eso-mix:	Esophagus; more than one tumor type; tumor types specified in published experiments.
for-mix:	Forestomach; more than one tumor type; tumor types specified in published paper.
for-MXA:	Forestomach; more than one tumor type, combined by NCI/NTP.
for-MXB:	Forestomach; more than one tumor type.
for-sqc:	Forestomach; squamous cell carcinoma.
for-tum:	Forestomach; tumor or more than one tumor type; tumor types not specified in published paper.
kid-mix:	Kidney: more than one tumor type; tumor types specified in published experiment.
kid-MXA:	Kidney; more than one tumor type, combined by NCI/NTP.
kid-tcc:	Kidney; transitional cell carcinoma.
kid-tla:	Kidney; tubular cell adenoma.
liv-esn:	Liver; eosinophilic nodule.
liv-hpc:	Liver; hepatocellular carcinoma.
liv-hpt:	Liver; hepatoma.
liv-MXA:	Liver; more than one tumor type, combined by NCI/NTP.
liv-MXB:	Liver; more than one tumor type
liv-nod:	Liver; nodular hyperplasia.
liv-mix:	Liver; more than one tumor type; tumor types specified in published experiment.
lun-alc:	Lung; alveolar cell carcinoma.
lun-mix:	Lung; more than one tumor type; tumor types specified in published experiment.
lun-MXA:	Lung; more than one tumor type, combined by NCI/NTP.
mam-tum:	Mammary tissue (other than or including more than mammary gland); tumor or more than one tumor type; tumor type not specified in published paper.
mei-ane:	Mesenteric intestine; angio-endothelioma, malignant.
mgl-acn:	Mammary gland; adenocarcinoma, NOS.
mgl-adc:	Mammary gland; adenocarcinoma.
mgl-ade:	Mammary gland; adenoma.
mgl-car:	Mammary gland; carcinoma.
mgl-mix:	Mammary gland; more than one tumor type; tumor types specified in published experiments.
mix-mix:	More than one site; sites specified in published experiment, more than one tumor type; tumor types specified in published experiment.

mgl-MXA:	Mammary gland; more than one tumor type, combined by NCI/NTP.
nas-adc:	Nasal cavity; adenocarcinoma.
nas-sqc:	Nasal cavity; squamous cell carcinoma.
pae-car:	Pancreas exocrine; carcinoma.
pec-mix:	Peritoneal cavity; more than one tumor type; tumor types specified in published experiment.
per-mix:	Peritoneum; more than one tumor type; tumor types specified in published experiment.
per-sar:	Peritoneum; sarcoma.
per-srn:	Peritoneum; sarcoma, NOS.
pre-mix:	Preputial gland; more than one tumor type; tumor types specified in published experiment.
res-mix:	Respiratory system; more than one tumor type; tumor types specified in published paper.
res-pam:	Respiratory system; papilloma.
ski-MXA:	Skin; more than one tumor type, combined by NCI/NTP.
spl-MXA:	Spleen; more than one tumor type, combined by NCI/NTP.
sub-hes:	Subcutaneous tissue; hemangiosarcoma.
sub-MXA:	Subcutaneous tissue; more than one tumor type; combined by NCI/NTP.
thm-lym:	Thymus gland; lymphoma.
thy-ade:	Thyroid gland; adenoma.
thy-ben:	Thyroid gland; benign tumor.
thy-mix:	Thyroid gland; more than one tumor type; tumor types specified in published experiment.
thy-MXA:	Thyroid gland; more than one tumor type, combined by NCI/NTP.
ubl-mix:	Urinary bladder; more than one tumor type; tumor types specified in published experiment.
ubl-MXA:	Urinary bladder; more than one tumor type, combined by NCI/NTP.
ubl-MXB:	Urinary bladder; more than one tumor type, combined by Gold et al.
ubl-ptc:	Urinary bladder; papillary transitional cell carcinoma
ubl-tcc:	Urinary bladder; transitional cell carcinoma.
unt-mix:	Urinary tract; more than one tumor type; tumor types specified in published paper.
ute-acn:	Uterus; adenocarcinoma.
zym-sqc:	Zymbal's gland; squamous cell carcinoma.

For geometric means:

geo-mean:	Varying sites and histopathology.
kid-mix:	Kidney: more than one tumor type; tumor types specified in published experiment.
liv & bil:	Liver and bile duct - site with varying histopathology.
liv-___:	Liver and varying histopathology.
lun & liv:	Liver and lung - site with varying histopathology.
lun & ute:	Lung and uterus - site with varying histopathology.
mam & mgl:	Mammary tissue (other than or including more than mammary gland) and mammary gland with varying histopathology.
mgl-___:	Mammary gland; varying histopathology.
mgl-mix:	Mammary gland; more than one tumor type; tumor types specified in published experiments.
stg & git:	Stomach, glandular and gastrointestinal tract with varying histopathology.
sub & ski:	Subcutaneous tissue and skin - site with varying histopathology.

Column F: The experimental exposure duration in weeks.

Column G: Human cancer potency estimate in units of $(mg/kg\text{-}day)^{-1}$. For explanation of how this estimate is derived, see the Methodology section (p. 1).

Column H: The no significant risk level in units of $\mu g/day$. This is the intake associated with a lifetime cancer risk of 10^{-5} or lower for an adult weighing 70 kg. For explanation of how this level is derived, see the Methodology section (p. 1).

APPENDIX 1 REFERENCES:

Anderson EL and the US Environmental Protection Agency Carcinogen Assessment Group (1983). Quantitative approaches in use to assess cancer risk. *Risk Analysis* 3:277-295.

Crouch EAC (1985). A Program for the IBM PC Designed to Fit End-Of-Life Data from Carcinogenesis Bioassays to the Multistage Model, EAC Crouch, Somerville, MA.

Crump KS, Howe RB, Van Landingham C, and Fuller WG (1991). **TOX_RISK** Version 3. **TOX**icology **RISK** Assessment Program. KS Crump Division, Clement International Corporation, 1201 Gaines Street, Ruston, Louisiana 71270.

Gold LS, Sawyer CB, Magaw R, Backman GM, de Veciana M, Levinson R, Hooper NK, Havender WR, Bernstein L, Peto R, Pike MK, Ames BN (1984). A carcinogenic potency database of the standardized results of animal bioassays. *Environmental Health Perspectives* 58:9-319.

Gold L, de Veciana M, Backman G, Magaw R, Lopipero P, Smith M, Blumenthal M, Levinson R, Bernstein L, Ames B (1986). Chronological Supplement to the Carcinogenic Potency Database: Standardized results of animal bioassays published through December 1982. *Environmental Health Perspectives* 67: 161-200.

Gold L, Slone T, Backman G, Magaw R, Da Costa M, Ames B (1987). Second chronological supplement to the Carcinogenic Potency Database: Standardized results of animal bioassays published through December 1984 and by the National Toxicology Program through May 1986. *Environmental Health Perspectives* 74: 237-329.

Gold L, Slone T, Bernstein L (1989). Summary of Carcinogenic Potency and Positivity for 492 Rodent Carcinogens in the Carcinogenic Potency Database. *Environmental Health Perspectives* 79: 259-272.

Gold L, Slone T, Backman G, Eisenberg S, Da Costa M, Wong M, Manley N, and Ames B (1990). Third chronological supplement to the Carcinogenic Potency Database: Standardized results of animal bioassays published through December 1986 and by the National Toxicology Program through June 1987. *Environmental Health Perspectives* 84: 215-285.

US Environmental Protection Agency (US EPA, 1988). *Recommendations for and Documentation of Biological Values for Use in Risk Assessment.* EPA/600/6-87/008. Office of Health and Environmental Assessment, Washington D.C.

APPENDIX 2: Example of Potency Derivation Using the Expedited Procedure

The expedited procedure for deriving a potency value from dose response data tabulated in the Gold et al. Carcinogenic Potency Database (1984, 1986, 1987, 1990) is outlined below. A specific example of the application of this procedure follows.

1. The Proposition 65 carcinogen and its associated datasets were located in the Gold et al. Carcinogenic Potency Database. Each dataset is labelled with an alphanumeric line number and consists of histopathology and dose incidence data for a particular tumor site in a particular sex and species of experimental animals.

2. All the datasets associated with the chemical of interest were examined. Data sets were evaluated according to the following procedure:

- The quality of the data sets was screened based on the number of dose groups, the number of animals per dose group, the dose levels used, the length of the study and the survival of the animals. Preference was given to studies of higher quality.

- Data sets with a statistically significant trend of increased tumor incidence with increased dose were used. Gold et al. calculated a two-tailed p-value for each data set; a p-value of less than 0.025 indicated statistical significance. There were exceptions to this rule. For example, the incidence of a rare tumor may not be statistically significant compared to concurrent controls, but could be clear evidence of the carcinogenicity of a particular chemical. In such cases, the data set would not be excluded based on statistical significance alone.

- If the observed result was judged by the author of the study in question to be a negative result, the data set was not used.

- Data sets were not selected if the endpoint was specified as "all tumor-bearing animals" (tba or TBA) or results were from a combination of unrelated tumor types and/or sites (in general, designated MXB MXB for the site and histopathology).

- Data sets that recorded malignant tumors or combined malignant and benign tumors were chosen, with preference given to the combined data. For example, if there was a data set for combined liver hepatocellular carcinomas and adenomas, it would be selected over one for liver hepatocellular carcinomas alone.

3. Potency analysis.

Animal cancer potency was estimated from the selected data sets using the linearized multistage model for low dose extrapolation; an adjustment for less than lifetime exposure was applied when necessary. Human potency was derived by multiplying the animal cancer potency value by an interspecies extrapolation factor. For details on this procedure see the methodology section of this document.

The goodness-of-fit of the multistage model to the dose-response curve was determined by a chi-square test, provided in the program Tox_Risk (Crump et al., 1991). A poor fit was indicated by a p-value of less than or equal to 0.05. Data sets adequately fit by the multistage model ($p > 0.05$) were selected, if possible. For data sets that were not adequately fit by the multistage model, the data points at the higher dose end of the curve (usually the high dose

group only) were excluded from the potency calculation to correct for the lack of fit (Anderson et al., 1983). In some cases, the poor fit was due to survival problems; when possible time-to-tumor analyses were performed for those chemicals.

The human potencies derived from the selected data sets were compared, and the most sensitive species was determined. If the bioassays in the sensitive species were conducted by the same researcher under the same laboratory conditions, the potency for the most sensitive sex was chosen. If there were multiple studies of similar quality within a particular sensitive species, a geometric mean of the different studies was taken.

Example: Chlorendic Acid

1. Location of data sets

Bioassay data for this chemical are summarized in the Carcinogenic Potency Database; the entry for this chemical is reproduced in Table A2-1. The datasets available were those from the National Toxicology Program (NTP, 1987) bioassays on male and female $B6C3F_1$ mice and F344/N rats. In general, one line number is assigned to each bioassay. For this example, the line numbers correspond to the different species/sex combinations: line 741, female mice; line 742, male mice; line 743, female rats; and line 744, male rats. Following each line number are dose incidence data for particular tumor sites and histopathology, labelled with letters. For example, data for liver hepatocellular carcinomas in male mice is found in line 742a.

2. Evaluation of data sets.

The quality of the data sets in terms of dose levels, group size and length of study was comparable. Additionally, none of the bioassays was compromised by poor survival.

Data sets with the following line numbers had statistically significant trends ($p<0.025$ as noted in column 15) of increased incidence with increased dose: 741, 741a, 741c, 741d, 741e, 742, 742a, 742e, 743, 743a, 743b, 743d, 744, 744a, 744b, 744c, 744d, 744e, 744f, 744j. One site (line number 742b) that did not show a statistically significant increase in tumors was still considered by NTP to be evidence of the carcinogenicity of chlorendic acid (as noted in the author's opinion column 16 by the letter "c"). Based on NTP's opinion that the result was significant, 742b was not excluded at this stage.

The increase in lung tumors in female mice (data tabulated in line number 741) was not considered by NTP to be related to treatment with chlorendic acid, as noted by a minus sign in the author's opinion column (column 16). Thus, line number 741 and the other line numbers tabulating female mice lung tumor data (741a, 741e) were excluded from consideration.

Line number 741c was a dose incidence data set for all tumor-bearing animals (site designation is TBA, listed in column 6), and thus was eliminated from consideration.

Line number 744 was a combination of unrelated tumors; liver neoplastic nodules and pancreas acinar-cell adenomas, designated MXB MXB (site and histopathology). This was excluded from consideration.

Line number 742c presented data for pancreas acinar-cell adenomas in male rats. Because no malignant tumors of this cell type were observed, there was no evidence that these adenomas would progress. This data set was excluded.

In male mice, liver tumors were observed. Line number 742a presented the data for liver hepatocellular carcinomas. Line number 742 presented the data for liver hepatocellular carcinomas and adenomas combined. Since the combined data set was available, 742a was excluded. Similarly, 743a, 743b, 744a, and 744e present data for one tumor type of a particular histopathology at a single site. Because data sets for combined tumors of the same histopathology at the same site were available in all those cases, the above line numbers were excluded.

After screening the data sets as described above, the following line numbers remained under consideration: 741d, 742, 742e, 743, 743d, 744b, 744c, 744d, 744f, 744j. 742 and 742e presented the same incidence data for combined liver hepatocellular carcinomas and adenomas in male mice. 742 was labelled as the incidence obtained directly from the NTP report (liv MXA). 742e (liv MXB), the same incidence as determined by Gold et al., was thus excluded as redundant. 743d and 744j were excluded as redundant for analogous reasons.

The data sets most suitable for potency analysis were: 741d, 742, 743, 744b, 744d.

3. Potency analysis

Human cancer potency was determined for all the line numbers under consideration. For each data set under consideration, a p-value of greater than 0.05 for the chi-square goodness-of-fit test was obtained, indicating that the fit was adequate.

Table A2-2 summarizes the results of the potency analyses. The potency values ranged from 0.020 $(mg/kg\text{-}day)^{-1}$, based on liver tumors in female mice, to 0.091 $(mg/kg\text{-}day)^{-1}$, based on liver tumors in male rats. The potency for the most sensitive species/sex, the male rat, was chosen as the human cancer potency.

APPENDIX 2 REFERENCES:

Anderson EL and the US Environmental Protection Agency Carcinogen Assessment Group (1983). Quantitative approaches in use to assess cancer risk. *Risk Analysis* 3:277-295.

Crump KS, Howe RB, Van Landingham C, and Fuller WG (1991). **TOX_RISK** Version 3. **TOX**icology **RISK** Assessment Program. KS Crump Division, Clement International Corporation, 1201 Gaines Street, Ruston, Louisiana 71270.

Gold LS, Sawyer CB, Magaw R, Backman GM, de Veciana M, Levinson R, Hooper NK, Havender WR, Bernstein L, Peto R, Pike MK, Ames BN (1984). A carcinogenic potency database of the standardized results of animal bioassays. *Environmental Health Perspectives* 58:9-319.

Gold L, de Veciana M, Backman G, Magaw R, Lopipero P, Smith M, Blumenthal M, Levinson R, Bernstein L, Ames B (1986). Chronological Supplement to the Carcinogenic Potency Database: Standardized results of animal bioassays published through December 1982. *Environmental Health Perspectives* 67: 161-200.

Gold L, Slone T, Backman G, Magaw R, Da Costa M, Ames B (1987). Second chronological supplement to the Carcinogenic Potency Database: Standardized results of animal bioassays published through December 1984 and by the National Toxicology Program through May 1986. *Environmental Health Perspectives* 74: 237-329.

Gold L, Slone T, Backman G, Eisenberg S, Da Costa M, Wong M, Manley N, and Ames B (1990). Third chronological supplement to the Carcinogenic Potency Database: Standardized results of animal bioassays published through December 1986 and by the National Toxicology Program through June 1987. *Environmental Health Perspectives* 84: 215-285.

National Toxicology Program (NTP, 1987). *Toxicology and Carcinogenesis Studies of Chlorendic Acid in F344 Rats and B6C3F$_1$ Mice (Feed Studies)*. NTP Technical Report Series No. 304. NIH Publication No. 87-2560, US Department of Health and Human Services (DHEW), NTP, Research Triangle Park, NC.

TABLE A2-1

EXAMPLE - CHLORENDIC ACID

Line number / Site/pathology identifier (letter)	Species	Sex	Strain	Route	Site	Histopathology	Exposure period / Units (months) / Experiment length	Notes	Plotted TD50 Value with Confidence Limits	Best estimate of TD50 (mg/kg-day)	Curve shape	Slope significance	Author's opinion
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)(9)(10)		(11) (12)	(13)	(14)	(15)	(16)
CHLORENDIC ACID									100ng..:..1ug....:..10.....:..100....:..1mg....:..10.....:..100....:..1g.....:..10					
741	M	f	b6c	eat	lun	MXA	24m24		: + :		343.mg	*	P<.003	-
a	M	f	b6c	eat	lun	a/a	24m24				412.mg	*	P<.002	
b	M	f	b6c	eat	MXA	MXA	24m24				1.17gm	*	P<.03	
c	M	f	b6c	eat	TBA	MXB	24m24				87.1mg	/	P<.0005	
d	M	f	b6c	eat	liv	MXB	24m24				348.mg	*	P<.02	
e	M	f	b6c	eat	lun	MXB	24m24				343.mg	*	P<.003	
742	M	m	b6c	eat	liv	MXA	24m24		: + :		141.mg	*	P<.004	c
a	M	m	b6c	eat	liv	hpc	24m24				206.mg	*	P<.009	c
b	M	m	b6c	eat	liv	hpa	24m24				387.mg	*	P<.08	c
c	M	m	b6c	eat	thy	fca	24m24				1.59gm	*	P<.04	
d	M	m	b6c	eat	TBA	MXB	24m24				227.mg	*	P<.2	
e	M	m	b6c	eat	liv	MXB	24m24				141.mg	*	P<.004	
f	M	m	b6c	eat	lun	MXB	24m24				no dre		P=1.	
743	R	f	f34	eat	liv	MXA	24m24		: + :		98.8mg	*	P<.0005	c
a	R	f	f34	eat	liv	nnd	24m24				162.mg	*	P<.004	c
b	R	f	f34	eat	liv	hpc	24m24				271.mg	*	P<.02	c
c	R	f	f34	eat	TBA	MXB	24m24				no dre		P=1.	
d	R	f	f34	eat	liv	MXB	24m24				98.8mg	*	P<.0005	
744	R	m	f34	eat	MXB	MXB	24m24		: + :		25.4mg	*	P<.0005	
a	R	m	f34	eat	liv	nnd	24m24				25.7mg	*	P<.0005	c
b	R	m	f34	eat	liv	MXA	24m24				32.2mg	*	P<.002	
c	R	m	f34	eat	pan	ana	24m24				131.mg	*	P<.005	c
d	R	m	f34	eat	lun	MXA	24m24				148.mg	*	P<.01	
e	R	m	f34	eat	lun	a/a	24m24				168.mg	*	P<.01	e
f	R	m	f34	eat	pre	MXA	24m24				59.4mg	\	P<.02	
g	R	m	f34	eat	sub	fbs	24m24				380.mg	*	P<.05	
h	R	m	f34	eat	pre	can	24m24				189.mg	*	P<.2	e
i	R	m	f34	eat	TBA	MXB	24m24				no dre		P=1.	
j	R	m	f34	eat	liv	MXB	24m24				32.2mg	*	P<.002	

Left side of database plot (Volume 1, Combined Plot of the Carcinogenic Potency Database)

TABLE A2 - 1

EXAMPLE - CHLORENDIC ACID

Line number / Site/pathology identifier (letter)	Publication number	Lower TD50 confidence limit (mg/kg-day)	Upper TD50 confidence limit (mg/kg-day)	Tumor incidence in control group	Dose received by first treatment group (mg/kg-day)	Tumor incidence in first treatment group	Dose received by second treatment group (mg/kg-day)	Tumor incidence in second treatment group	Pathology	"Berkeley code"
(17)	(18)(19)	(20)	(21)	(22)	(23)	(24)	(25)	(26)	(27)	(28)
CHLORENDIC ACID 115-28-6										
741	c55072	153.mg	1.94gm	1/50	79.1mg	5/50	160.mg	6/50	lun:a/a,a/c.	s
a	c55072	177.mg	1.68gm	0/50	79.1mg	4/50	160.mg	4/50		s
b	c55072	367.mg	n.s.s.	0/50	79.1mg	1/50	160.mg	3/50	moy:hes; spl:hes.	s
c	c55072	46.6mg	350.mg	29/50	79.1mg	32/50	160.mg	32/50		
d	c55072	150.mg	52.5gm	3/50	79.1mg	7/50	160.mg	7/50	liv:hpa,hpc,nmd.	
e	c55072	153.mg	1.94gm	1/50	79.1mg	5/50	160.mg	6/50	lun:a/a,a/c.	
742	c55072	72.2mg	1.17gm	13/50	73.0mg	23/50	149.mg	27/50	liv:hpa,hpc.	
a	c55072	101.mg	8.47gm	9/50	73.0mg	17/50	149.mg	20/50		
b	c55072	150.mg	n.s.s.	5/50	73.0mg	9/50	149.mg	10/50		
c	c55072	474.mg	n.s.s.	0/50	73.0mg	0/50	149.mg	3/50		s
d	c55072	74.7mg	n.s.s.	35/50	73.0mg	31/50	149.mg	39/50		
e	c55072	72.2mg	1.17gm	13/50	73.0mg	23/50	149.mg	27/50	liv:hpa,hpc,nmd.	
f	c55072	379.mg	n.s.s.	15/50	73.0mg	4/50	149.mg	9/50	lun:a/a,a/c.	
743	c55072	56.0mg	283.mg	1/50	30.7mg	5/50	61.9mg	16/50	liv:hpc,nmd.	
a	c55072	80.3mg	1.11gm	1/50	30.7mg	3/50	61.9mg	11/50		
b	c55072	122.mg	n.s.s.	0/50	30.7mg	3/50	61.9mg	5/50		
c	c55072	41.7mg	n.s.s.	48/50	30.7mg	48/50	61.9mg	48/50		
d	c55072	56.0mg	283.mg	1/50	30.7mg	5/50	61.9mg	16/50	liv:hpa,hpc,nmd.	
744	c55072	16.2mg	57.9mg	2/50	24.5mg	22/50	49.5mg	23/50	liv:nmd; pan:ana.	c
a	c55072	16.3mg	58.7mg	2/50	24.5mg	21/50	49.5mg	23/50		
b	c55072	18.2mg	127.mg	5/50	24.5mg	22/50	49.5mg	23/50	liv:hpc,nmd.	s
c	c55072	63.4mg	1.04gm	0/50	24.5mg	4/50	49.5mg	6/50		
d	c55072	69.7mg	10.1gm	0/50	24.5mg	4/50	49.5mg	5/50	lun:a/a,a/c.	s
e	c55072	75.9mg	8.51gm	0/50	24.5mg	3/50	49.5mg	5/50		
f	c55072	26.2mg	n.s.s.	1/50	24.5mg	10/50	(49.5mg	4/50)	pro:adn,can,sqp.	s
g	c55072	130.mg	n.s.s.	0/50	24.5mg	1/50	49.5mg	3/50		s
h	c55072	68.2mg	n.s.s.	1/50	24.5mg	8/50	49.5mg	4/50		
i	c55072	25.7mg	n.s.s.	50/50	24.5mg	49/50	49.5mg	50/50		
j	c55072	18.2mg	127.mg	5/50	24.5mg	22/50	49.5mg	23/50	liv:hpa,hpc,nmd.	

Right side of database plot (Volume 2, Combined Plot of the Carcinogenic Potency Database)

Table A2-2: Chlorendic Acid: Summary of Human Cancer Potencies

Line #	Sex, Strain, Species	Site and Histopathology	Human Cancer Potency $(mg/kg\text{-}day)^{-1}$	P-Value[a]
741d	Female $B6C3F_1$ mice	Liver hepatocellular carcinomas, adenomas, neoplastic nodules	0.020	0.47
742	Male $B6C3F_1$ mice	Liver hepatocellular carcinomas, adenomas,	0.071	0.59
743	Female F344/N rats	Liver hepatocellular carcinomas, neoplastic nodules	0.036	0.93
744b	Male F344/N rats	Liver hepatocellular carcinomas, neoplastic nodules	0.091	0.10
744d	Male F344/N rats	Lung alveolar/bronchiolar carcinomas, adenomas	0.022	0.48

[a] P-value for chi-square goodness-of-fit test; a p-value of greater than 0.05 indicates an adequate fit. See text for details.

APPENDIX 3: POTENCY DERIVATION AND DATA SET SELECTION

This Appendix describes the data available in Gold et al. for potency derivation for the 140 Proposition 65 chemicals included in this report. The selection of the data set(s) used as the basis for each potency estimate is described and the relevant study citations (as provided by Gold et al.) are given.

A-alpha-C (2-amino-9H-pyrido[2,3-b]indole)

Cancer Potency: 0.40 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 2 $\mu g/day$

Results from the study of Ohgaki et al. (1984) in male and female CDF1 mice are listed. The more sensitive sex is the female. The potency is based on the incidence of combined benign and malignant tumors of the liver, the most sensitive site.

Ohgaki H, Matsukura N, Morino K, Kawachi T, Sugimura T and Takayama S (1984). Carcinogenicity in mice of mutagenic compounds from glutamic acid and soybean globulin pyrolysates. *Carcinogenesis* 5: 815-819.

Acetamide

Cancer Potency: 0.070 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 10 $\mu g/day$

Gold et al. list the results from the study of Fleischman et al. (1980) in both sexes of F344 rats and C57BL/6 mice, and from another experiment on male Wistar rats. The liver was the target site for rats in both studies. Tumors of the hematopoietic system were observed in male mice. Cancer potency is based on hepatocellular carcinomas in male F344 rats, the most sensitive species and sex tested.

Fleischman RW, Baker JR, Hagopian M, Wade GG, Hayden DW, Smith ER, Weisburger JH and Weisburger EK (1980). Carcinogenesis bioassay of acetamide, hexanamide, adipamide, urea and p-tolylurea in mice and rats. *J. Environ. Pathol. Toxicol.* 3: 149-170.

2-Acetylaminofluorene

Cancer Potency: 3.8 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.2 $\mu g/day$

A number of studies on 2-AAF carcinogenicity are listed; those which employed multiple, low dose groups were selected for analysis. The study by Ogiso et al. (1985), in which liver tumors in male F344 rats were observed, appears to be the most sensitive.

Ogiso T, Tatematsu M, Tamano S, Tsuda H and Ito N (1985). Comparative effects of carcinogens on the induction of placental glutathione S-transferase-positive liver nodules in a short-term assay and of hepatocellular carcinomas in a long-term assay. *Toxicol. Pathol.* 13: 257-265.

Actinomycin D

Cancer Potency: 8700 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.00008 $\mu g/day$

The only study in the Gold et al. database is that performed in male and female Charles River CD rats via intraperitoneal injection. The study was reported by both Skipper (1976) and Weisburger (1977). Tumors were observed at multiple sites in both sexes, with the greatest increases in incidences being for sarcomas of the peritoneum. Cancer potency is based on males, the more sensitive sex.

Skipper HE (1976). *Booklet 1, Phase I Studies on the Carcinogenic Activity of Anticancer Drugs in Mice and Rats.* Final report. Southern Research Institute, Birmingham, AL.

Weisburger EK (1977). Bioassay program for carcinogenic hazards of cancer chemotherapeutic agents. *Cancer* 40: 1935-1949.

AF-2;[2-(2-furyl)-3-(5-nitro-2-furyl)]acrylamide

Cancer Potency: 0.24 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 3 $\mu g/day$

Studies were performed in multiple species (mice, rats and hamsters). Cancer potency is based on mammary gland tumors in female rats, the most sensitive species and sex tested. Two studies were performed in female rats, one in Wistar rats by Takayama and Kuwabara (1977), the other in Sprague-Dawley rats by Cohen et al. (1977). Cancer potency is the geometric mean of the cancer potencies estimated from these two studies.

Cohen SM, Ichikawa M and Bryan GT (1977). Carcinogenicity of 2-(2-furyl)-3-(5-nitro-2-furyl) acrylamide (AF-2) fed to female Sprague-Dawley rats. *Gann* 68: 473-476.

Takayama S, and Kuwabara N (1977). Carcinogenic activity of 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide, a food additive, in mice and rats. *Cancer Lett.* 3: 115-120.

2-Amino-anthraquinone

Cancer Potency: 0.033 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 20 $\mu g/day$

Gold et al. tabulate results from the NCI (1978) feeding study in male and female $B6C3F_1$ mice and Fischer 344 rats. Benign and malignant hepatocellular tumors were induced in male and female mice and male rats. The potency is based on the dose response data for these tumors in the more sensitive sex and species, the male rat.

National Cancer Institute (NCI, 1978). *Bioassay of 2-Aminoanthraquinone for Possible Carcinogenicity Carcinogenesis.* Technical Report Series, Technical Report No. 144. NTIS PB-287 739. US Department of Health, Education, and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

ortho-Aminoazotoluene

Cancer Potency: 3.8 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.2 $\mu g/day$

Listed are the results of the feeding study by Waters (1937) in male CFLP mice and male and female albino rats. Despite the small numbers of animals per group, significant increases in liver tumors were seen in both sexes of rats. Cancer potency is based on liver tumors in the female, the more sensitive sex.

Waters LL (1937). o-Aminoazotoluene as a carcinogenic agent. *Yale J. Biol. Med.* 10: 179-184.

4-Aminobiphenyl

Cancer Potency: 21 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.03 $\mu g/day$

This agent is identified as a known human carcinogen by the International Agency for Research on Cancer (IARC, 1987). The classification is based on increased incidences of bladder cancers in those occupationally exposed. Only results from experiments in mice are listed by Gold et al. Animal bioassay and epidemiology studies on benzidine, a structurally similar compound also known to induce bladder cancer in humans, indicate that humans are significantly more sensitive to the carcinogenic effects of benzidine than mice (CDHS, 1988). This may also be the case for 4-aminobiphenyl. The potency value given here is based on the most sensitive mouse study listed by Gold et al. -- the gavage study by Clayson et al. (1967) in (C57 X IF)F1 female mice. This should be taken as an interim value until a more detailed risk assessment can be performed. There are a number of studies on the carcinogenic effects of 4-aminobiphenyl in dogs which should be examined, in addition to the epidemiologic data.

International Agency for Research on Cancer (IARC, 1987). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans.* Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42. Supplement 7. IARC, Lyon, France.

Clayson DB, Lawson TA and Pringle JAS (1967). The carcinogenic action of 2-aminodiphenylene oxide and 4-aminodiphenyl on the bladder and liver of the C57 x IF mouse. *Br. J. Cancer* 21: 755-762.

California Department of Health Services (CDHS, 1988). *Risk-Specific Intake Levels for the Proposition 65 Carcinogen: Benzidine.* Reproductive and Cancer Hazard Assessment Section, CDHS, Berkeley, CA.

3-Amino-9-ethylcarbazole hydrochloride

Cancer Potency: 0.078 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 9 $\mu g/day$

Gold et al. list the results of the NCI (1978) feeding study in male and female $B6C3F_1$ mice and Fischer 344 rats. Potency is based on the benign and malignant liver tumors in the male rat, the apparently most sensitive sex and species. Gold et al. provide the results for the high dose group only. We retrieved the incidences of liver tumors from the controls, low and high dose group from the original study and fit the multistage polynomial to these data.

National Cancer Institute (NCI, 1978). *Bioassay of 3-Amino-9-Ethylcarbazole Hydrochloride for Possible Carcinogenicity.* Carcinogenesis Technical Report Series, Technical Report No. 93. DHEW Publication No. (NIH) 78-1337. US Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

1-Amino-2-methylanthraquinone

Cancer Potency: 0.15 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 5 $\mu g/day$

Gold et al. list the results of the NCI (1978) feeding study in male and female $B6C3F_1$ mice and Fischer 344 rats. The NTP (1991) designates the results from the studies in male and female rats and female mice as positive. Survival was significantly reduced in treated mice.

Tumors were observed at multiple sites in the male rat. Potency is based on benign and malignant liver tumors in the male rat, the apparently most sensitive sex and species.

National Cancer Institute (NCI, 1978). *Bioassay of 1-Amino-2-methylanthraquinone for Possible Carcinogenicity*. Carcinogenesis Technical Report Series, Technical Report No. 111. US Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

National Toxicology Program (NTP, 1991). *Chemical Status Report*. US Department of Health and Human Services, NTP, Research Triangle Park, NC.

2-Amino-5-(5-nitro-2-furyl)-1,3,4-thiadiazole

Cancer Potency: 16 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.04 $\mu g/day$

The only study listed by Gold et al. is a feeding experiment in female Sprague-Dawley rats (Cohen et al., 1975). Potency is based on the dose response data for benign and malignant tumors at the most sensitive site, the mammary gland. All but one of the animals dosed with the compound developed mammary tumors (32 animals with tumor in 33 total animals in the treatment group), in contrast to only a few in the control group (2 animals with tumor in 24 total controls). If the one animal without tumor died early and therefore was not at risk, the potency calculated here is an underestimate.

Cohen SM, Erturk E, Von Esch AM, Crovetti AJ and Bryan GT (1975). Carcinogenicity of 5-nitrofurans and related compounds with amino-heterocyclic substituents. *J. Nat. Cancer Inst.* 54: 841-850.

Amitrole

Cancer Potency: 0.94 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.7 $\mu g/day$

Results from studies on mice, rats and hamsters are listed. Wistar rats are more sensitive than the strain of hamsters studied, and appear to be more sensitive than the mice. The most sensitive of the three species tested is difficult to determine, however. One strain of tested mice is less sensitive (NMRI) than the hamster and rat strains tested. Nearly all treated animals in studies on the other mouse strain ($B6C3F_1$) developed liver tumors so it can not be determined whether the rats tested are actually more sensitive than this mouse strain, or whether the apparent difference would persist with testing at lower doses. The studies in rats were performed at much lower dose than were those in $B6C3F_1$ mice. The cancer potency is based on the dose response data for benign thyroid tumors in female rats (Steinhoff et al., 1983). Significant elevations of malignant thyroid tumors were also observed, indicating that the benign tumors can progress to malignancy. Combined incidence data for thyroid tumors (data on the number of animals developing benign, malignant, or both combined) were not given. The default methodology would be to fit the multistage polynomial to the combined incidences. Thus, the cancer potency given here should be seen as an underestimate.

Steinhoff D, Weber H, Mohr U and Boehme K (1983). Evaluation of amitrole (aminotriazole) for potential carcinogenicity in orally dosed rats, mice, and golden hamsters. *Toxicol. Appl. Pharmacol.* 69: 161-169.

ortho-Anisidine

Cancer Potency: 0.14 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 5 $\mu g/day$

The potency given is based on the analysis of the dose response data for *o*-anisidine hydrochloride (discussed below), adjusted for differences in the molecular weight of the two compounds (see the glossary to Appendix 1 for explanation).

National Cancer Institute (NCI, 1978). *Bioassay of ortho-Anisidine for Possible Carcinogenicity.* Carcinogenesis Technical Report Series, Technical Report No. 89. US Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

ortho-Anisidine Hydrochloride

Cancer Potency: 0.11 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 7 $\mu g/day$

Gold et al. list the results of the NCI (1978) feeding study in male and female $B6C3F_1$ mice and Fischer 344 rats. The compound induced benign and malignant tumors of the urinary bladder in both sexes in both species. Cancer potency is based on dose response data for these tumors in the most sensitive sex and species--male rats.

National Cancer Institute (NCI, 1978). *Bioassay of ortho-Anisidine for Possible Carcinogenicity.* Carcinogenesis Technical Report Series, Technical Report No. 89. US Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

Aramite

Cancer Potency: 0.030 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 20 $\mu g/day$

Gold et al. list several studies: Oral studies in male and female $B6AKF_1$ and $B6C3F_1$ mice (Innes, 1968; Innes et al., 1969) and feeding studies in both sexes (combined) of CFN rats (Popper et al. 1960), Wistar FDRL rats (Popper et al. 1960,) Food and Drug Research Laboratory (FDRL) "stock" rats (Oser and Oser, 1960), and female and male Osborne Mendel rats (Radomski et al. 1965; Deichmann et al., 1967). The studies in mice were performed at relatively high dose levels (approximately 150 mg/kg-day); only one strain/sex showed significant increases in liver tumors. The studies in Osborne Mendel rats were performed at relatively low doses (10 mg/kg-day or less) and were apparently not of sufficient sensitivity to detect an effect. Three multiple dose studies in CFN, FDRL "stock", and Wistar FDRL rats showed significant increases in liver tumors. Of these three strains, the FDRL "stock" was the least sensitive. An additional study in Sprague-Dawley rats (Popper et al., 1960) performed at the same dose levels as the studies in CFN and Wistar FDRL rats reported no increases in liver tumors. The data summarized here suggest that there are significant sensitivity differences between the various strains and species. Cancer potency is taken as the geometric mean of potencies derived from the multiple dose studies in CFN, FDRL "stock" and Wistar FDRL rats which showed significant increases in liver tumors (Popper et al., 1960; Oser and Oser, 1960).

Innes JRM (1968). *Evaluation of carcinogenic, teratogenic, and mutagenic activities of selected pesticides and industrial chemicals.* Volume 1: Carcinogenic study.

Bionetics Research Laboratories, Inc. Distributed by National Technical Information Service, Springfield, VA.

Innes JRM, Ulland BM, Valerio MG, Petrucelli L, Fishbein L, Hart ER, Pallota AJ, Bates RR, Falk HL, Gart JJ, Klein M, Mitchell I and Peters J (1969). Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: a preliminary note. *J. Nat. Cancer Inst.* 42:1101-1114.

Popper H, Sternberg SS, Oser BL and Oser M (1960). The carcinogenic effect of aramite in rats. A study of hepatic nodules. *Cancer* 13:1035-1046.

Oser BL and Oser M (1960). 2-(p-Tert-butylphenoxy) isopropyl 2-chloroethyl sulfite (aramite). 1. Acute, subacute, and chronic oral toxicity. *Toxicol. Appl. Pharmacol.* 2:441-457.

Deichmann WB, Keplinger M, Sala F and Glass E (1967). Synergism among oral carcinogens: IV. The simultaneous feeding of four tumorigens to rats. *Toxicol. Appl. Pharmacol.* 11:88-103.

Radomski JL, Deichmann WB, Macdonald WE and Glass EM (1965). Synergism among oral carcinogens: I. Results of the simultaneous feeding of four tumorigens to rats. *Toxicol. Appl. Pharmacol.* 7:652-656.

Auramine

Cancer Potency: 0.88 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.8 $\mu g/day$

Gold et al. provide data from the study by Williams and Bonser (1962) who administered auramine in feed to male and female albino and CBA mice and male Wilmslow Wistar rats. The study authors reported increases in hepatomas for all strains and sexes tested. The rat was the more sensitive of the two species. Potency is based on the dose response data for the male rat.

Williams MHC and Bonser GM (1962). Induction of hepatomas in rats and mice following the administration of auramine. *Br. J. Cancer* 16: 87-91.

Azaserine

Cancer Potency: 11 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.06 $\mu g/day$

Two studies in Wistar rats are reported. In a moderately sized study Longnecker et al. (1981) treated 34 Wistar rats (both sexes) with azaserine by intraperitoneal injection; 76 rats served as controls. In a second study (McGuinness et al., 1983), also by intraperitoneal injection, only 5 animals were treated with the compound. None of the 5 treated animals in the small study developed tumors, whereas approximately 20% of the animals in the larger study developed pancreatic carcinomas. Cancer potency is based on the Longnecker et al. (1981) study.

Longnecker DS, Roebuck BD, Yager JD, Lilja HS and Siegmund B (1981). Pancreatic carcinoma in azaserine-treated rats: induction, classification and dietary modulation of incidence. *Cancer* 47: 1562-1572.

McGuinness EE, Hopwood D and Wormsley KG (1983). Potentiation of pancreatic carcinogenesis in the rat by DL-ethionine-induced pancreatitis. *Scand. J. Gastroenterol.* 18: 189-192.

Azathioprine

Cancer Potency: 1.8 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.4 $\mu g/day$

IARC (1987) determined that human data provide sufficient evidence for the carcinogenicity of azathioprine, based on findings of non-Hodgkin's lymphoma, squamous cell cancers of the skin, hepatobiliary carcinomas and mesenchymal tumors in patients treated with this drug. Animal data is limited. The only study listed in Gold et al. showed an increase of squamous cell carcinomas of the ear duct in female Fischer 344 rats (Frankel et al., 1970). The incidence was not significantly increased above controls (3 of 25 treated animals developed tumors, in contrast to 0 of 12 control animals), but these tumors are rare in this strain of rat (J Haseman, personal communication, 1991). Until such time as a more detailed risk assessment can be performed, we recommend that the potency value derived from the animal data be used.

International Agency for Research on Cancer (IARC, 1987). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42. Supplement 7. IARC, Lyon, France.

Frankel HH, Yamamoto RS, Weisburger EK and Weisburger JH (1970). Chronic toxicity of azathioprine and the effect of this immunosuppressant on liver tumor induction by the carcinogen N-hydroxy-N-2-fluorenylacetamide. *Toxicol. Appl. Pharmacol.* 17: 462-480.

Benzyl Violet 4B (FD & C Violet No. 1)

Cancer Potency: 0.020 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 30 $\mu g/day$

Listed are feeding studies in male and female ASH-CS1 mice and albino Sprague-Dawley rats and female Sprague-Dawley rats. Tumors were not observed to increase in the studies in the mice, but dose rates used were significantly below those used in the rat studies. The studies in rats only lasted one year. Even so elevated incidences of mammary gland tumors were seen in females in both studies, at roughly the same incidence levels. In the Uematsu and Miyaji (1973) study, the incidences did not achieve statistical significance but group sizes were small (10 animals in the control group; 16 in the treatment group). The potency is based on dose response data for mammary gland carcinomas in the larger study by Ikeda et al. (1974); incidences in treated rats in this study were significantly greater than controls ($p < 0.005$).

Uematsu K and Miyaji T (1973). Induction of tumors in rats by oral administration of technical acid violet 6B. *J. Nat. Cancer Inst.* 51: 1337-1338.

Ikeda Y, Horiuchi S, Imoto A, Kodama Y, Aida Y and Kobayashi K (1974). Induction of mammary gland and skin tumours in female rates by the feeding of benzyl violet 4B. *Toxicology* 2: 275-284.

beta-Butyrolactone

Cancer Potency: 1.0 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.7 $\mu g/day$

beta-Butyrolactone is carcinogenic in mice by skin application and by subcutaneous injection, and in rats by oral administration and by subcutaneous injection (IARC, 1976). The gavage study by Van Duuren et al. (1966) showing increased incidences of squamous cell carcinomas of the forestomach in female Eastern Sprague-Dawley rats is the only one listed in Gold et al. Group sizes were small -- only 5 animals in the control and treatment groups. However 3 of the 5 (i.e., 60%) in the treatment group developed forestomach carcinomas, which are rare in untreated Sprague-Dawley rats. Potency is therefore estimated from the dose response data on the forestomach carcinomas.

International Agency for Research on Cancer (IARC, 1976). *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man.* Cadmium, nickel, some epoxides, miscellaneous industrial chemicals and general considerations on volatile anaesthetics. Volume 11. IARC, Lyon, France.

Van Duuren BL, Langseth L, Orris L, Teebor G, Nelson N and Kuschner M (1966). Carcinogenicity of epoxides, lactones, and peroxy compounds. IV. Tumor response in epithelial and connective tissue in mice and rats. *J. Nat. Cancer Inst.* 37: 825-838.

Captafol

Cancer Potency: 0.15 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 5 $\mu g/day$

The results from the feeding study in male and female $B6C3F_1$ mice by Ito et al. (1984) are given. Tumors were observed at multiple sites, with the most sensitive sites being the liver in females and the small intestine in males. Cancer potency is based on the dose response data for liver tumors in females, the more sensitive sex.

Ito N, Ogiso T, Fukushima S, Shibata M and Hagiwara A (1984). Carcinogenicity of captafol in $B6C3F_1$ mice. *Gann* 75:853-865.

Captan

Cancer Potency: 0.0023 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 300 $\mu g/day$

Gold et al. list results from the NCI (1977) feeding study in both sexes of $B6C3F_1$ mice and from the Innes (1968) and Innes et al. (1969) experiments in the same species and strain. The results from the NCI (1977) feeding study in Osborne Mendel rats are also given. In addition, results of borderline statistical significance were seen in the Innes (1968) and Innes et al. (1969) studies in mice and the NCI (1977) study in rats. According to the coding of Gold et al., study authors characterized these as negative findings. The NCI study in mice was run at considerably higher dose levels and resulted in increases in adenocarcinomas and adenomatous polyps of the duodenum in both sexes. Cancer potency is based on the males, since they are slightly more sensitive than females. An additional study not in the Gold et al. database indicated a higher carcinogenic potency for captan based on induction of adenocarcinomas and adematous polyps of the duodenum in Swiss CD-1 mice (Chevron, 1981). This study will be considered in the development of a revised potency estimate for captan.

Chevron Environmental Health Center (Chevron, 1981). *Lifetime oncogenic feeding study of captan technical (SX-944) in CD-1 mice (ICR derived).* Report no. SOCAL 1150.

Innes JRM (1968). *Evaluation of carcinogenic, teratogenic, and mutagenic activities of selected pesticides and industrial chemicals.* Volume 1: Carcinogenic study. Bionetics Research Laboratories, Inc. Distributed by National Technical Information Service, Springfield, VA.

Innes JRM, Ulland BM, Valerio MG, Petrucelli L, Fishbein L, Hart ER, Pallota AJ, Bates RR, Falk HL, Gart JJ, Klein M, Mitchell I and Peters J (1969). Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: a preliminary note. *J. Nat. Cancer Inst.* 42:1101-1114.

National Cancer Institute (NCI, 1977). *Bioassay of Captan for Possible Carcinogenicity.* Carcinogenesis Technical Report Series, Technical Report No. 15. US Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

Chlorambucil

Cancer Potency: 440 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.002 $\mu g/day$

IARC (1987) found the evidence of carcinogenicity in humans sufficient for chlorambucil based on the occurrence of acute nonlymphocytic leukemia in patients receiving the drug. A variety of cancers have been observed in experimental studies in animals. Gold et al. list results from studies by Skipper (1976), Weisburger (1977) and Berger et al. (1986) in Swiss mice and Charles River and Sprague-Dawley rats. Mice appear to be more sensitive. In cancer potency evaluation, the results in the more sensitive sex, site and species are used -- lung tumors in female Swiss mice administered chlorambucil by intraperitoneal injection (Weisburger, 1977).

International Agency for Research on Cancer (IARC, 1987). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans.* Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42. Supplement 7. IARC, Lyon, France.

Berger MR, Petru E, Habs M and Schmahl D (1986). Long-term toxicology effects of prednimustine in comparison with chlorambucil, prednisolone, and chlorambucil plus prednisolone in Sprague-Dawley rats. *Seminars in Oncol.* 13: 8-13.

Skipper HE (1976). *Booklet 1, Phase I Studies on the Carcinogenic Activity of Anticancer Drugs in Mice and Rats.* Final report. Southern Research Institute, Birmingham, AL.

Weisburger EK (1977). Bioassay program for carcinogenic hazards of cancer chemotherapeutic agents. *Cancer* 40: 1935-1949.

Chlordecone (Kepone)

Cancer Potency: 16 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.04 $\mu g/day$

Results from the NCI (1976) study on male and female B6C3F$_1$ mice and Osborne Mendel rats and an additional study of low power in Sprague-Dawley rats are listed. Mice appear to be more sensitive than rats; the NCI (1976) rat study is not as powerful as the mouse study however. Liver tumors were significantly increased in both male and female treated mice. Cancer potency is based on the increased incidence of benign and malignant liver tumors in male mice, the more sensitive sex.

National Cancer Institute (NCI, 1976). *Report on the Carcinogenesis Bioassay of Kepone*. NTIS Publication No. PB 264018. US Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

Chlorendic acid

Cancer Potency: 0.091 (mg/kg-day)$^{-1}$
10^{-5} Risk Specific Intake: 8 μg/day

Results of the NTP (1987) feeding study in male and female B6C3F$_1$ mice and F344 rats are listed. Benign and malignant liver tumors were observed in both sexes and species; lung tumors were increased in treated male rats and mice. Cancer potency is based on the most sensitive species, sex and site: male rat liver (benign and malignant tumors).

National Toxicology Program (NTP, 1987). *Toxicology and Carcinogenesis Studies of Chlorendic Acid in F344 Rats and B6C3F$_1$ Mice (Feed Studies)*. NTP Technical Report Series No. 304. NIH Publication No. 87-2560. US Department of Health and Human Services, NTP, Research Triangle Park, NC.

Chlorinated paraffins (Average chain length, C12)

Cancer Potency: 0.089 (mg/kg-day)$^{-1}$
10^{-5} Risk Specific Intake: 8 μg/day

Results of the NTP (1986) gavage study in male and female B6C3F$_1$ mice and F344 rats are listed. Benign and malignant liver tumors were observed in both sexes and species; significant elevations in tumor incidences at other sites were also observed. Estimates of cancer potency are similar for male and female mice and male rats. Cancer potency is based on dose response data for benign and malignant liver tumors in female mice.

National Toxicology Program (NTP, 1986). *Toxicology and Carcinogenesis Studies of Chlorinated Paraffins (C12, 60% Chlorine) in F344/N Rats and B6C3F$_1$ Mice (Gavage Studies)*. NTP Technical Report Series No. 308. US Department of Health and Human Services, NTP, Research Triangle Park, NC.

Chlorodibromomethane

Cancer Potency: 0.094 (mg/kg-day)$^{-1}$
10^{-5} Risk Specific Intake: 7 μg/day

Results of the NTP (1985) gavage study in male and female B6C3F$_1$ mice and Fischer 344 rats are listed. According to the NTP, the study in rats provided no evidence of carcinogenic activity, the results in the male mice were equivocal, and the study in the female mice provided some evidence of carcinogenic activity. For this reason, data from the female mice is used for potency estimation. The most sensitive site is the liver.

National Toxicology Program (NTP, 1985). *Toxicology and Carcinogenesis Studies of Chlorodibromomethane in F344/N Rats and B6C3F$_1$ Mice (Gavage Studies).* NTP Technical Report Series No. 282. NIH Publication No. 85-2538. US Department of Health and Human Services, NTP, Research Triangle Park, NC.

Chloromethyl methyl ether (technical grade)

Cancer Potency: 2.4 (mg/kg-day)$^{-1}$
10^{-5} Risk Specific Intake: 0.3 μg/day

IARC (1987) notes that "numerous epidemiological studies and case reports from around the world have demonstrated that workers exposed to chloromethyl methyl ether and/or bis(chloromethyl)-ether have an increased risk for lung cancer." The bioassay cited in Gold et al. is the inhalation study by Laskin et al. (1975) on male Syrian Golden hamsters and Sprague-Dawley rats. Gold et al. report incidences for mixtures of unspecified tumor types. IARC (1987) notes for this same study that "in rats and hamsters, it produced a low incidence of tumors of the respiratory tract..." Further details on the tumors seen are given in DHHS (1983): Of 74 Sprague-Dawley rats treated by Laskin et al. (1975), 1 developed a squamous cell carcinoma of the lung, another developed a epithelial esthesioneuroepiloma; neither of these were seen in untreated control rats. The DHHS report also notes that exposed rats had approximately double the incidence of bronchial hyperplasia compared to the control animals. Among the 90 Syrian Golden hamsters, one developed an adenocarcinoma, and another a tracheal squamous cell papilloma; neither of these tumor types were seen in 88 untreated hamsters. Although the incidences are low, the findings are significant because 1) respiratory tumors are seen in man, 2) similar tumors were observed in an inhalation study of bis(chloromethyl)ether, which also produces respiratory cancers in man (nasal esthesioneuroepitheliomas and respiratory tumors seen in exposed Sprague-Dawley rats), and 3) these tumor types are rare in these strains. The more sensitive of the two species appears to be the rat; thus, potency is based on the results of the rat study.

International Agency for Research on Cancer (IARC, 1987). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans.* Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42. Supplement 7. IARC, Lyon, France.

Laskin S, Drew RT, Cappiello V, Kuschner M, and Nelson N (1975). Inhalation carcinogenicity of alpha halo ethers. II. Chronic inhalation studies with chloromethyl methyl ether. *Arch. Environ. Health* 30: 70-72.

US Department of Health and Human Services, National Institutes of Health/National Cancer Institute (DHHS, 1983). *Survey of compounds which have been tested for carcinogenic activity.* NIH Publication No. 83-2607.

3-Chloro-2-methylpropene

Cancer Potency: 0.14 (mg/kg-day)$^{-1}$
10^{-5} Risk Specific Intake: 5 μg/day

Results of the NTP (1986) gavage study in male and female B6C3F$_1$ mice and Fischer 344 rats are listed. Increased incidences of forestomach tumors were observed in treated mice and rats of both sexes. Mice are more sensitive than rats, and males appear to be the more sensitive sex. Cancer potency is based on dose response data for the combined incidence of benign and malignant forestomach tumors in male mice.

National Toxicology Program (NTP, 1986). *Toxicology and Carcinogenesis Studies of 3-Chloro-2-methylpropene in F344/N Rats and B6C3F$_1$ Mice (Gavage Studies).* NTP Technical Report Series No. 300. NIH Publication No. 86-2556. US Department of Health and Human Services, NTP, Research Triangle Park, NC.

4-Chloro-ortho-phenylenediamine

Cancer Potency: 0.016 (mg/kg-day)$^{-1}$
10^{-5} Risk Specific Intake: 40 μg/day

Results of the NCI (1978) feeding study in male and female B6C3F$_1$ mice and Fischer 344 rats are listed. Benign and malignant neoplasms of the liver were elevated in treated male and female mice. Liver and stomach tumors were also observed in treated rats; these tumors are relatively uncommon in this strain. In addition, substantial increases in the incidences of urinary bladder cancers were seen in rats of both sexes. Rats appear to be more sensitive than mice. Quantitative analysis of dose response data for urinary bladder tumors indicate that male and female rats have nearly the same sensitivity. The upper confidence bound on potency for data on male rats is slightly higher, and this is the value recommended for 4-chloro-*ortho*-phenylenediamine.

National Cancer Institute (NCI, 1978). *Bioassay of 4-Chloro-o-Phenylenediamine for Possible Carcinogenicity.* Carcinogenesis Technical Report Series No. 63. US Department of Health, Education and Welfare , NCI Carcinogenesis Testing Program, Bethesday, MD.

Chlorothalonil

Cancer Potency: 0.0031 (mg/kg-day)$^{-1}$
10^{-5} Risk Specific Intake: 200 μg/day

Gold et al. list the results of the NCI (1978) feeding study in male and female Osborne Mendel rats and B6C3F$_1$ mice. NTP (1991) characterized the study in mice as negative. Increases in benign and malignant kidney tumors were seen in both sexes of rats. Cancer potency estimates are similar for male and female rat kidney tumors, with the value for the males slightly higher. This is the value recommended for chlorothalonil.

National Cancer Institute (1978). *Bioassay of Chlorothalonil for Possible Carcinogenicity.* Carcinogenesis Technical Report Series No. 41. US Department of Health, Education and Welfare Publication No. (NIH) 79-1716. NCI Carcinogenesis Testing Program, Bethesda, MD.

National Toxicology Program (NTP, 1991). *Chemical Status Report.* US Department of Health and Human Services, NTP, Research Triangle Park, NC.

p-Chloro-o-toluidine (4-chloro-o-toluidine)

Cancer Potency: 0.27 (mg/kg-day)$^{-1}$
10^{-5} Risk Specific Intake: 3 μg/day

On the basis of positive bioassay results, the hydrochloride salt of 4-chloro-*o*-toluidine was classified as a compound with sufficient evidence of carcinogenicity in animals by IARC (1987). Cancer potency for p-chloro-o-toluidine is based on the bioassay results for the hydrochloride, adjusted for differences in molecular weight. Results of multiple studies on 4-chloro-*o*-toluidine hydrochloride are reported in Gold et al. The NCI (1979) performed

feeding studies in male and female $B6C3F_1$ mice and Fischer 344 rats. In addition, Weisburger et al. (1978) performed 2 feeding studies in each sex of CD-1 HaM/ICR mice and a single study in male Charles River CD rats. Rats appear to be less sensitive than the mice. Vascular tumors in mice were induced in treated mice of both strains and sexes. Cancer potency is estimated by taking the geometric mean of the 4 potencies derived from dose response data for vascular tumors from each of the 4 studies in mice (1 in male CD-1, 1 in female CD-1, and one in each sex of $B6C3F_1$ mice). Survival was poor for the NCI study in male $B6C3F_1$ mice. Potency for that study was therefore derived using a time-to-tumor analysis (Crump et al., 1991).

Crump KS, Howe RB, Van Landingham C, and Fuller WG (1991). **TOX_RISK** Version 3. **TOX**icology **RISK** Assessment Program. KS Crump Division, Clement International Corporation, 1201 Gaines Street, Ruston, Louisiana 71270.

International Agency for Research on Cancer (IARC, 1987). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42. Supplement 7. IARC, Lyon, France.

National Cancer Institute (NCI, 1979). *Bioassay of 4-Chloro-o-Toluidine Hydrochloride for Possible Carcinogenicity*. Carcinogenesis Technical Report Series No. 165. US Department of Health, Education and Welfare Publication No. (NIH) 79-1716. NCI Carcinogenesis Testing Program, Bethesda, MD.

Weisburger EK, Russfield AB, Homburger F, Weisburger JH, Roger E, Van Dongen CG and Chu K (1978). Testing of twenty-one aromatic amines or derivatives for long-term toxicity or carcinogenicity. *J. Environ. Pathol. Toxicol.* 2: 325-356.

Chlorozotocin

Cancer Potency: $240\ (mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: $0.003\ \mu g/day$

The only studies listed by Gold et al. were those by Habs et al. (1979) who administered chlorozotocin to male and female Sprague-Dawley rats by intraperitoneal injection. Both male and female rats had significant increases in tumors of the peritoneal cavity. Cancer potency is based on the dose response data for these tumors in male rats, the more sensitive sex.

Habs M, Eisenbrand G, and Schmahl D (1979). Carcinogenic activity in Sprague-Dawley rats of 2[3-(2-chloroethyl)-3-nitrosoureido]-D-glucopyranose (chlorozotocin). *Cancer Lett.* 8: 133-137.

CI Basic Red 9 Monohydrochloride (p-rosaniline hydrochloride)

Cancer Potency: $0.25\ (mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: $3\ \mu g/day$

Data are available for male and female Syrian Golden hamsters (gavage), $B6C3F_1$ mice (feed), Fischer 344 rats (feed) and Sprague-Dawley rats (gavage). According to the tabulation of Gold et al., results from the gavage studies in hamsters and Sprague-Dawley rats were negative. Results from the NTP (1986) feeding studies in $B6C3F_1$ mice and F344 rats were positive, with tumors seen at numerous sites. Male and female F344 rats and female mice seem to be equally sensitive. The upper bound estimate of potency derived from data in the

female mouse (on benign and malignant liver tumors) is slightly higher than for the sensitive rat strain, and is recommended for estimation of cancer risk in humans.

National Toxicology Program (NTP, 1986). *Toxicology and Carcinogenesis Studies of C.I. Basic Red 9 Monohydrochloride in F344/N Rats and B6C3F$_1$ Mice (Feed Studies).* NTP Technical Report Series No. 196. NIH Publication No. 86-2541. US Department of Health and Human Services, NTP, Research Triangle Park, NC.

Cinnamyl anthranilate

Cancer Potency: 0.0046 (mg/kg-day)$^{-1}$
10^{-5} Risk Specific Intake: 200 μg/day

Results of the NCI (1980) feeding study in male and female B6C3F$_1$ mice and Fischer 344 rats are listed. Adenomas and adenocarcinomas were induced in male Fischer rats, and benign and malignant liver tumors were observed in mice of both sexes. Mice were more sensitive than the rat. Potencies derived from liver tumor data in male and female mice were similar, with the upper confidence bound on the female slightly higher than for the male. Cancer potency derived from the female mice data is selected here.

National Cancer Institute (NCI, 1979). *Bioassay of Cinnamyl Anthranilate for Possible Carcinogenicity*. Carcinogenesis Technical Report Series No. 196. NTIS No. PB 295835. US Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

para-Cresidine

Cancer Potency: 0.15 (mg/kg-day)$^{-1}$
10^{-5} Risk Specific Intake: 5 μg/day

Results of the NCI (1979) feeding study in male and female B6C3F$_1$ mice and Fischer 344 rats are listed. Urinary bladder tumors as well as tumors at other sites were observed in mice and rats of both sexes. The most sensitive site appears to be the urinary bladder. Both sexes of both species show similar sensitivities at this site. The potency derived from dose response data on female mice (benign and malignant urinary bladder tumors) is slightly greater than for the other groups and is taken as the best estimate here. Because survival was poor for the study in female mice, the potency was derived using a time-to-tumor analysis (Crump et al., 1991).

Crump KS, Howe RB, Van Landingham C, and Fuller WG (1991). **TOX_RISK** Version 3. **TOX**icology **RISK** Assessment Program. KS Crump Division, Clement International Corporation, 1201 Gaines Street, Ruston, Louisiana 71270.

National Cancer Institute (NCI, 1979). *Bioassay of p-Cresidine for Possible Carcinogenicity*. Carcinogenesis Technical Report Series No. 142. NTIS No. PB 295835. US Department of Health, Education and Welfare (DHEW), NCI Carcinogenesis Testing Program, Bethesda, MD.

Cupferron

Cancer Potency: 0.22 (mg/kg-day)$^{-1}$
10^{-5} Risk Specific Intake: 3 μg/day

Results of the NCI (1978) feeding study in male and female $B6C3F_1$ mice and Fischer 344 rats are listed. Benign and malignant vascular tumors as well as tumors at other sites were observed in mice and rats of both sexes. Cancer potency is based on the data for vascular tumors in the male rat because the rat is the more sensitive of the species tested, and the male appears to be slightly more sensitive than the female.

National Cancer Institute (NCI, 1978). *Bioassay of Cupferron for Possible Carcinogenicity*. Carcinogenesis Technical Report Series No. 100. NTIS Publication No. PB 287409. US Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

Cyclophosphamide (anhydrous)

Cancer Potency: $0.61\ (mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: $1\ \mu g/day$

The potency for the anhydrous form of cyclophosphamide was derived from the potency for the hydrate using a molecular weight conversion (see glossary to Appendix 1 for explanation).

Cyclophosphamide (hydrated)

Cancer Potency: $0.57\ (mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: $1\ \mu g/day$

Dose response data for the multiple dose study of Schmahl and Habs (1979) in Sprague-Dawley rats of both sexes provides the best dose response data and is fairly consistent with the data for the other listed studies in mice and rats. Cancer potency is based on transitional cell carcinomas of the urinary bladder in rats.

Schmahl D and Habs M (1979). Carcinogenic action of low-dose cyclophosphamide given orally to Sprague-Dawley rats in a lifetime experiment. *Int. J. Cancer* 23: 706-712.

D & C Red 9

Cancer Potency: $0.0053\ (mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: $100\ \mu g/day$

NTP (1982) performed a feed study in male F344 rats and found significant increases in tumors of the spleen (sarcomas, fibrosarcomas, leiomyosarcomas, osteosarcomas). Because this is the only study listed in Gold et al. which showed significant increases in tumors, it is selected as the basis of the cancer potency.

National Toxicology Program (NTP, 1982). *Toxicology and Carcinogenesis Studies of D & C Red 9 in F344/N Rats and $B6C3F_1$ Mice (Feed Study)*. NTP Technical Report Series No. 225. NIH Publication No. 82-1781. US Department of Health and Human Services, NTP, Research Triangle Park, NC.

Dacarbazine

Cancer Potency: $49\ (mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: $0.01\ \mu g/day$

Gold et al. list studies in male and female Swiss mice (intraperitoneal injection) and Sprague-Dawley female rats (feed). Neither study used the route of exposure most relevant to humans (i.v. injection). The study in the female Swiss mice (Weisburger, 1977; Skipper, 1976) which showed increases in lung tumors was chosen because the potency estimate produced was the highest.

Skipper HE (1976). *Booklet 1, Phase I Studies on the Carcinogenic Activity of Anticancer Drugs in Mice and Rats.* Final Report. Southern Research Institute, Birmingham, AL.

Weisburger EK (1977). Bioassay program for carcinogenic hazards of cancer chemotherapeutic agents. *Cancer* 40: 1935-1949.

Daminozide

Cancer Potency: $0.018\ (mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 40 μg/day

In the study by NCI (1978) in male and female $B6C3F_1$ mice and F344 rats, NCI reported that adenocarcinomas of the endometrium and leiomyosarcomas of the uterus in female F344 rats were induced by daminozide, and that daminozide may have induced hepatocellular carcinomas in male mice. Because the results of the NCI mice study are equivocal, they do not serve as the basis of the potency calculation. An additional study by Toth et al. (1977) showed a clear increase in tumors of the vasculature in both male and female Swiss albino mice. This study serves as the basis of the potency calculation given here because it is consistent quantitatively with the finding in the NCI study in female rats, and because there is a strong increase in tumor incidence with daminozide exposure. The potency estimate for male mice is slightly greater than for the female mice and so is selected here. However, the confidence bounds on the two estimates overlap, so this difference in potencies between the two sexes may be an artifact of the sensitivity of the study.

National Cancer Institute (NCI, 1978). *Bioassay of Daminozide for Possible Carcinogenicity.* Carcinogenesis Technical Report Series No. 83. NTIS Publication No. PB 285073. US Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

Toth B, Wallcave L, Patil K, Schmeltz I and Hoffman D (1977). Induction of tumors in mice with the herbicide succinic acid 2,2-dimethylhydrazide. *Cancer Res.* 37: 3497-3500.

Dantron

Cancer Potency: $0.076\ (mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 9 μg/day

Gold et al. list the results of two feeding studies by Mori et al. (1985, 1986) in male ACI rats and male C3H/HeN mice. Dantron produced significant increases of hepatocellular carcinomas in male mice and adenomas/adenocarcinomas of the large intestine in male rats. The cancer potency derived from the study in mice is slightly larger than that derived from the study in rats. On this basis, the mouse is identified as the more sensitive species for potency derivation.

Mori H, Sugie S, Niwa K, Takahashi M, and Kawai K (1985). Induction of intestinal tumours in rats by chrysazin. *Br. J. Cancer.* 52: 781-783.

Mori H, Sugie, S, Niwa K, Yoshimi N, Tanaka T, and Hirono (1986). Carcinogenicity of chrysazin in large intestine and liver of mice. *Jpn. J. Cancer Res.* 77: 871-876.

2,4-Diaminoanisole

Cancer Potency: 0.023 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 30 $\mu g/day$

Cancer potency was derived from that for the sulfate using a molecular weight conversion (see below and glossary to Appendix 1 for explanation).

2,4-Diaminoanisole sulfate

Cancer Potency: 0.013 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 50 $\mu g/day$

Gold et al. list the results of the NCI (1978) feeding studies in male and female F344 rats and $B6C3F_1$ mice, and the feeding study by Evarts and Brown (1980) in female F344 rats. Cancer potency is based on dose response data for benign and malignant thyroid tumors in male rats, the most sensitive sex and species.

National Cancer Institute (NCI, 1978). *Bioassay of Dapsone for Possible Carcinogenicity.* Carcinogenesis Technical Report Series No. 20. NTIS Publication No. PB 279940. US Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

Evarts RP and Brown CA (1980). 2,4-Diaminozide sulfate: early effect on thyroid gland morphology and late effect on glandular tissue of Fischer 344 rats. *J. Nat. Cancer Inst.* 65: 197-204.

4,4'Diaminodiphenyl ether (4,4'-oxydianiline)

Cancer Potency: 0.14 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 5 $\mu g/day$

Gold et al. list the results of the NCI (1980) feeding studies in male and female $B6C3F_1$ mice and F344 rats. Liver tumors were observed in both sexes and both species; thyroid tumors were also observed in some of these studies. Cancer potency is based on dose response data for benign and malignant liver tumors in male rats, the most sensitive sex and species.

National Cancer Institute (NCI, 1980). *Bioassay of 4,4'-Oxydianiline for Possible Carcinogenicity.* Carcinogenesis Technical Report Series No. 205. NIH Publication No. 80-1761. US Department of Health and Human Services, NCI Carcinogenesis Testing Program, and National Toxicology Program.

2,4-Diaminotoluene

Cancer Potency: 3.8 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.2 $\mu g/day$

Gold et al. list the results of the NCI (1978) feeding studies in male and female $B6C3F_1$ mice and F344 rats. Significant increases in tumors were seen in rats of both sexes and in female mice. The study results indicate that rats are more sensitive than mice. The female rat

appears to be slightly more sensitive than the male, although the study is not sensitive enough to definitively distinguish between the two. Cancer potency is based on mammary gland tumors in the female rat. Because survival was poor for the study in female rats, the potency was derived using a time-to-tumor analysis (Crump et al., 1991).

Crump KS, Howe RB, Van Landingham C, and Fuller WG (1991). **TOX_RISK** Version 3. **TOX**icology **RISK** Assessment Program. KS Crump Division, Clement International Corporation, 1201 Gaines Street, Ruston, Louisiana 71270.

National Cancer Institute (NCI, 1978). *Bioassay of 2,4-Diaminotoluene for Possible Carcinogenicity*. Carcinogenesis Technical Report Series No. 162. NTIS Publication No. PB 293593. US Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

Dibenz[a,h]anthracene

Cancer Potency:	4.1 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake:	0.2 $\mu g/day$

Cancer potency is derived from the only dose response data set available -- a drinking water study which reported alveolar carcinomas of the lung in male DBA/2 mice (Snell et al. 1962).

Snell KC and Stewart HL (1962). Pulmonary adenomatosis induced in DBA/2 mice by oral administration of dibenz[a,h]anthracene. *J. Nat. Cancer Inst.* 28: 1043-1051.

1,1-Dichloroethane

Cancer Potency:	0.0057 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake:	100 $\mu g/day$

Gold et al. list the results of the NCI (1977) gavage studies in male and female $B6C3F_1$ mice and Osborne Mendel rats. Cancer potency is based on mammary gland adenocarcinomas observed in female rats, the most sensitive of the species/sex combinations tested. Because survival was poor for the study in female rats, the potency was derived using a time-to-tumor analysis (Crump et al., 1991).

Crump KS, Howe RB, Van Landingham C, and Fuller WG (1991). **TOX_RISK** Version 3. **TOX**icology **RISK** Assessment Program. KS Crump Division, Clement International Corporation, 1201 Gaines Street, Ruston, Louisiana 71270.

National Cancer Institute (NCI, 1977). *Bioassay of 1,1-Dichloroethane for Possible Carcinogenicity*. Carcinogenesis Technical Report Series No. 66. NTIS Publication No. PB 283345. US Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

Diethylstilbestrol (DES)

Cancer Potency:	350 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake:	0.002 $\mu g/day$

DES is a known human carcinogen, causing clear cell adenocarcinoma of the vagina and cervix in women exposed *in utero*, testicular cancer in males exposed *in utero*, and breast cancer in women exposed to DES during pregnancy. Cases of primary breast cancer and other cancers have been reported in males treated with DES for prostatic cancer. The Gold et al.

database does not include information on *in utero* risks. Gold et al. report on a number of studies in mice and rats. The studies in rats are relative insensitive due to small numbers of animals. Mouse studies varied in quality with the most sensitive performed by Okey et al. (1964), Gass et al. (1964), Gass and Allaben (1977) in male C3H/AnCum and female C3H mice. Cancer potency is estimated by taking the geometric mean of potencies derived from these studies.

Okey AB and Gass GH (1968). Continuous versus cyclic estrogen administration: mammary carcinoma in C3H mice. *J. Nat Cancer Inst* 40: 225-230.

Gass GH, Coats D and Graham N (1964). Carcinogenic dose-response curve to oral diethylstilbestrol. *J. Nat. Cancer Inst.* 33: 971-977.

Gass GH and Allaben WT (1977). Preliminary report on the carcinogenic dose-response curve to oral vitamin D2. *IRCS Med. Sci.: Libr. Compend.* 5: 477.

Diglycidyl resorcinol ether

Cancer Potency:	1.7 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake:	0.4 $\mu g/day$

Gold et al. list the results of the gavage studies performed by NTP in male and female $B6C3F_1$ mice and F344 rats. Rats appear to be the more sensitive species. NTP performed two studies in each sex of rats (average dose of 8.49 mg/kg-day given in Gold et al.). The first used doses of 25 and 50 mg/kg-day (average doses of 17.7 and 35.7 mg/kg-day given in Gold et al.), and in the second 12 mg/kg-day was administered. Because survival was significantly compromised in the studies at higher doses, we rely on the results from the low dose studies. Based on the results from the low dose studies, male rats were slightly more sensitive than females. Cancer potency is based on forestomach tumors observed in low dose male rat study.

National Toxicology Program (NTP, 1986). *Toxicology and Carcinogenesis Studies of Diglycidyl Resorcinol Ether in F344/N Rats and $B6C3F_1$ Mice (Gavage Studies).* NTP Technical Report Series No. 257. NIH Publication No. 87-2513. US Department of Health and Human Services, NTP, Research Triangle Park, NC.

Dihydrosafrole

Cancer Potency:	0.044 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake:	20 $\mu g/day$

Gold et al. list studies for $B6AKF_1$ and $B6C3F_1$ mice and Osborne Mendel rats. Tumors were observed at multiple sites in the mice and in the esophagus of rats. Based on dose response analyses of these data, the rats appear to be more sensitive. Cancer potency is calculated from dose response data for esophageal tumors in Osborne Mendel rats (Hagan et al., 1965).

Hagan EC, Jenner PM, Jones WI, Fitzhugh OG, Long EL, Brouwer JG and Webb WK (1965). Toxic properties of compounds related to safrole. *Toxicol. Appl. Pharmacol.* 7: 18-24.

4-Dimethylaminoazobenzene

Cancer Potency:	4.6 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake:	0.2 $\mu g/day$

The feed study by Kirby and Peacock (1947) on female Wistar albino rats is the only one listed in Gold et al. Cancer potency is based on liver tumors in these animals.

Kirby AHM and Peacock PR (1947). The induction of liver tumors by 4-aminoazobenzene and its N:N-dimethyl derivative in rats on a restricted diet. *J. Pathol.* 59: 1-18.

trans-2[(Dimethylamino)methylimino]-5-[2-(5-nitro-2-furyl)vinyl] -1,3,4-oxadiazole

Cancer Potency: 0.44 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 2 $\mu g/day$

The only study listed in the Gold et al. database is the feeding study by Cohen et al. (1975) in female Sprague-Dawley rats. Cancer potency is based on dose response data for the most sensitive site, mammary gland adenocarcinomas.

Cohen SM, Erturk E, Von Esch AM, Crovetti AJ and Bryan GT (1975). Carcinogenicity of 5-nitrofurans and related compounds with amino-heterocyclic substituents. *J. Nat. Cancer Inst.* 54: 841-850.

7,12-Dimethylbenzanthracene

Cancer Potency: 250 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.003 $\mu g/day$

The only study listed in the Gold et al. database is the feeding study by Chouroulinkov et al. (1967) in female albino mice. Significant increases in malignant angioendotheliomas of the mesenteric intestine and forestomach papillomas were observed in animals treated with 0.39 mg/kg-day. Cancer potency is based on the angioendotheliomas of the mesenteric intestine.

Chouroulinkov I, Gentil A and Guerin M (1967). Etude de l'activite carcinogene du 9,10-dimethyl-benzanthracene et du 3,4-benzopyrene administres par voie digestive. *Bull. Cancer* 54: 67-78.

Dimethylcarbamyl chloride

Cancer Potency: 13 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.05 $\mu g/day$

Gold et al. list two studies -- an inhalation study in male Syrian Golden hamsters (Sellukumar et al., 1980) and an intraperitoneal injection study in female Ha/ICR mice (Van Duuren et al., 1974). Nasal squamous cell carcinomas were observed in approximately half of the treated animals in the hamster study. Sarcomas of the abdomen were found in slightly more than a quarter of the treated mice. The hamster study was performed on a greater number of animals and the hamster appears to be the more sensitive species. Therefore, potency was based on the nasal squamous cell carcinomas in the male hamster.

Sellakumar AR, Laskin S, Kuschner M, Rusch G, Katz GV, Snyder CA and Albert RE (1980). Inhalation carcinogenesis by dimethylcarbamoyl chloride in Syrian golden hamsters. *J. Environ. Pathol. Toxicol.* 4: 107-115.

Van Duuren BL, Goldschmidt BM, Katz C, Seidman I and Paul JS (1974). Carcinogenic activity of alkylating agents. *J. Nat. Cancer Inst.* 53: 695-700.

1,2-Dimethylhydrazine

Cancer Potency: 550 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.001 $\mu g/day$

Studies are available in Gold et al. for 1,2-dimethylhydrazine dihydrochloride. These are drinking water studies on male and female Syrian Golden hamsters (Toth, 1967a) and albino Swiss mice (Toth and Wilson, 1971). Highly significant incidences of angiosarcomas were observed at a number of sites in both sexes and species. Nearly all animals treated with the compound developed these tumors. Cancer potency is based on male mice, the species/strain with the highest calculated potency value. An upper bound estimate could not be obtained for the female, however, because all of the animals developed tumors. Thus, the sensitivity of the female cannot be determined. Additionally, in the study on males, there were few animals without tumors and corrections for survival were not possible given the available data. For these reasons, the cancer potency presented here may be seen as an underestimate. The potency for 1,2-dimethylhydrazine was derived from that for the dihydrochloride using a molecular weight conversation (see glossary to Appendix 1 for explanation).

Toth B and Wilson RB (1971). Blood vessel tumorigenesis by 1,2-dimethylhydrazine dihydrochloride (symmetrical). *Am. J. Pathol.* 64: 585-600.

Toth B (1967a). Studies on the incidence, morphology, transplantation and cell-free filtration of malignant lymphomas in the Syrian golden hamster. *Cancer Res.* 27: 1430-1442.

Dimethylvinyl chloride

Cancer Potency: 0.045 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 20 $\mu g/day$

The results of the NTP (1986) gavage study in $B6C3F_1$ mice and F344 rats of both sexes are given. The compound induced tumors at multiple target sites in all species/sexes tested (e.g., nasal cavity, forestomach, esophagus, thyroid). Based on quantitative analysis of these data, all groups show similar sensitivities. The calculated potencies from the female mouse data are somewhat higher than for the other groups. Cancer potency is based on dose response data for benign and malignant forestomach tumors in female mice.

National Toxicology Program (NTP, 1986). *Toxicology and Carcinogenesis Studies of Dimethylvinyl Chloride (1-chloro-2-methyl-propene) in F344/N Rats and $B6C3F_1$ Mice (Gavage Studies).* NTP Technical Report Series No. 316. NIH Publication No. 86-2572. US Department of Health and Human Services, NTP, Research Triangle Park, NC.

Direct Black 38

Cancer Potency: 7.4 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.09 $\mu g/day$

Gold et al. list the NCI (1978) results of the short term feeding study in male and female F344 rats. After only 13 weeks, benign and malignant liver tumors were observed in both sexes. Cancer potency is derived from the study in males, the slightly more sensitive sex.

National Cancer Institute (NCI, 1978). *13-Week Subchronic Toxicity Studies of Direct Blue 6, Direct Black 38, and Direct Brown 95 Dyes.* Carcinogenesis Technical Report Series No. 108. US Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

Direct Blue 6

Cancer Potency: 7.4 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.09 $\mu g/day$

Gold et al. list the NCI (1978) results of the short term feeding study in male and female F344 rats. After only 13 weeks, benign and malignant liver tumors were observed in both sexes. Cancer potency is derived from the study in males, the slightly more sensitive sex.

National Cancer Institute (NCI, 1978). *13-Week Subchronic Toxicity Studies of Direct Blue 6, Direct Black 38, and Direct Brown 95 Dyes.* Carcinogenesis Technical Report Series No. 108. US Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

Direct Brown 95

Cancer Potency: 6.7 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.1 $\mu g/day$

The NCI (1978) short term feeding studies in male and female F344 rats are the only ones listed by Gold et al. Cancer potency is derived from the dose response data for benign and malignant liver tumors observed in female rats after 13 weeks of treatment.

National Cancer Institute (NCI, 1978). *13-Week Subchronic Toxicity Studies of Direct Blue 6, Direct Black 38, and Direct Brown 95 Dyes.* Carcinogenesis Technical Report Series No. 108. US Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

Disperse Blue 1

Cancer Potency: 0.0045 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 200 $\mu g/day$

Results from the NTP (1986) feeding studies in male and female $B6C3F_1$ mice and F344 rats are listed. Benign and malignant tumors of the urinary bladder were observed in rats of both sexes, with the male being slightly more sensitive. Dose response data for these tumors in the male are used as the basis of the potency assessment.

National Toxicology Program (NTP, 1986). *Toxicology and Carcinogenesis Studies of Disperse Blue 1 (a commercial dye containing approximately 50% 1,4,5,8-tetra amino anthraquinone, 30% other compounds structurally related to 1,4,5,8-tetra amino anthraquinone and 20% water in F344/N Rats and $B6C3F_1$ Mice (Feed Studies).* NTP Technical Report Series No. 299. NIH Publication No. 86-2555. US Department of Health and Human Services, NTP, Research Triangle Park, NC.

Estradiol 17β (Estradiol 17 beta)

Cancer Potency: 39 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.02 $\mu g/day$

Listed are results of feeding studies in female C3H and C3H/HeJ mice. Significant increases in mammary gland adenocarcinomas were observed by Highman et al. (1980) in C3h/HeJ mice. This study serves as the basis of the potency calculation.

Highman B, Greenman DL, Norvell MJ, Farmer J and Shellenberger TE (1980). Neoplastic and preneoplastic lesions induced in female C3H mice by diets containing diethylstilbestrol or 17beta-estradiol. *J. Environ. Pathol. Toxicol.* 4: 81-95.

Ethyl-4,4'-dichlorobenzilate (chlorobenzilate)

Cancer Potency: 0.11 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 7 $\mu g/day$

Gold et al. list the results of the NCI (1978) feeding studies in male and female $B6C3F_1$ mice and Osborne Mendel rats, the oral studies in male and female $B6C3F_1$ and $B6AKF_1$ mice by Innes (1968) and Innes et al. (1969) and the study in Cartworth Farms rats by Horn et al. (1955). No significant increases in tumors were found in the study in Cartworth Farms rats, and results in both male and female Osborne Mendel rats are characterized by NTP (1991) as "equivocal". Significant increases in tumors were observed in most of the studies in mice, the more sensitive species. Cancer potency is derived by taking the geometric mean of the potency values calculated from all studies showing significant increases in liver tumors: the NCI (1978), Innes (1968) and Innes et al. (1969) studies on male $B6C3F_1$ mice; the NCI (1978) study on female $B6C3F_1$ mice; the Innes (1968) and Innes et al. (1969) studies on male $B6AKF_1$ mice.

National Cancer Institute (NCI, 1978). *Bioassay of Chlorobenzilate for Possible Carcinogenicity*. Carcinogenesis Technical Report Series No. 75. NTIS Publication No. PB 287123. US Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

National Toxicology Program (NTP, 1991). *Chemical Status Report*. US Department of Health and Human Services, NTP, Research Triangle Park, NC.

Innes JRM (1968). *Evaluation of carcinogenic, teratogenic, and mutagenic activities of selected pesticides and industrial chemicals*. Volume 1: Carcinogenic study. Bionetics Research Laboratories, Inc. Distributed by National Technical Information Service, Springfield, VA.

Innes JRM, Ulland BM, Valerio MG, Petrucelli L, Fishbein L, Hart ER, Pallota AJ, Bates RR, Falk HL, Gart JJ, Klein M, Mitchell I and Peters J (1969). Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: a preliminary note. *J. Nat. Cancer Inst.* 42:1101-1114.

Horn H, Black J, Bruce R and Paynter OE (1955). *Toxicology of chlorobenzilate.* In: Agricultural and Food Chemistry: Past, Present, Future, Vol. 3 (R. Teranishi, Ed.). Avi Publishing Company, Inc., Westport, CT, pp. 752-756.

Ethylene thiourea (ETU)

Cancer Potency: 0.045 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 20 $\mu g/day$

Several studies are listed in Gold et al. Innes (1968) and Innes et al. (1969) administered ethylene thiourea to small groups of both sexes of $B6C3F_1$ and $B6AKF_1$ mice, Graham et al.

(1975) performed relatively large multiple dose studies in Charles River CD rats of both sexes, and Weisburger et al. (1981) and Ulland et al. (1972) conducted moderately sized studies in male and female Charles River CD rats. Because all male $B6C3F_1$ and female $B6AKF_1$ mice treated with ETU developed liver tumors, an upper bound estimate on potency could not be determined for these studies. The lower bound estimates of cancer potency derived from the mice data are consistent with potencies derived from the studies in rats. Cancer potencies derived from the rat studies are consistent with one another. The value selected is derived from the highest quality study, which had a large sample size and used multiple dose groups (Graham, 1975). The target site chosen for the analysis was the thyroid in the Charles River CD rats, the most sensitive site.

Innes JRM (1968). *Evaluation of carcinogenic, teratogenic, and mutagenic activities of selected pesticides and industrial chemicals.* Volume 1: Carcinogenic study. Bionetics Research Laboratories, Inc. Distributed by National Technical Information Service, Springfield, VA.

Innes JRM, Ulland BM, Valerio MG, Petrucelli L, Fishbein L, Hart ER, Pallota AJ, Bates RR, Falk HL, Gart JJ, Klein M, Mitchell I and Peters J (1969). Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: a preliminary note. *J. Nat. Cancer Inst.* 42:1101-1114.

Graham SL, Davis KJ, Hansen WH and Graham CH (1975). Effects of prolonged ethylene thiourea ingestion on the thyroid of the rat. *Food Cosmet. Toxicol.* 13: 493-499.

Ulland BM, Weisburger JH, Weisburger EK, Rice JM and Cypher R (1972). Brief communication: thyroid cancer in rats from ethylene thiourea intake. *J. Nat. Cancer Inst.* 49:583-584.

Weisburger EK, Ulland BM, Nam J, Gart JJ and Weisburger JH (1981). Carcinogenicity tests of certain environmental and industrial chemicals. *J. Nat. Cancer Inst.* 67:75-88.

Ethyleneimine

Cancer Potency:	65 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake:	0.01 $\mu g/day$

Listed are the oral studies in male and female $B6C3F_1$ and $B6AKF_1$ mice by Innes (1968) and Innes et al. (1969). Significant increase in lung and liver tumors were observed in both sexes and both strains. Cancer potency is derived by taking the geometric mean of potencies for lung tumors in male and female $B6AKF_1$ and liver tumors in male $B6C3F_1$ mice. The results for the female $B6C3F_1$ mice were not included because all animals developed tumors, precluding the estimation of potency from that study.

Innes JRM (1968). *Evaluation of carcinogenic, teratogenic, and mutagenic activities of selected pesticides and industrial chemicals.* Volume 1: Carcinogenic study. Bionetics Research Laboratories, Inc. Distributed by National Technical Information Service, Springfield, VA.

Innes JRM, Ulland BM, Valerio MG, Petrucelli L, Fishbein L, Hart ER, Pallota AJ, Bates RR, Falk HL, Gart JJ, Klein M, Mitchell I and Peters J (1969). Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: a preliminary note. *J. Nat. Cancer Inst.* 42:1101-1114.

2-(2-Formylhydrazino)-4-(5-nitro-2-furyl)thiazole (FNT)

Cancer Potency: 2.3 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.3 $\mu g/day$

Gold et al. list results for a number of feeding studies -- one in male Syrian Golden Hamsters, two studies in female Swiss mice, one each in female Buffalo and Holtzman albino rats, and two studies in female and one in male Sprague-Dawley rats. Significant increases in tumors were seen in all studies. Results are quantitatively consistent across the different species and strains. Cancer potency is estimated from the dose-response data for mammary gland adenocarcinomas in female Sprague-Dawley rats, reported by Cohen et al. (1973). This study was the most powerful in terms of the number of animals and dose levels used.

Cohen SM, Erturk E, Von Esch AM, Crovetti AJ and Bryan GT (1973). Carcinogenicity of 5-nitrofurans, 5-nitroimidazoles, 4-nitrobenzenes, and related compounds. *J. Nat. Cancer Inst.* 51: 403-417.

Glu-P-1 (2-amino-6-methyldipyrido[1,2-a:3',2'-d]imidazole)

Cancer Potency: 4.8 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.1 $\mu g/day$

Results are available for studies by Ohgaki et al. (1984) in male and female CDF1 mice and by Takayama et al. (1984) in male and female F344 rats. Tumors are induced in all experiments at multiple target sites. All sex/species combinations appear to have nearly the same sensitivity overall, with potency slightly higher when derived from the most sensitive target site (liver) in female mice. Because tumor incidence approached 100% for tested animals, potency may be underestimated.

Ohgaki H, Matsukura N, Morino K, Kawachi T, Sugimura T and Takayama S (1984). Carcinogenicity in mice of mutagenic compounds from glutamic acid and soybean globulin pyrolysates. *Carcinogenesis* 5: 815-819.

Takayama S, Masuda M, Mogami M, Ohgaki H, Sato S and Sugimura T (1984). Induction of cancers in the intestine, liver and various other organs of rats by feeding mutagens from glutamic acid pyrolysate. *Gann* 75: 207-213.

Glu-P-2 (2-aminodipyrido[1,2-a:3',2'-d]imidazole)

Cancer Potency: 1.4 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.5 $\mu g/day$

Results are available for studies by Ohgaki et al. (1984) in male and female CDF1 mice and by Takayama et al. (1984) in male and female F344 rats. Tumors are induced in all experiments at multiple target sites. All sex/species combinations appear to have similar sensitivities overall, with potency slightly higher when derived from the most sensitive target site (liver) in female mice. Because tumor incidence approaches 100% for tested animals, potency may be underestimated.

Ohgaki H, Matsukura N, Morino K, Kawachi T, Sugimura T and Takayama S (1984). Carcinogenicity in mice of mutagenic compounds from glutamic acid and soybean globulin pyrolysates. *Carcinogenesis* 5: 815-819.

Takayama S, Masuda M, Mogami M, Ohgaki H, Sato S and Sugimura T (1984). Induction of cancers in the intestine, liver and various other organs of rats by feeding mutagens from glutamic acid pyrolysate. *Gann* 75: 207-213.

Gyromitrin (acetaldehyde methylformylhydrazone)

Cancer Potency: 10 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.07 $\mu g/day$

Results of the study in male and female albino Swiss mice by Toth et al. (1981) are listed. Tumors were observed at multiple sites. The most sensitive site appears to be the preputial gland in male mice. Cancer potency is estimated from the combined incidence of benign and malignant tumors for this site.

Toth B, Smith JW and Patil KD (1981). Cancer induction in mice with acetaldehyde methylformylhydrazone of the false morel mushroom. *J. Nat. Cancer Inst.* 67: 881-887.

HC Blue 1

Cancer Potency: 0.051 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 10 $\mu g/day$

Results of the NTP (1985) studies in $B6C3F_1$ mice and F344 rats of both sexes are listed. Mice are more sensitive than rats. Female mice may be slightly more sensitive than male mice, although the studies are not of sufficient sensitivity for a definitive determination to be made. Cancer potency is based on dose response data for combined liver tumor incidences in female mice.

National Toxicology Program (NTP, 1986). *Toxicology and Carcinogenesis Studies of HC Blue 1 in F344/N Rats and $B6C3F_1$ Mice (Feed Studies).* NTP Technical Report Series No. 271. NTIS Publication No. PB 86-114683. US Department of Health and Human Services, NTP, Research Triangle Park, NC.

Hexachloroethane

Cancer Potency: 0.039 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 20 $\mu g/day$

Results are listed for the gavage studies by NCI (1978) in male and female $B6C3F_1$ mice and Osborne Mendel rats. Results from the more recent study by NTP (1989) in rats are not listed. NCI reported significant increases in liver carcinomas for both sexes of mice. Cancer potency is estimated from dose response data in females, the more sensitive sex.

National Cancer Institute (NCI, 1978). *Bioassay of Hexachloroethane for Possible Carcinogenicity.* Carcinogenesis Technical Report Series No. 68. NTIS Publication No. PB 90170895. US Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

National Toxicology Program (NTP, 1989). *Toxicology and Carcinogenesis Studies of Hexachloroethane in F344/N Rats (Gavage Studies).* NTP Technical Report Series No. 361. NTIS Publication No. 89-2816. US Department of Health and Human Services, NTP, Research Triangle Park, NC.

Hydrazobenzene (1,2-diphenylhydrazine)

Cancer Potency: 0.87 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.8 $\mu g/day$

Results are listed for the feeding studies by NCI (1978) in male and female $B6C3F_1$ mice and F344 rats. Significant increases in tumors at particular sites were found for all sex/species combinations tested. Cancer potency is derived from dose response data for combined benign and malignant liver tumors in male rats, the most sensitive sex and species.

National Cancer Institute (NCI, 1978). *Bioassay of Hydrazobenzene for Possible Carcinogenicity*. Carcinogenesis Technical Report Series No. 92. NTIS Publication No. PB 285791. US Department of Health, Education and Welfare (DHEW), NCI Carcinogenesis Testing Program, Bethesda, MD.

IQ (2-Amino-3-methylimidazo[4,5-f]quinoline)

Cancer Potency: 1.4 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.5 $\mu g/day$

Results are given for feeding studies in both sexes of CDF1 mice by Ohgaki et al. (1984) and in both sexes of F344/DuCrj rats reported later by Ohgaki et al. (1986). Increased incidences of tumors were observed at a number of sites in all species/sex combinations. The male rat is the most sensitive sex and species. Cancer potency is estimated from dose response data for squamous cell carcinomas of the Zymbal gland, the most sensitive site in male rats.

Ohgaki H, Kusama K, Matsukura N, Morino K, Hasegawa H, Sato S, Takayama S and Sugimura T (1984). Carcinogenicity in mice of a mutagenic compound, 2-amino-3-methylimidazo[4,5-f]quinoline, from broiled sardine, cooked beef and beef extract. *Carcinogenesis* 5: 921-924.

Ohgaki H, Hasegawa H, Kato T, Suenaga M, Ubukata M, Sato S, Takayama S and Sugimura T (1986). Carcinogenicity in mice and rats of heterocyclic amines in cooked foods. *Environ. Health Perspect.* 67: 129-134.

Lasiocarpine

Cancer Potency: 7.8 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.09 $\mu g/day$

The following studies, all on F344 rats, are included in the Gold et al. database: the feeding studies in males and females by NCI (1978); the study in males given lasiocarpine by intraperitoneal injection by Svoboda and Reddy (1972); and the study in males given the compound in feed by Rao et al. (1978). The studies performed by NCI in male and female rats were the highest quality in terms of number of treatment groups and number of animals per group. The sensitivities between the two sexes were similar. Potency is based on dose response data for the combined benign and malignant tumors of the liver in the male rat (NCI, 1978). Because survival was poor for the NCI study in male rats, potency was derived using a time-to-tumor analysis (Crump et al., 1991).

Crump KS, Howe RB, Van Landingham C, and Fuller WG (1991). **TOX_RISK** Version 3. **TOX**icology **RISK** Assessment Program. KS Crump Division, Clement International Corporation, 1201 Gaines Street, Ruston, Louisiana 71270.

National Cancer Institute (NCI, 1978). *Bioassay of Lasiocarpine for Possible Carcinogenicity.* Carcinogenesis Technical Report Series No. 39. NTIS Publication No. PB 278641. US Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

Svoboda DJ and Reddy JK (1972). Malignant tumors in rats given lasiocarpine. *Cancer Res.* 32: 908-911.

Rao MS and Reddy JK (1978). Malignant neoplasms in rats fed lasiocarpine. *Br. J. Cancer* 37: 289-293.

Lead acetate

Cancer Potency: 0.28 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 3 $\mu g/day$

Results for a total of 7 studies in rats and mice are listed. No significant increases in tumors were observed in mice. Koller et al. (1985) observed transitional cell carcinomas of the kidney in 13 of 16 male Sprague-Dawley rats given lead acetate via drinking water. Cancer potency was derived from this study.

Koller LD, Kerkvliet NI and Exon JH (1985). Neoplasia induced in male rats fed lead acetate, ethyl urea, and sodium nitrite. *Toxicol. Pathol.* 13: 50-57.

Lead subacetate

Cancer Potency: 0.038 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 20 $\mu g/day$

Feeding studies in male and female Syrian Golden hamsters and Swiss mice, and male Sprague-Dawley and male and female Wistar rats are listed in Gold et al. No significant findings are reported for the studies in hamsters or mice. Significant increases in kidney tumors are observed in the study in male Sprague-Dawley rats by Kasprzak et al. (1985) and the two studies in female and male Wistar rats by Van Esch et al. (1962). Because all five studies are of similar quality, the geometric mean of the potencies derived from these studies is taken.

Kasprzak KS, Hoover KL and Poirier LA (1985). Effects of dietary calcium acetate on lead subacetate carcinogenicity in kidneys of male Sprague-Dawley rats. *Carcinogenesis* 6: 279-282.

Van Esch GJ, Van Genderen H and Vink HH (1962). The induction of renal tumors by feeding of basic lead acetate to rats. *Br. J. Cancer* 16: 289-297.

Me-A-alpha-C (2-amino-3-methyl-9H-pyrido(2,3-b)indole)

Cancer Potency: 1.2 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.6 $\mu g/day$

Results of the feeding studies in male and female CDF1 mice performed by Ohgaki et al. (1984) are listed. Significant increases in benign and malignant liver tumors and hemangioendothelial sarcomas were observed in both sexes. Sensitivity is similar for males and females. Cancer potency is based on dose response data for hemangioendothelial sarcomas in males, the apparently more sensitive sex.

Ohgaki H, Matsukura N, Morino K, Kawachi T, Sugimura T and Takayama S (1984). Carcinogenicity in mice of mutagenic compounds from glutamic acid and soybean globulin pyrolysates. *Carcinogenesis* 5: 815-819.

Melphalan

Cancer Potency: 130 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.005 $\mu g/day$

Results from intraperitoneal studies in male and female Swiss mice and Charles River CD rats by Skipper (1976) and Weisburger (1977) are given. All of the tested species/sex combinations show similar sensitivities based on quantitative analysis of the dose response data. Cancer potency is estimated from data for tumors of the peritoneum in male rats, the apparently most sensitive group tested.

Skipper HE (1976). *Booklet 1, Phase I Studies on the Carcinogenic Activity of Anticancer Drugs in Mice and Rats. Final Report.* Southern Research Institute, Birmingham, AL.

Weisburger EK (1977). Bioassay program for carcinogenic hazards of cancer chemotherapeutic agents. *Cancer* 40: 1935-1949.

3-Methylcholanthrene

Cancer Potency: 22 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.03 $\mu g/day$

Results of 3 studies in male Long Evans rats, one study in an unspecified strain of female rats, and 10 studies in female Wistar rats are included in the Gold et al. database. All studies in female rats found highly significant increases in tumors of the mammary gland. Cancer potency is taken as the geometric mean of cancer potencies estimated from 9 of the 10 studies in female rats (Shay et al., 1962; Gruenstein et al., 1964; Shay et al., 1961). The upper bound on potency could not be estimated from one of the studies by Shay et al. (1961), because 100% of the treated animals developed mammary gland tumors.

Shay H, Gruenstein M and Kessler WB (1962). Methylcholanthrene induced breast cancer in the rat: studies on mechanism of inhibition by large doses of estrogen. *Morphological Precursors of Cancer.* L. Severi, Ed. Div. Canc. Res., Perugia, pp. 305-318.

Gruenstein M, Shay H and Shimkin MB (1964). Lack of effect of norethynodrel (Enovid) on methylcholanthrene-induced mammary carcinogenesis in female rats. *Cancer Res.* 24: 1656-1658.

Shay H, Gruenstein M and Kessler WB (1961). Experimental mammary adenocarcinoma of rats: some consideration of methylcholanthrene dosage and hormonal treatment. *J. Nat. Cancer Inst.* 27: 503-513.

4,4'-Methylene bis(2-chloroaniline)

Cancer Potency: 1.5 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.5 $\mu g/day$

A number of studies are available for Charles River CD and Wistar II rats, as well as a single study in female beagle dogs. The compound induced papillary transitional cell carcinomas of the urinary bladder in dogs, whereas the liver was the most common target site in the rat studies. Dogs are more sensitive to the carcinogenic effects of the compound than rats. The compound is similar in structure to benzidine, a human bladder carcinogen, which appears to be significantly more potent in humans than rodents. The Stula et al. (1977) dog study is used as the basis of potency estimation, even though small numbers of animals are used, because dogs may be better predictors of human carcinogenicity of this compound than rodents.

Stula EF, Barnes JR, Sherman H, Reinhardt CF and Zapp JA (1977). Urinary bladder tumors in dogs from 4,4'-methylene-bis(2-chloroaniline) (MOCA). *J. Environ. Pathol. Toxicol.* 1: 31-50.

4,4'-Methylene bis(2-methylaniline)

Cancer Potency: $0.92\ (mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: $0.8\ \mu g/day$

A single study (Stula et al., 1975) in male and female Charles River CD rats is listed by Gold et al. The most sensitive site in the more sensitive sex, liver hepatocellular carcinomas in females, is used as the basis of the cancer potency estimate.

Stula EF, Sherman H, Zapp JA and Clayton JW (1975). Experimental neoplasia in rats from oral administration of 3,3'-dichlorobenzidine, 4,4'-methylene-bis(2-chloroaniline), and 4,4'-methylene-bis(2-methylaniline). *Toxicol. Appl. Pharmacol.* 31: 159-176.

4,4'-Methylenedianiline

Cancer Potency: $1.6\ (mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: $0.4\ \mu g/day$

The potency for the compound was derived from the potency for the dihydrochloride using a molecular weight conversion (see glossary to Appendix 1 for explanation).

4,4'-Methylenedianiline dihydrochloride

Cancer Potency: $1.2\ (mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: $0.6\ \mu g/day$

Results are listed for the drinking water studies by NTP (1983) in male and female $B6C3F_1$ mice and F344 rats. Significant increases in tumors of the liver or thyroid or both are observed for all sex/species combinations tested, with male mice the most sensitive. Cancer potency is based on the combined incidence of benign and malignant liver tumors in male mice.

National Toxicology Program (NTP, 1983). *Toxicology and Carcinogenesis Studies of 4,4'-Methylenedianiline Dihydrochloride in F344/N Rats and $B6C3F_1$ Mice (Drinking Water Studies).* NTP Technical Report Series No. 248. NTIS Publication No. PB 83238824. US Department of Health and Human Services, NTP, Research Triangle Park, NC.

Methyl methanesulfonate

Cancer Potency: 0.099 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 7 $\mu g/day$

Gold et al. list only the drinking water study by Clapp et al. (1968) in male RF mice. The most sensitive site is the lung in terms of the magnitude of the potency. However, only lung adenomas, usually non-lethal tumors, were reported. According to the current Carcinogen Guidelines (CDHS, 1985), benign tumors are used only as supporting evidence in identifying agents as carcinogens. In selecting data sets for dose reponse evaluation, data sets are sometimes excluded if there is no evidence that a tumor will progress to malignancy. Therefore, cancer potency is based on malignant lymphomas observed in the thymus gland, the next most sensitive site.

Clapp NK, Craig AW and Toya RE (1968). Oncogenicity by methyl methanesulfonate in male RF mice. *Science* 161: 913-914.

California Department of Health Services (CDHS, 1985). *Guidelines for Chemical Carcinogen Risk Assessments and Their Scientific Rationale.* California Department of Health Services, Health and Welfare Agency, Sacramento, CA.

2-Methyl-1-nitroanthraquinone

Cancer Potency: 4.3 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.2 $\mu g/day$

Results are listed for the feeding studies by NCI (1978) in male and female $B6C3F_1$ mice and F344 rats. Increases in tumors were seen at multiple target sites in both species. Mice are more sensitive than rats. Both sexes of mice have similar sensitivity, with the default analysis resulting in slightly greater potency in males than females. Cancer potency is based on dose response data for hemangiosarcomas observed in subcutaneous tissue in male mice.

National Cancer Institute (NCI, 1978). *Bioassay of 2-Methyl-1-Nitroanthraquinone for Possible Carcinogenicity.* Carcinogenesis Technical Report Series No. 29. NTIS Publication No. PB 277439. US Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

N-Methyl-N'-nitro-N-nitrosoguanidine

Cancer Potency: 8.3 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.08 $\mu g/day$

Gold et al. list results from a number of drinking water studies of varying quality in male and female rats. Cancer potency is the geometric mean from the best studies -- those studies run at relatively low dose levels which lasted longer than 80 weeks and had at least 20 animals in the control group. These criteria lead to taking the geometric mean of potencies estimated from dose response data for: 1) benign and malignant tumors of the glandular stomach of male F344 rats reported by Lijinsky and Reuber (1984); 2) the tumors of the same target site in the same strain but observed for a slightly longer period of time reported by Lijinsky and Reuber (1984); and, 3) gastrointestinal tract tumors in male Wistar rats reported by Arffmann et al. (1981).

Lijinsky W and Reuber MD (1984). Comparison of nitrosocimetidine with nitrosomethylnitroguanidine in chronic feeding tests in rats. *Cancer Res.* 44: 447-449.

Arffman EJL, Rasmussen KS and Hansen FN (1981). Effect of some fatty acid methyl esters on gastrointestinal carcinogenesis by N-methyl-N'-nitro-N-nitrosoguanidine in rats. *J. Nat. Cancer Inst.* 67: 1071-1075.

Methylthiouracil

Cancer Potency: 0.40 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 2 $\mu g/day$

Gold et al. list the results of two small studies, one by Christov and Raichev (1972) in hamsters (strain not specified), and the other by Jemec (1977) in C3H/FIB mice. Significant increases in tumors were observed only for the thyroid gland in female hamsters. Cancer potency is based on the dose response data for these tumors.

Christov K and Raichev R (1972). Thyroid carcinogenesis in hamsters after treatment with 131-iodine and methylthiouracil. *Cancer Res. Clin. Oncol.* 77: 171-179.

Jemec B (1977). Studies of the tumorigenic effect of two goitrogens. *Cancer* 40: 2188-2202.

Michler's ketone

Cancer Potency: 0.86 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.8 $\mu g/day$

Results are listed for the feeding studies by NCI (1979) in male and female $B6C3F_1$ mice and F344 rats. Rats are more sensitive than mice, with male and female rats having similar sensitivity. Cancer potency is derived from dose response data for liver tumors in female rats.

National Cancer Institute (NCI, 1977). *Bioassay of Michler's Ketone for Possible Carcinogenicity.* Carcinogenesis Technical Report Series No. 181. NTIS Publication No. PB 299855. US Department of Health, Education and Welfare (DHEW), NCI Carcinogenesis Testing Program, Bethesda, MD.

Mirex

Cancer Potency: 18 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.04 $\mu g/day$

Gold et al. list the results of the studies by Innes (1968) and Innes et al. (1969) in both sexes of $B6C3F_1$ and $B6AKF_1$ mice, and in an insensitive study in rats (low doses and smaller numbers of animals). Elevated incidences of liver tumors are seen in both sexes of both strains studied by Innes (1968) and Innes et al. (1969). Potency values for these 4 data sets are consistent with one another. The cancer potency is taken as the geometric mean of values derived from these 4 sets of data (male and female $B6C3F_1$ and $B6AKF_1$ mice).

Innes JRM (1968). *Evaluation of carcinogenic, teratogenic, and mutagenic activities of selected pesticides and industrial chemicals.* Volume 1: Carcinogenic study. Bionetics Research Laboratories, Inc. Distributed by National Technical Information Service, Springfield, VA.

Innes JRM, Ulland BM, Valerio MG, Petrucelli L, Fishbein L, Hart ER, Pallota AJ, Bates RR, Falk HL, Gart JJ, Klein M, Mitchell I and Peters J (1969). Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: a preliminary note. *J. Nat. Cancer Inst.* 42: 1101-1114.

Mitomycin C

Cancer Potency: 8200 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.00009 $\mu g/day$

The results of the intraperitoneal injection studies of Skipper (1976) and Weisburger (1977) in both sexes of Charles River CD rats are given. Both sexes exhibit similar sensitivity for the induction of sarcomas of the peritoneum by mitomycin C. The cancer potency is based on the dose response data in female rats.

Skipper HE (1976). *Booklet 1, Phase I Studies on the Carcinogenic Activity of Anticancer Drugs in Mice and Rats.* Final report. Southern Research Institute, Birmingham, AL.

Weisburger EK (1977). Bioassay program for carcinogenic hazards of cancer chemotherapeutic agents. *Cancer* 40: 1935-1949.

Monocrotaline

Cancer Potency: 10 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.07 $\mu g/day$

Data is given for two gavage experiments run under the same conditions by Newberne and Rogers (1973). Both studies showed significantly increased incidences of liver hepatocellular carcinomas in male Charles River CD rats. The higher of the two cancer potencies derived from these studies is selected.

Newberne PM and Rogers AE (1973). Nutrition, monocrotaline, and aflatoxin B1 in liver carcinogenesis. *Plant Foods Man* 1: 23-31.

2-Napthylamine

Cancer Potency: 1.8 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.4 $\mu g/day$

The results of studies in mice, rats and primates (rhesus monkeys) are reported. The compound is similar in structure to benzidine, a human bladder carcinogen, which appears to be significantly more potent in humans than rodents. Cancer potency for 2-naphthylamine is based on the combined incidence of benign and malignant tumors of the urinary bladder in rhesus monkeys (Conzelman et al., 1969).

Conzelman GM, Moulton JE, Flanders LE, Springer K and Crout DW (1969). Induction of transitional cell carcinoma of the urinary bladder in monkeys fed 2-naphthylamine. *J. Nat. Cancer Inst.* 42: 825-831.

Nitrilotriacetic acid (NTA)

Cancer Potency: 0.0053 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 100 $\mu g/day$

Listed are the results from the NCI (1977) feeding studies in male and female $B6C3F_1$ mice and F344 rats, and the drinking water studies in MRC rats of both sexes. NTP (1991) characterizes the four feeding studies as positive; the drinking water studies were negative. The liver and urinary tract are the target sites identified in the feeding studies. Female rats appear to be the most sensitive sex/species combination. However, due to the uncertainties in the dose response evaluation of these data, the most sensitive sex/species can not be unequivocally ascertained. Cancer potency is based on benign and malignant liver tumors observed in female rats.

National Cancer Institute (NCI, 1977). *Bioassay of Nitrilotriacetic Acid (NTA) for Possible Carcinogenicity*. Carcinogenesis Technical Report Series No. 6. NTIS Publication No. PB 266177. US Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

National Toxicology Program (NTP, 1991). *Chemical Status Report*. US Department of Health and Human Services, NTP, Research Triangle Park, NC.

Nitrilotriacetic acid, trisodium salt, monohydrate

Cancer Potency: 0.010 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 70 $\mu g/day$

Gold et al. list the results of the NCI (1977) feeding studies in male and female $B6C3F_1$ mice and F344 rats, an additional NCI (1977) feeding study in F344 rats of both sexes, and the drinking water studies in Charles River CD male rats (Goyer et al., 1981). The mice studies are characterized as negative, and so are not included in the potency evaluation. In addition, the results for the lower dose NCI studies in male and female rats were equivocal, and thus are excluded from the potency evaluation. As with NTA, the liver and urinary tract are the target sites for carcinogenesis in the rat. Among the remaining rat studies, significant variation in carcinogenic activity is observed, with the rats exposed via drinking water showing greater sensitivity. Cancer potency is taken as the geometric mean of potency values from four data sets: 1) and 2) the two data sets for kidney tumors in male Charles River rats (Goyer et al., 1981); 3) the data set for urinary tract tumors in male F344 rats (benign and malignant combined for the kidney, bladder, ureter) (NCI, 1977); and 4) the data set for urinary tract tumors for female F344 rats (NCI, 1977).

National Cancer Institute (NCI, 1977). *Bioassay of Nitrilotriacetic Acid (NTA) for Possible Carcinogenicity*. Carcinogenesis Technical Report Series No. 6. NTIS Publication No. PB 266177. US Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

Goyer RA, Falk HL, Hogan M, Feldman DD and Richter W (1981). Renal tumors in rats given trisodium nitrilotriacetic acid in drinking water for 2 years. *J. Nat. Cancer Inst.* 66: 869-880.

5-Nitroacenaphthene

Cancer Potency: 0.13 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 6 $\mu g/day$

Listed are feeding studies by Takemura et al. (1974) in female Syrian Golden hamsters, and by NCI (1978) in male and female $B6C3F_1$ mice and F344 rats. The compound induced increases in tumor incidences at multiple sites in rats and female mice. Rats are the most sensitive

species; the sensitivity of males is similar to that of females. The cancer potency is based on the combined incidence of benign and malignant tumors of the ear canal in female rats.

National Cancer Institute (NCI, 1978). *Bioassay of 5-Nitroacenaphthene for Possible Carcinogenicity*. Carcinogenesis Technical Report Series No. 118. NTIS Publication No. PB 287347. US Department of Health, Education and Welfare (DHEW), NCI Carcinogenesis Testing Program, Bethesda, MD.

Takemura N, Hashida C and Terasawa M (1974). Carcinogenic action of 5-nitroacenaphthene. *Br. J. Cancer* 30: 481-483.

5-Nitro-o-anisidine

Cancer Potency: 0.049 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 10 $\mu g/day$

Gold et al. list the results of the NCI (1978) feeding studies in male and female $B6C3F_1$ mice and F344 rats. Significant results were observed for male and female rats and female mice. The rats were significantly more sensitive than mice, and male rats were more sensitive than females. Tumors occurred at multiple sites. Cancer potency is based on tumors of the skin, the most sensitive site in male rats.

National Cancer Institute (NCI, 1978). *Bioassay of 5-Nitro-o-anisidine for Possible Carcinogenicity*. Carcinogenesis Technical Report Series No. 127. NTIS Publication No. PB 287411. US Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

Nitrofen

Cancer Potency: 0.082 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 9 $\mu g/day$

Gold et al. list the results of the NCI (1978) feeding studies in male and female $B6C3F_1$ mice and Osborne Mendel rats and NCI (1979) feeding studies in $B6C3F_1$ mice and F344 rats. Rats appear to be less sensitive than mice. Cancer potency is therefore estimated from the data in mice. Cancer potency is the geometric mean of the values estimated from liver tumors in male and female mice observed in the two NCI feeding studies.

National Cancer Institute (NCI, 1979). *Bioassay of Nitrofen for Possible Carcinogenicity*. Carcinogenesis Technical Report Series No. 184. NTIS Publication No. PB 296038. US Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

National Cancer Institute (NCI, 1978). *Bioassay of Nitrofen for Possible Carcinogenicity*. Carcinogenesis Technical Report Series No. 26. NTIS Publication No. PB 277440. US Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

Nitrofurazone

Cancer Potency: 1.3 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.5 $\mu g/day$

Gold et al. list 2 studies by Morris et al. (1969) in female Holtzman albino rats and one by Erturk et al. (1970) in female Sprague-Dawley rats all run at similar dose levels. In all 3 studies the majority of animals developed mammary gland tumors. All treated animals in one of the Morris et al. (1969) studies developed mammary tumors; the other study by these same researchers was of slightly shorter duration, and for this reason may not have been as sensitive. The lower bound estimate on potency from the Morris study with 100% incidence of mammary tumors in Holtzman rats is slightly less than the upper bound estimate derived from the study in Sprague-Dawley rats. Thus, had the study been run at lower dose levels, the resulting potency value may have been higher than that estimated from the dose-response data by Erturk (i.e., Holtzman rats may be more sensitive than Sprague-Dawley rats). The best study in Gold et al. for the derivation of potency is by Erturk et al. (1970) in female Sprague-Dawley rats because it has significantly more animals in the control group than the other studies. However, for the reasons given above, the potency derived from this study may be an underestimate.

Morris JE, Price JM, Lalich JJ and Stein RJ (1969). The carcinogenic activity of some 5-nitrofuran derivatives in the rat. *Cancer Res.* 29: 2145-2156.

Erturk E, Morris JE, Cohen SM, Price JM and Bryan GT (1970). Transplantable rat mammary tumors induced by 5-nitro-2-furaldehyde semicarbazone and by formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl]hydrazide. *Cancer Res.* 30: 1409-1412.

1-[(5-Nitrofurfurylidene)-amino]-2-imidazolidinone

Cancer Potency: $1.8\ (mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: $0.4\ \mu g/day$

The feeding study by Cohen et al. (1963) in female Sprague-Dawley rats is the only one available for cancer potency estimation. All 31 treated animals developed mammary gland tumors. Twenty-nine out of the 31 developed mammary gland adenocarcinomas. Because the combined incidence of mammary gland tumors is 100%, it is not possible to estimate an upper bound potency from that data set. Because no other data are available in Gold et al., we recommend that the dose response data for mammary gland adenocarcinomas be used to estimate potency, although this will produce an underestimate.

Cohen SM, Erturk E, Von Esch AM, Crovetti AJ and Bryan GT (1973). Carcinogenicity of 5-nitrofurans, 5-nitroimidazoles, 4-nitrobenzenes, and related compounds. *J. Nat. Cancer Inst.* 51: 403-417.

N-[4-(5-Nitro-2-furyl)-2-thiazolyl]acetamide

Cancer Potency: $1.5\ (mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: $0.5\ \mu g/day$

Gold et al. list the results from one feeding study in male Syrian Golden hamsters and two studies in female Sprague-Dawley rats. The hamsters are the more sensitive species and the urinary bladder is the most sensitive site. Cancer potency is therefore derived from dose response data for the combined incidence of malignant and benign tumors of the urinary bladder (Croft and Bryan, 1973).

Croft WA and Bryan GT (1973). Production of urinary bladder carcinomas in male hamsters by N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide, N-[4-(5-nitro-2-furyl)-2-thiazolyl]acetamide, or formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl]hydrazide. *J. Nat. Cancer Inst.* 51: 941-949.

p-Nitrosodiphenylamine

Cancer Potency: 0.022 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 30 $\mu g/day$

Results of NCI (1979) feeding studies in male and female $B6C3F_1$ mice and F344 rats are listed. The NTP (1991) characterizes the studies in male rats and male mice as positive. Significant increases in malignant liver tumors were observed in males of both species, with rats displaying greater sensitivity to the compound. However, survival was significantly reduced in the study in male mice, so the apparently lower sensitivity of these animals may have been due to the fact that they were at risk for a shorter time period than the rats. Cancer potency is based on the dose response data for liver tumors in male rats.

National Cancer Institute (NCI, 1979). *Bioassay of p-Nitrosodiphenylamine for Possible Carcinogenicity*. Carcinogenesis Technical Report Series No. 190. NTIS Publication No. PB 295100. US Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

National Toxicology Program (NTP, 1991). *Chemical Status Report*. US Department of Health and Human Services, NTP, Research Triangle Park, NC.

N-Nitroso-N-methylurethane

Cancer Potency: 110 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.006 $\mu g/day$

The gavage study by Herrold (1966) in Syrian Golden hamsters is the only study listed in Gold et al. All treated animals developed epidermoid carcinomas of the forestomach, so an upper bound on potency cannot be obtained from this site. Cancer potency is based on epidermoid carcinomas of the esophagus.

Herrold KM (1966). Epidermoid carcinomas of esophagus and forestomach induced in Syrian hamsters by N-nitroso-N-methylurethan. *J. Nat. Cancer Inst.* 37: 389-394.

N-Nitrosomorpholine

Cancer Potency: 6.7 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.1 $\mu g/day$

Gold et al. list results from the drinking water study in male and female Syrian Golden hamsters by Ketkar et al. (1983). Tumors of the respiratory system and liver were observed at significant levels in both studies. Females were slightly more sensitive than males. Cancer potency is based on tumors of the respiratory system, the more sensitive site, in female hamsters.

Ketkar MB, Holste J, Preussmann R and Althoff J (1983). Carcinogenic effect of nitrosomorpholine administered in the drinking water to Syrian golden hamsters. *Cancer Lett.* 17: 333-338.

N-Nitrosonornicotine

Cancer Potency: 1.4 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.5 $\mu g/day$

Numerous studies have demonstrated the carcinogenicity of N-nitrosonornicotine (IARC, 1985). The drinking water studies in male and female Syrian Golden hamsters by Hecht et al. (1983) are the only ones listed in Gold et al. Tumors of the respiratory system were observed in both studies. Males were slightly more sensitive than females. Cancer potency is based on papillomas of the respiratory system in male hamsters.

Hecht SS, Young R and Maeura Y (1983). Comparative carcinogenicity in F344 rats and Syrian golden hamsters of N'-nitrosonornicotine and N'-nitrosonornicotine-1-N-oxide. *Cancer Lett.* 20: 333-340.

International Agency for Research on Cancer (IARC, 1985). *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans.* Tobacco habits other than smoking; betel-quid and areca-nut chewing; and some related nitrosamines. Volume 37. IARC, Lyon, France.

N-Nitrosopiperidine

Cancer Potency:	9.4 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake:	0.07 $\mu g/day$

Gold et al. list results from drinking water studies in male and female Syrian Golden hamsters, feeding studies in male ICR mice, feeding studies in rhesus and cynomologous monkeys, intraperitoneal studies in rhesus monkeys (combined data for males and females), and drinking water studies in Sprague-Dawley rats (combined data for males and females). N-Nitrosopiperidine induced liver tumors in all species and strains. Hamsters are the least sensitive of the species tested. The majority of treated primates developed liver tumors, including all cynomologous monkeys given the compound in feed. Rats and mice exhibit sensitivity similar to primates. Because treatment groups in the primate studies are small and incidences observed are high, accurate estimates of cancer potency cannot be obtained from these studies. Of the dose response data available for rats and mice, the highest quality data set is reported by Eisenbrand et al. (1980) for liver tumors in Sprague-Dawley rats. In this study, multiple dose groups were used and the lowest dose groups were large (78 and 75 animals in the two lowest dose groups). Cancer potency is derived from this data set.

Eisenbrand G, Habs M, Schmahl D and Preussman R (1980). *Carcinogenicity of N-nitroso-3-hydroxypyrrolidine and dose-response study with N-nitrosopiperidine in rats.* In: IARC Scientific Publication #31. (E.A. Walker, L Criciute, M Castegnaro, and M Borzsonyi, Eds.), World Health Organization, International Agency for Research on Cancer, Lyon, France, pp. 657-663.

Phenacetin

Cancer Potency:	0.0022 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake:	300 $\mu g/day$

Feeding studies are listed for male and female $B6C3F_1$ and C57BL mice, Sprague-Dawley rats (2 studies), and female Wistar rats. In these studies, the liver and urinary bladder were the most common target sites for carcinogenesis. No increases in tumors were reported for Wistar rats. Sprague-Dawley rats appear to be more sensitive than the two mouse strains studied. The studies in Sprague-Dawley rats by Isaka et al. (1979) were of greater sensitivity in terms of numbers of animals per group and number of treatment groups than the study by Johansson (1981). Cancer potency is estimated from the results for the Isaka et al. (1979) study. Quantitatively, male and female rats in this study are of similar sensitivity. Cancer potency is estimated from the dose response data in male rats for nasal adenocarcinomas.

Johansson SL (1981). Carcinogenicity of analgesics: long-term treatment of Sprague-Dawley rats with phenacetin, phenazone, caffeine and paracetamol (acetamidophen). *Int. J. Cancer* 27: 521-529.

Isaka H, Yoshii H, Otsuji A, Koike M, Nagai Y, Koura M, Sugiyasu K and Kanabayashi T (1979). Tumors of Sprague-Dawley rats induced by long-term feeding of phenacetin. *Gann* 70: 29-36.

Phenazopyridine

Cancer Potency:	0.17 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake:	4 $\mu g/day$

Cancer potency for phenazopyridine is calculated from the value for phenazopyridine hydrochloride. For more explanation, see below and the glossary to Appendix 1.

Phenazopyridine hydrochloride

Cancer Potency:	0.15 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake:	5 $\mu g/day$

Gold et al. list the results of NCI (1978) feeding studies in male and female $B6C3F_1$ mice and F344 rats. The most sensitive species/sex combination is female mice. Cancer potency is estimated from dose response data for the combined incidence of benign and malignant liver tumors in these animals.

National Cancer Institute (NCI, 1978). *Bioassay of Phenazopyridine Hydrochloride for Possible Carcinogenicity.* Carcinogenesis Technical Report Series No. 99. NTIS Publication No. PB 286207. US Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

Phenesterin

Cancer Potency:	150 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake:	0.005 $\mu g/day$

Gold et al. list the results of NCI (1978) gavage studies in male and female $B6C3F_1$ mice and Sprague-Dawley rats. Quantitatively, the female mice are of the same or slightly greater sensitivity than male mice or female rats. Cancer potency is estimated from the combined incidence of benign and malignant tumors of the lung, the most sensitive site in female mice. Because survival was poor for the study in female mice, potency was derived using a time-to-tumor analysis (Crump et al., 1991).

Crump KS, Howe RB, Van Landingham C, and Fuller WG (1991). **TOX_RISK** Version 3. **TOX**icology **RISK** Assessment Program. KS Crump Division, Clement International Corporation, 1201 Gaines Street, Ruston, Louisiana 71270.

National Cancer Institute (NCI, 1978). *Bioassay of Phenesterin for Possible Carcinogenicity.* Carcinogenesis Technical Report Series No. 60. NTIS Publication No. PB 283361. US Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

Phenobarbital

Cancer Potency: 0.46 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 2 $\mu g/day$

Results from studies in mice, rats, and hamsters are listed. The studies in rats and hamsters did not produce significant results. For the positive studies in mice, the liver was the target site for carcinogenesis. Studies in mice were performed at similar dose levels, but with very different results. In some studies all treated animals developed tumors, whereas in others none developed tumors. The studies were performed in various strains of mice, so these results may be indicative of strain differences. Cancer potency is estimated from the positive study exhibiting low background incidence in controls and having the largest number of animals in control and exposed groups -- the study on male C3H/He mice by Evans et al. (1986).

Evans JG, Collins MA, Savage SA, Lake BG and Butler WH (1986). The histology and development of hepatic nodules in C3H/He mice following chronic administration of phenobarbitone. *Carcinogenesis* 7: 627-631.

Phenoxybenzamine

Cancer Potency: 3.1 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.2 $\mu g/day$

Cancer potency is derived from the potency value for phenoxybenzamine hydrochloride, as described below and in the glossary to Appendix 1.

National Cancer Institute (NCI, 1978). *Bioassay of Phenoxybenzamine Hydrochloride for Possible Carcinogenicity.* Carcinogenesis Technical Report Series No. 72. NTIS Publication No. PB 285095. US Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

Phenoxybenzamine hydrochloride

Cancer Potency: 2.7 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.3 $\mu g/day$

Gold et al. list the results of NCI (1978) intraperitoneal studies in male and female $B6C3F_1$ mice and F344 rats. Cancer potency is based on sarcomas of the peritoneum of male rats, the most sensitive target site in the most sensitive sex and species tested.

National Cancer Institute (NCI, 1978). *Bioassay of Phenoxybenzamine Hydrochloride for Possible Carcinogenicity.* Carcinogenesis Technical Report Series No. 72. NTIS Publication No. PB 285095. US Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

o-Phenylphenate, sodium

Cancer Potency: 0.0030 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 200 $\mu g/day$

Gold et al. list the results of several studies in $B6C3F_1$ mice and F344/DuCrj rats. Rats appear to be more sensitive than mice. There is one study in male rats with multiple dose groups (Hiraga and Fujii, 1981). This is used as the basis of the potency determination because of its greater power to define the dose response curve and because rats are the more

sensitive strain. Cancer potency is based on dose response data for the combined incidence of benign and malignant urinary tract tumors observed in this study.

Hiraga K and Fujii T (1981). Induction of tumors of the urinary system in the F344 rats by dietary administration of sodium o-phenylphenate. *Food Cosmet. Toxicol.* 19: 303-310.

Ponceau MX (D & C Red No. 5)

Cancer Potency: 0.0045 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 200 $\mu g/day$

Gold et al. list feeding studies on male and female DDY mice and three strains of rats. Tumors of the liver were reported in all studies. The sensitivities of rats and mice appear to be similar. Cancer potency is based on dose response data for liver tumors from the study of highest quality in the more sensitive sex -- the multiple dose study in female CFE rats by Grasso et al. (1969). Although this study showed liver nodules only, other studies showed progression to carcinomas in the same species (rat). Because the Grasso et al. (1969) study provided much better dose response data, it was chosen for this analysis.

Grasso P, Lansdown ABG, Kiss IS, Gaunt IF and Gangolli SD (1969). Nodular hyperplasia in the rat liver following prolonged feeding of ponceau MX. *Food Cosmet. Toxicol.* 7: 425-442.

Ponceau 3R (FD & C Red No. 1)

Cancer Potency: 0.016 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 40 $\mu g/day$

Gold et al. list the results of eight feeding studies in: 1) Bethesda black rats (both sexes combined) by Hansen et al. (1963), 2) Osborne Mendel rats (both sexes combined) by Hansen et al. (1963), 3) Wistar rats (four studies, both sexes combined) by Mannell et al. (1964), 4) male rats of an unspecified strain by Grice et al. (1961), 5) female rats of an unspecified strain also by Grice et al. Increases in liver tumors were observed in treated animals in all eight studies. Tumors of the bile duct were also observed in some studies. None of the eight studies stood out as the most appropriate for potency estimation, so potency was taken as the geometric mean of values generated from the most sensitive site in each of the studies.

Grice HC, Mannell WA and Allmark MG (1961). Liver tumors in rats fed ponceau 3R. *Toxicol. Appl. Pharmacol.* 3: 509-520.

Hansen WH, Davis KJ, Fitzhug OG and Nelson AA (1963). Chronic oral toxicity of ponceau 3R. *Toxicol. Appl. Pharmacol.* 5: 105-118.

Mannell WA (1964). Further investigations on production of liver tumors in rats by ponceau 3R. *Food Cosmet. Toxicol.* 2: 169-174.

Potassium bromate

Cancer Potency: 0.49 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 1 $\mu g/day$

Gold et al. list results from drinking water studies in male and female $B6C3F_1$ mice and F344 rats, as well as feeding studies in male and female "Theiller's Original" mice. Rats appear to

be significantly more sensitive to the carcinogenic effects of potassium bromate than do mice. Male and female rats are of similar sensitivity. Cancer potency is estimated from the dose response data for combined benign and malignant kidney tumors in male rats.

Kurokawa Y, Hayashi Y, Maekawa A, Takahashi M, Kokubo T and Odashima S (1983). Carcinogenicity of potassium bromate administered orally to F344 rats. *J. Nat. Cancer Inst.* 71: 965-972.

Procarbazine

Cancer Potency: 14 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.05 $\mu g/day$

Cancer potency is derived from the value for the hydrochloride, after correcting for differences in molecular weight. For more details see below and the glossary to Appendix 1.

Procarbazine hydrochloride

Cancer Potency: 12 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.06 $\mu g/day$

Gold et al. list results from intraperitoneal injection studies in male and female $B6C3F_1$ mice, Swiss mice, and Sprague-Dawley rats (2 studies per sex), and from mixed exposure studies in male and female cynomologous monkeys. The studies in primates are difficult to compare with the rodent studies, because study designs are so different. Mice and rats have similar sensitivities, with mice perhaps slightly more sensitive than rats. Cancer potency is derived from studies in mice (NCI, 1979; Skipper, 1976; Weisburger, 1977). Because no particular study in mice stands out as the most appropriate, potency is derived by taking the geometric mean of potencies derived from 1) male $B6C3F_1$ mice (benign and malignant lung tumors), 2) female $B6C3F_1$ mice (uterine adenocarcinomas), 3) male Swiss mice (lung tumors), and 4) female Swiss mice (lung tumors).

National Cancer Institute (NCI, 1979). *Bioassay of Procarbazine Hydrochloride for Possible Carcinogenicity.* Carcinogenesis Technical Report Series No. 19. NTIS Publication No. PB 299902. US Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

Skipper HE (1976). *Booklet 1, Phase I Studies on the Carcinogenic Activity of Anticancer Drugs in Mice and Rats.* Final report. Southern Research Institute, Birmingham, AL.

Weisburger EK (1977). Bioassay program for carcinogenic hazards of cancer chemotherapeutic agents. *Cancer* 40: 1935-1949.

1,3-Propane sultone

Cancer Potency: 2.4 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.3 $\mu g/day$

Gold et al. report the results of the gavage studies by Weisburger et al. (1981) in male and female Charles River CD rats. The sexes are of similar sensitivity. Cancer potency is estimated from dose response data in male rats for uncommon malignant gliomas of the cerebellum, the most sensitive site in males.

Weisburger EK, Ulland BM, Nam J, Gart JJ and Weisburger JH (1981). Carcinogencity tests of certain environmental and industrial chemicals. *J. Nat. Cancer Inst.* 67: 75-88.

beta-Propiolactone

Cancer Potency: 14 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.05 $\mu g/day$

Gold et al. report results for gavage studies in male and female Ha/ICR mice and female Sprague-Dawley and Eastern Sprague-Dawley rats. Forestomach tumors, including squamous cell carcinomas, were observed in both sexes of mice, and stomach tumors were observed in both studies in female rats. All groups exhibited similar sensitivity. Cancer potency is estimated from dose response data for forestomach tumors in male mice (Van Duuren et al., 1979), which are perhaps slightly more sensitive than the rat.

Van Duuren BL, Goldschmidt BM, Loewengart G, Smith AC, Melchionne S, Seidman I and Roth D (1979). Carcinogenicity of halogenated olefinic and aliphatic hydrocarbons in mice. *J. Nat. Cancer Inst.* 63: 1433-1439.

Propylthiouracil

Cancer Potency: 1.0 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.7 $\mu g/day$

Gold et al. report dose response data for feeding studies in C57BL mice (both sexes combined) and male Long Evans rats, and drinking water studies in male and female Wistar albino rats. Gold et al. also report on an inadequate drinking water study in Wistar rats exposed to the compound for only 6 months. This study is of lower power compared to the other studies due to the substantially shorter dosing period and much smaller group sizes. In the study in C57BL mice propylthiouracil induced pituitary adenomas; in each positive rat study it induced thyroid tumors. Quantitatively, rats were more sensitive than the mice studied. In the positive studies, rats exhibited similar sensitivities. Cancer potency is estimated from the rat study with the largest number of animals in the treatment and control groups -- the study by Lindsay et al. (1966) in male Long Evans rats. This study detected thyroid adenomas only; studies in other strains of rats found both malignant and benign thyroid tumors.

Lindsay S, Nichols CW and Chaikoff IL (1966). Induction of benign and malignant thyroid neoplasms in the rat. Induction of thyroid neoplasms by injection of 131-I with or without the feeding of diets containing propylthiouracil and/or desiccated thyroid. *Arch. Pathol.* 81: 308-316.

Reserpine

Cancer Potency: 11 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.06 $\mu g/day$

Gold et al. list the results of NCI (1982) feeding studies in male and female $B6C3F_1$ mice and F344 rats. In addition, feeding studies in male and female Wistar rats and female C3H mice are reported. NTP (1991) characterizes the results for the NCI studies in male and female mice and male rats as positive, and the study in female rats as negative. Results for the studies in Wistar rats and C3H mice are negative and suggest that the strains may not have been as sensitive as those used by NCI since similar dose levels were used in all experiments. Cancer

potency is estimated from benign and malignant adrenal tumors in male F344 rats, the most sensitive species/strain/sex tested.

National Cancer Institute (NCI, 1982). *Bioassay of Reserpine for Possible Carcinogenicity*. Carcinogenesis Technical Report Series No. 193. NTIS Publication No. PB 83165761. US Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

National Toxicology Program (NTP, 1991). *Chemical Status Report*. US Department of Health and Human Services, NTP, Research Triangle Park, NC.

Safrole

Cancer Potency:	0.22 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake:	3 $\mu g/day$

A number of studies are available in various strains of rats and mice. Mice appear to be slightly more sensitive than rats. No particular study stands out as being the most suitable for potency estimation. Thus, the potencies derived from the numerous studies available in mice, the presumably more sensitive species, are used to calculate a geometric mean. The following 12 data sets in mice are used: 1) benign and malignant liver tumors in female $B6AKF_1$ and 2) male $B6AKF_1$ reported by Innes (1968) and Innes et al. (1969); 3) benign and malignant liver tumors in female $B6C3F_1$ and 4) male $B6C3F_1$ reported by Vesselinovitch et al. (1979); 5) hepatocellular tumors in male $B6C3F_1$ mice reported by Innes (1968) and Innes et al. (1969); 6) hepatocellular adenomas in male BALB/c mice reported by Lipsky et al. (1981) (carcinomas were also observed in this study, but the combined incidence of benign and malignant tumors was not reported in Gold et al.); 7) hepatocellular carcinomas in female CDF1 by Wislocki et al. (1977); 8) hepatomas in female CDF1 mice reported by Boberg et al. (1983); 9) and 10) hepatomas reported by Miller et al. (1983) in female CDF1 mice (2 exposure scenarios); 11) hepatocellular carcinomas in male CDF1 mice reported by Wislocki et al. (1977); and 12) hepatocellular adenomas in male CDF1 mice reported by Borchert et al. (1973).

Innes JRM (1968). *Evaluation of carcinogenic, teratogenic, and mutagenic activities of selected pesticides and industrial chemicals*. Volume 1: Carcinogenic study. Bionetics Research Laboratories, Inc. Distributed by National Technical Information Service, Springfield, VA.

Innes JRM, Ulland BM, Valerio MG, Petrucelli L, Fishbein L, Hart ER, Pallota AJ, Bates RR, Falk HL, Gart JJ, Klein M, Mitchell I and Peters J (1969). Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: a preliminary note. *J. Nat. Cancer Inst.* 42: 1101-1114.

Vesselinovitch SD, Rao KVN and Mihailovich N (1979). Transplacental and lactational carcinogenesis by safrole. *Cancer Res.* 39: 4378-4380.

Lipsky MM, Hinton DE, Klaunig JE and Trump BF (1981). Biology of hepatocellular neoplasia in the mouse. I. Histogenesis of safrole-induced hepatocellular carcinoma. *J. Nat. Cancer Inst.* 67: 365-371.

Wislocki PG, Miler EC, Miller JA, McCoy EC and Rosenkranz HS (1977). Carcinogenic and mutagenic activities of safrole, 1'-hydroxysafrole and some known or possible metabolites. *Cancer Res.* 37: 1883-1891.

Boberg EW, Miller EC, Miller JA, Pland A and Liem A (1983). Strong evidence from studies with brachymorphic mice and pentachlorophenol that 1'-sulfooxysafrole is the major ultimate electrophilic and carcinogenic metabolite of 1'-hydroxysafrole in mouse liver. *Cancer Res.* 43: 5163-5173.

Miller EC, Swanson AB, Phillips DH, Fletcher TL, Liem A and Miler JA (1983). Structure-activity studies of the carcinogenicities in the mouse and rat of some naturally occurring and synthetic alkenylbenzene derivatives related to safrole and estragole. *Cancer Res.* 43: 1124-1134.

Borchert P, Miller JA, Miller EC and Shires TK (1973). 1'-Hydrosafrole, a proximate carcinogenic metabolite of safrole in the rat and mouse. *Cancer Res.* 33: 590-600.

Sterigmatocystin

Cancer Potency: 35 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.02 $\mu g/day$

Listed are feeding studies in male and female BD I mice; male ACI/n, Donryu and Wistar rats; and a gavage study in Wistar rats (incidences of both sexes combined). In addition, there is a gavage study in Wistar rats (sexes combined). Sterigmatocystin induced liver tumors in all studies listed. In the reported studies rats are, in general, more sensitive than the mice studied. No study in rats stands out as the most appropriate for potency estimation. Cancer potency is taken as the geometric mean of potencies from the data sets for the five rat studies. Data sets used are for: liver tumors in 1) male ACI/n rats (Maekawa et al. 1979) and 2) male Donryu rats (Ohtsubo et al. 1978); hepatocellular carcinomas in the studies reported by Purchase et al (1970) in Wistar rats (sexes combined) treated 3) by gavage, and 4) by feeding; and 5) liver carcinomas reported by Terao et al. (1978) in male Wistar rats.

Maekawa A, Kajiwara T, Odashima S and Kurata H (1979). Hepatic changes in male ACI/N rats on low dietary levels of sterigmatocystin. *Gann* 70: 777-781.

Ohtsubo K, Saito M, Kimura H and Tsuruta O (1978). High incidence of hepatic tumours in rats fed mouldy rice contaminated with Aspergillus versicolor containing sterigmatocystin. *Food Cosmet. Toxicol.* 16: 143-149.

Purchase IFH and van der Watt JJ (1970). Carcinogenicity of sterigmatocystin. *Food Cosmet. Toxicol.* 8: 289-295.

Terao K, Aikawa T and Kera KA (1978). A synergistic effect of nitrosodimethylamine on sterigmatocystin carcinogenesis in rats. *Food Cosmet. Toxicol.* 16: 591-596.

Streptozotocin

Cancer Potency: 110 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.006 $\mu g/day$

Gold et al. list the results of the intraperitoneal studies in male and female Swiss mice and Charles River CD rats (Skipper, 1976; Weisburger, 1977). Tumors were observed at multiple sites. Mice were more sensitive than rats, and female mice were slightly more sensitive than male mice. Cancer potency is estimated from the most sensitive site in female mice, the lung.

Skipper HE (1976). *Booklet 1, Phase I Studies on the Carcinogenic Activity of Anticancer Drugs in Mice and Rats.* Final report. Southern Research Institute, Birmingham, AL.

Weisburger EK (1977). Bioassay program for carcinogenic hazards of cancer chemotherapeutic agents. *Cancer* 40: 1935-1949.

Styrene oxide

Cancer Potency: 0.16 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 4 $\mu g/day$

Gold et al. list the gavage studies in male and female $B6C3F_1$ mice and F344 rats by Lijinsky et al. (1986) and in Sprague-Dawley rats by Maltoni et al. (1981). Benign and malignant tumors of the forestomach were observed in all tests. Rats and mice are of similar sensitivity, with the mice studied perhaps slightly less sensitive overall than the rats. In the study in F344 rats, animals were treated for 2 years, in contrast to the Sprague-Dawley study in which animals were treated for one year and then observed for 2 subsequent years without treatment. Cancer potency is taken from the continuous exposure study of Lijinsky for F344 rats. Males and females are of similar sensitivity, with males exhibiting slightly greater sensitivity than females. Cancer potency is therefore estimated from dose response data for the male rat forestomach, the most sensitive target site in these studies.

Lijinsky W (1986). Rat and mouse forestomach tumors induced by chronic oral administration of styrene oxide. *J. Nat. Cancer Inst.* 77: 471-476.

Maltoni C (1981). Early results of the experimental assessments of the carcinogenic effects of one epoxy solvent: styrene oxide. *Adv. Mod. Environ. Toxicol.* 2: 97-110.

Sulfallate

Cancer Potency: 0.19 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 4 $\mu g/day$

Gold et al. list the results of NCI (1978) feeding studies in male and female $B6C3F_1$ mice and Osborne Mendel rats. Significant increases in tumors are observed at several sites in the four species/sex combinations tested. Quantitatively the results for the rats and female mice are similar, although rats are slightly more sensitive than mice. The dose response data in the female rat is of better quality than that in the male rat. For this reason, the female serves as the basis of the potency calculation. The most sensitive target site in female rats is the mammary gland. Cancer potency is based on dose response data for adenocarcinomas of the mammary gland in female rats.

National Cancer Institute (NCI, 1978). *Bioassay of Sulfallate for Possible Carcinogenicity.* Carcinogenesis Technical Report Series No. 115. NTIS Publication No. PB 286386. US Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

1,1,2,2-Tetrachloroethane

Cancer Potency: 0.27 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 3 $\mu g/day$

Gold et al. list the results of NCI (1978) gavage studies in male and female $B6C3F_1$ mice and Osborne Mendel rats. Significant results are not seen for rats, whereas highly significant increases in liver tumors are observed in both sexes of mice, with almost identical sensitivity. Cancer potency is estimated from dose response data for hepatocellular carcinomas in female mice rather than in male mice because the confidence bounds around the estimate are smaller in females.

National Cancer Institute (NCI, 1978). *Bioassay of 1,1,2,2-Tetrachloroethane for Possible Carcinogenicity*. Carcinogenesis Technical Report Series No. 27. NTIS Publication No. PB 277453. US Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

Thioacetamide

Cancer Potency: $6.1\ (mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: $0.1\ \mu g/day$

Listed are results from the study by Gothoskar et al. (1970) in male and female Swiss mice. Hepatomas were seen in all treated male mice, precluding estimation of the upper bound on potency in these animals. Females were slightly less sensitive; six of the seven dosed female mice developed hepatomas. Because this is the only dose response data available in Gold et al., the data for the females are used to derive potency. The value presented here may be an underestimate, but is useful as an interim value.

Gothoskar SV, Talwalkar GV and Bhide SV (1970). Tumorigenic effect of thioacetamide in Swiss strain mice. *Br. J. Cancer* 24: 498-503.

4,4'-Thiodianiline

Cancer Potency: $15\ (mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: $0.05\ \mu g/day$

Gold et al. list the results of NCI (1978) feeding studies in male and female $B6C3F_1$ mice and F344 rats. Tumors of the thyroid and liver are observed in all species/sex combinations tested, with rats more sensitive than mice. Male and female rats exhibit similar sensitivity. Cancer potency is estimated from dose response data for carcinomas of the uterus, the most sensitive site in female rats. Because survival was poor for the study in female rats, potency was derived using a time-to-tumor analysis (Crump et al., 1991).

Crump KS, Howe RB, Van Landingham C, and Fuller WG (1991). **TOX_RISK** Version 3. **TOX**icology **RISK** Assessment Program. KS Crump Division, Clement International Corporation, 1201 Gaines Street, Ruston, Louisiana 71270.

National Cancer Institute (NCI, 1978). *Bioassay of 4,4'-Thiodianiline for Possible Carcinogenicity*. Carcinogenesis Technical Report Series No. 47. NTIS Publication No. PB 280360. US Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

Thiourea

Cancer Potency: $0.072\ (mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: $10\ \mu g/day$

Listed are drinking water studies in female C3H mice, mixed exposure (drinking water and intraperitoneal injection) and drinking water studies in Hebrew University male rats, and feeding studies in Osborne Mendel rats. A positive response was observed only in the studies in Hebrew University rats, perhaps because the doses used were considerably higher than in the other studies. Thiourea induced epidermoid carcinoma of the eyelid and auricular region in both the mixed exposure and drinking water study; potencies of similar magnitude were derived from these studies. Cancer potency is based on the analysis of dose response data for the drinking water study (Vasquez-Lopez, 1949).

Vasquez-Lopez E (1949). The effects of thiourea on the development of spontaneous tumours on mice. *Br. J. Cancer* 3: 401-414.

Toluene diisocyanate

Cancer Potency: 0.039 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 20 $\mu g/day$

Gold et al. list the results of NTP (1986) gavage studies in male and female $B6C3F_1$ mice and F344 rats. Rats are more sensitive than mice. Male and female rats have similar sensitivities. Cancer potency is based on the dose response data in male rats for fibromas and fibrosarcomas of the subcutaneous tissue, the most sensitive target site.

National Toxicology Program (NTP, 1986). *Toxicology and Carcinogenesis Studies of Toluene Diisocyanate in F344/N Rats and B6C3F$_1$ Mice (Gavage Studies).* NTP Technical Report Series No. 251. NTIS Publication No. 87115176. US Department of Health and Human Services, NTP, Research Triangle Park, NC.

ortho-Toluidine

Cancer Potency: 0.18 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 4 $\mu g/day$

Cancer potency is derived from that for the hydrochloride (see below and in the glossary to Appendix 1 for explanation).

National Cancer Institute (NCI, 1979). *Bioassay of ortho-Toluidine Hydrochloride for Possible Carcinogenicity.* Carcinogenesis Technical Report Series No. 66. NTIS Publication No. PB 290908. US Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

ortho-Toluidine hydrochloride

Cancer Potency: 0.13 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 5 $\mu g/day$

Gold et al. list the results of feeding studies in male and female $B6C3F_1$ mice and F344 rats (NCI, 1979), in male and female CD-1 HaM/ICR mice and Charles River CD rats (Weisburger et al., 1978; Russfield et al. 1973), and in male F344 rats (Hecht et al.; 1982). Positive results were observed for all studies, with induction of tumors at multiple sites (e.g., liver, urinary tract, mammary gland, skin and subcutaneous tissue). Male rats appear to be more sensitive than mice or female rats. Cancer potency is based on the male rat. The geometric mean of potency values derived from the most sensitive sites in the Weisburger et al. (1978), Russfield et al. (1973), Hecht et al. (1982), and NCI (1979) studies is used as the

potency estimate. Survival was poor for the NCI study in male rats. Potency for that study was therefore derived using a time-to-tumor analysis (Crump et al., 1991).

Crump KS, Howe RB, Van Landingham C, and Fuller WG (1991). **TOX_RISK** Version 3. **TOX**icology **RISK** Assessment Program. KS Crump Division, Clement International Corporation, 1201 Gaines Street, Ruston, Louisiana 71270.

National Cancer Institute (NCI, 1979). *Bioassay of ortho-Toluidine Hydrochloride for Possible Carcinogenicity.* Carcinogenesis Technical Report Series No. 66. NTIS Publication No. PB 290908. US Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

Hecht SS, El-Bayoumy K, Rivenson A and Fiala E (1982). Comparative carcinogenicity of o-toluidine hydrochloride and o-nitrosotoluene in F344 rats. *Cancer Lett.* 16: 103-108.

Weisburger EK, Russfield AB, Homburger F, Weisburger JH, Boger E, Van Dongen CG and Chu K (1978). Testing of twenty-one aromatic amines or derivatives for long-term toxicity or carcinogenicity. *J. Environ. Pathol. Toxicol.* 2: 325-356.

Russfield AB, Homburger F, Boger E, Van Donger CG, Weisburger EK and Weisburger JH (1973). *Carcinogenicity of Chemicals in Man's Environment.* Final Report, Contract No. NIH-NCI-E-68-1311. Bio-research Consultants, Inc., Cambridge, MA.

Tris(1-aziridinyl)phosphine sulfide (Thiotepa)

Cancer Potency:	12 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake:	0.06 $\mu g/day$

Gold et al. list the results of intraperitoneal studies in male and female $B6C3F_1$ mice and Sprague-Dawley rats (NCI, 1978), and the intravenous injection study in male BR 46 rats (Schmahl et al., 1970). Rats and mice appear to be of similar sensitivities, with the female mice perhaps slightly less sensitive than the male mice or rats. Cancer potency is based on the geometric mean of potencies from the male Sprague-Dawley rat (leukemia) and female Sprague-Dawley rat (uterine adenocarcinoma) intraperitoneal studies.

National Cancer Institute (NCI, 1978). *Bioassay of Tris(1-aziridinyl)phosphine sulfide (Thiotepa) for Possible Carcinogenicity.* Carcinogenesis Technical Report Series No. 58. NTIS Publication No. PB 285702. US Department of Health, Education and Welfare (DHEW), NCI Carcinogenesis Testing Program, Bethesda, MD.

Schmahl D and Osswald H (1970). Experimentalle Untersuchungen uber carcinogene Wirkungen von Krebs-Chemotherapeutica und Immunosuppressiva. *Arzneim.-Forsch.* 20: 1461-1467.

Tris(2,3-dibromopropyl)phosphate

Cancer Potency:	2.3 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake:	0.3 $\mu g/day$

Gold et al. list the results of NCI (1978) feeding studies in male and female $B6C3F_1$ mice and F344 rats, and of the gavage study in male F344 rats by Reznik et al. (1981). The Reznik study, which had only 5 animals in the treatment group and lasted only one year, was

negative. All other studies showed significant increases in tumors at multiple sites. Cancer potency is derived from the NCI (1978) dose response data for kidney tumors in male rats, the most sensitive sex/species combination tested.

National Cancer Institute (NCI, 1978). *Bioassay of Tris(2,3-dibromopropyl)phosphate for Possible Carcinogenicity*. Carcinogenesis Technical Report Series No. 76. NTIS Publication No. PB 280271. US Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

Reznik G, Reznik-Schuller HM, Rice JM and Hague BF (1981). Pathogenesis of toxic and neoplastic renal lesions induced by the flame retardant tris(2,3-dibromopropyl)phosphate in F344 rats, and development of colonic adenomas after prolonged oral administration. *Lab. Invest.* 44: 74-83.

Trp-P-1 (Tryptophan-P-1; 3-amino-1,4-dimethyl-5H-pyrido[4,3-b]indole)

Cancer Potency: 26 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.03 $\mu g/day$

Gold et al. list the results for studies on the acetate: the feeding studies by Matsukura et al. (1981) in male and female CDF1 mice and by Takayama et al. (1985) in male and female F344/DuCrj rats. Trp-P-1 acetate induced liver tumors in all studies. The rats are significantly more sensitive than mice. Male and female rats are of equivalent sensitivity. Cancer potency for Trp-P-1 acetate is derived from dose response data for liver tumors in female rats. Cancer potency of Trp-P-1 is derived from that for the acetate following the procedures described in the glossary to Appendix 1.

Matsukura N, Kawachi T, Morino K, Ohgaki H and Sugimura T (1981). Carcinogenicity in mice of mutagenic compounds from a tryptophan pyrolyzate. *Science* 213: 346-347.

Takayama S, Nakatsuru Y, Ohgaki H, Sato S and Sugimura T (1985). Carcinogenicity in rats of a mutagenic compound, 3-amino-1,4-dimethyl-5H-pyrido[4,3-b]indole, from tryptophan pyrolysate. *Jpn. J. Cancer Res.* 76: 815-817.

Trp-P-2 (Tryptophan-P-2; 3-amino-1-methyl-5H-pyrido[4,3-b]indole)

Cancer Potency: 3.2 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake: 0.2 $\mu g/day$

Gold et al. list the results for studies on the acetate: the feeding studies by Matsukura et al. (1981) in male and female CDF1 mice and by Hosaka et al. (1981) on male and female ACI rats. Trp-P-2 acetate induced liver tumors in mice and female rats. The female rats and female mice are significantly more sensitive than males. Mice showed a greater propensity for developing malignant tumors. Thus, cancer potency for Trp-P-2 acetate is derived from dose response data for liver tumors in female mice. Cancer potency of Trp-P-2 is derived from that for the acetate following the procedures described in the glossary to Appendix 1.

Matsukura N, Kawachi T, Morino K, Ohgaki H and Sugimura T (1981). Carcinogenicity in mice of mutagenic compounds from a tryptophan pyrolyzate. *Science* 213: 346-347.

Hosaka S, Matsushima T, Hirono I and Sugimura T. (1981). Carcinogenic activity of 3-amino-1-methyl-5H-pyrido[4,3-b]indole (trp-P-2), a pyrolysis product of tryptophan. *Cancer Lett.* 13: 23-28.

Vinyl trichloride (1,1,2-Trichloroethane)

Cancer Potency:	0.072 $(mg/kg\text{-}day)^{-1}$
10^{-5} Risk Specific Intake:	10 $\mu g/day$

Gold et al. list the results of NCI (1978) gavage studies in male and female $B6C3F_1$ mice and Osborne Mendel rats. The NTP (1991) considers the findings in mice of both sexes positive, and in rats negative. The compound induced adrenal pheochromocytomas and malignant liver tumors in both sexes of mice. Females appear to be slightly more sensitive than males. Cancer potency is based on the dose response data for hepatocellular carcinomas in female mice.

National Cancer Institute (NCI, 1978). *Bioassay of 1,1,2-Trichloroethane for Possible Carcinogenicity*. Carcinogenesis Technical Report Series No. 74. NTIS Publication No. PB 283337. US Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

National Toxicology Program (NTP, 1991). *Chemical Status Report*. US Department of Health and Human Services, NTP, Research Triangle Park, NC.