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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

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This paper is the third chronological supplement to the Carcinogenic Potency Database that first appeared in this journal in 1984 (*1–4*). We report here results of carcinogenesis bioassays published in the general literature between January 1985 and December 1986, and in Technical Reports of the National Toxicology Program between June 1986 and June 1987. This supplement includes results of 337 long-term, chronic experiments of 121 compounds, and reports the same information about each experiment in the same plot format as the earlier papers, e.g., the species and strain of animal, the route and duration of compound administration, dose level, and other aspects of experimental protocol, histopathology, and tumor incidence, TD_{50} (carcinogenic potency) and its statistical significance, dose response, opinion of the author about carcinogenicity, and literature citation. The reader needs to refer to the 1984 publication for a guide to the plot of the database, a complete description of the numerical index of carcinogenic potency, and a discussion of the sources of data, the rationale for the inclusion of particular experiments and particular target sites, and the conventions adopted in summarizing the literature. The four plots of the database are to be used together as results published earlier are not repeated. In all, the four plots include results for approximately 4000 experiments on 1050 chemicals. Appendix 14 of this paper is an alphabetical index to all chemicals in the database and indicates which plot(s) each chemical appears in. A combined plot of all results from the four separate papers, that is ordered alphabetically by chemical, is available from the first author, in printed form or on computer tape or diskette.

Background

Development of the Carcinogenic Potency Database (CPDB) began a decade ago, when efforts to use animal bioassays to analyze the carcinogenic process in rodent experiments and to evaluate possible hazards to humans were hampered by the lack of a standardized method of comparing test results. Experimental protocols as well as the type of information reported in the literature are quite diverse, and this large body of information was underused. Moreover, quantitative estimates of carcinogenic potency with a single measure had not been made for the large number of substances that had been tested chronically in rodents; such a measure is required to compare rodent potency to other factors such as mutagenicity, teratogenicity, chemical structure, and

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human exposure. The CPDB provides a standardized resource of both qualitative and quantitative information on the literature of chronic, long-term cancer tests (*1-3*), including results published in the general literature and in Technical Reports of the National Cancer Institute/National Toxicolgy Program (NCI/NTP). This is the fourth paper to present a portion of the CPDB in plot format. The first two papers in 1984, Gold et al. (*1*) and Peto et al. (*4*), included the published literature through June 1981, a description of our numerical index of carcinogenic potency (TD_{50}), and the statistical procedures adopted for estimating it from experimental data. Briefly, TD_{50} may be defined as follows: for a given target site(s), if there are no tumors in control animals, then TD_{50} is that chronic dose rate in mg/kg body weight/day that would induce tumors in half the animals tested at the end of a standard lifespan for the species. Since the tumor(s) of interest often does occur in control animals, TD_{50} is more precisely defined as that chronic dose rate that will halve the probability of remaining tumor-free throughout the standard lifespan of the species (*4,5*). The range of significant TD_{50} values for carcinogens in the CPDB is more than 10 millionfold.

A detailed guide to the plot of the database was included in the 1984 paper (*1*); it described the contents, field by field, and discussed the sources of data, the criteria for the inclusion of particular experiments and particular target sites, and the conventions adopted in summarizing the literature. The second (*2*) and third (*3*) plots were chronological supplements, and the current plot covers general literature published in 1985 and 1986 as well as NTP Technical Reports between June 1986 and June 1987. It is our intention that the four plots be used together, and that readers who are not familar with the CPDB will first read the 1984 papers when using the plot in this paper. We have not duplicated earlier results, and thus for complete data on each chemical that appears in more than one plot, all four publications are necessary.

Each plot of the database provides the same set of information about each experiment in the same format, including: the species, strain, and sex of animal tested; features of the experimental protocol such as route of administration, duration of dosing, dose level in mg/kg body weight/day, and duration of experiment; histopathology and tumor incidence; carcinogenic potency and its statistical significance; shape of the dose-response curve; opinion of the author as to the carcinogenicity; and literature citation. A word of caution is necessary about the limitations of the database. We have included only long-term tests of individual compounds that fit a set of criteria compatible with calculating potency; many animal cancer tests are excluded. Moreover, we have not attempted to evaluate whether or not a compound is a carcinogen; rather, we report the published opinions of the investigators whose data we present, as well as the statistical significance of the TD_{50} calculated from their results. Furthur discussion of the criteria for the database and the limitations can be found in (*1*).

In this fourth plot, the author's opinion column for the NTP bioassays reflects a new set of interpretive categories that NTP adopted in 1983 and redefined in 1986. Two of the categories are considered positive by NTP. We report the NTP evaluations using the codes "c" for clear evidence of carcinogenic activity; "p" for "some evidence of carcinogenic activity" in an experiment that is positive but where the strength of the response is less than that required for clear evidence; "e" for equivocal evidence of carcinogenic activity; and "-" for no evidence of carcinogenic activity. The full definitions of the NTP levels of evidence are given in Appendix 11. For the general literature the "author's opinion" column is "+" for a positive opinion, "−" for a negative opinion; in other cases the column for the literature is blank, including unclear and borderline opinions.

The appendices to each of the four plots provide the same types of information for the data in that publication, and are given the same appendix numbers. Appendix 1 lists alphabetically the compounds included in the current plot and their common synonyms; Appendix 2 provides a list of those same compounds ordered by Chemical Abstracts Service (CAS) Registry number. The next several appendices provide codes and definitions required for using the plot: strains of test animal (Appendix 3); routes of administration (Appendix 4); sites of tumor induction (Appendix 5); histopathology (Appendix 6); notecodes (Appendix 7); dose-response curve symbols (Appendix 8); reference codes (Appendix 9); NCI/NTP bioassays evaluated as inadequate (Appendix 10); and author's opinion codes (Appendix 11). Appendices 12 and 13 give full bibliographic information for all experiments reported in this plot: the bibliography for the general literature (Appendix 12) and a list of the NCI/NTP Technical Reports (Appendix 13). Appendix 14 lists the 1053 chemicals that appear in any of the four plots, and indicates which plot contains results of experiments on each chemical; it is ordered alphabetically by chemical name and common synonym.

We are continuing to update the Carcinogenic Potency Database with papers published after 1986, and are also attempting to add earlier papers that we overlooked in our literature search. Therefore, we would appreciate information about any tests that the reader notices are missing.

Plot in This Supplement

The plot of the database below includes results of 337 long-term, chronic experiments on 121 chemicals. It reports results for 20 compounds from Technical Reports of the NTP published between June 1986 and June 1987, and results for 102 compounds published in the general literature between January 1985 and December 1986. Experiments in rats, mice, and hamsters are reported here for compounds representing a

variety of chemical classes, with a variety of uses. Some are naturally occurring substances (e.g., acetaldehyde, hydrazine, and formaldehyde); food additives (e.g., potassium bromate and butylated hydroxyanisole); industrial compounds (e.g., methylene chloride and benzene); and drugs (e.g., phenobarbital and acetaminophen). Of the 121 chemicals, 44 were also included in the first, second, or third plots, and we have flagged these with a triple asterisk (***) after the chemical name in the plot. For some substances, only a few experiments are reported here, but several experiments were previously reported, e.g., 2-acetylaminofluorene and ethyl alcohol. The TD_{50} values for the compounds in this supplementary plot fall within the range of values reported earlier.

Analyses of the Database

Taken together, the four plots of the CPDB include more than 4000 experiments on 1050 chemicals that meet the inclusion rules of the database and are therefore suitable for estimating TD_{50}. Although the inclusion rules assure some consistency in experimental protocol, there is great diversity in the database. Most of the chemicals have been tested in rats or mice; however, some have been tested in hamsters, dogs, or monkeys. Experiments with 96 different mouse strains and 72 rat strains are included. For a given chemical, the database may contain only a single experiment or several experiments. For example, among the 788 chemicals tested in rats, 28% have only one rat test and 52% have two tests; however, 13 chemicals have more than 10 tests. Overall about half of the 1050 chemicals in the database are positive in at least one experiment according to the opinion of the published author. This proportion is similar for rats and mice.

Our group has used the CPDB to address many issues relevant to chemical carcinogenesis and interspecies extrapolation. We summarize this work below and refer the reader to the published papers.

With respect to the measurement of carcinogenic potency, two methods for estimating TD_{50} from animal bioassays have been compared, one based on lifetable data and one based on summary incidence data (*6*). Second, we have shown that the potency calculated from experimental results is restricted to an approximately 30-fold range surrounding the maximum dose tested in a standard bioassay (*7*). Third, for chemicals that are positive in more than one test in a species, our analysis indicates that the most potent TD_{50} value from among all positive tests is similar to other measures that average TD_{50} values or functions of values (*8*). For the chemicals that induce tumors in rats or mice, we have presented a concise tabulation of the most potent TD_{50} values and a summary of the evaluations of carcinogenicity in each sex-species group (*8*).

Correlation studies of carcinogenic potency have been conducted. We have discussed some tautologous aspects of the good correlation in potency between rats and mice (*7*) and have reported a weak association of mutagenic potency and carcinogenic potency for 80 chemicals that are both mutagenic in Salmonella and carcinogenic in rats or mice (*9*).

Reproducibility of results in animal bioassays has been investigated in 70 "near-replicate" comparisons consisting of two or more tests of the same chemical, administered by the same route, and using the same sex and strain of rodent. Overall there was good reproducibility of positivity, target site, and TD_{50} in rats, mice, and hamsters (*10*). We have described the potencies of compounds that induce tumors at particular target sites in rats and mice and have examined other indicators of a chemical's hazard including whether or not tumors were induced at more than one site in a single sex-species group of animal, whether or not tumors may have caused the death of the animal or were found at sacrifice, and whether or not metastases of induced tumors occurred (*11*).

We have proposed a rough index of possible carcinogenic hazard to humans, HERP, that compares for a given chemical, the chronic dose rate at which humans are exposed (mg/kg/day) to the TD_{50} in rodents. We have computed HERP values for a variety of man-made and naturally occurring substances to which people may be exposed and have constructed a scale to rank possible hazards. This ranking suggests that carcinogenic hazards from current levels of pesticide residues or water pollution are likely to be of minimal concern relative to the background levels of natural substances, though one cannot say whether these natural exposures are likely to be of major or minor importance in human cancer (*12-17*). In a separate analysis we rank the potential carcinogenic hazards (PERP) permitted to U.S. workers from exposures to 41 rodent carcinogens that are regulated with Permissible Exposure Levels (PELs) by the U.S. Occupational, Safety, and Health Administration (*18*). For some substances, exposures at the PEL would be close to the dose rate that produces tumors in 50% of test animals.

Approximately half of the chemicals tested in rodent bioassays are positive in at least one experiment, and among chemicals tested for mutagenicity as well as for carcinogenicity in both rats and mice, three-quarters are either mutagens or carcinogens. We have discussed how representative this positive rate might be of the proportion of all chemicals that would be positive if tested in rodents, or the proportion of all chemicals that are potentially carcinogenic to humans (*12,19*).

The issue of extrapolating carcinogenesis results from one species to another has been addressed in an analysis of prediction between two closely related species, rats and mice. We have examined how well one can predict from rats to mice and from mice to rats, and discuss three factors that affect the accuracy of prediction: chemical class, mutagenicity, and

the dose level at which a chemical is toxic. Additionally, we have described the frequency of a carcinogenic response in each target organ and have determined the predictive value of individual target sites in one species for carcinogenicity in the second species (*19*).

We are continuing to calculate HERP and PERP values as we expand the CPDB and to conduct several additional analyses, e.g., the reproducibility of bioassay results when chemicals are administered by different routes, the comparison of results in rodents and monkeys, and the amounts of rodent carcinogens that occur naturally in edible plants.

Errata in Earlier Plots

A few omissions and errors in the first plot of the CPDB (*1*) have come to our attention. The CAS number for D & C Red No. 10 was omitted; it should be 1248-18-6. The CAS number for 2-chloro-5-(3,5-dimethylpiperidinosulfonyl)benzoic acid was reported incorrectly; it should be 37087-94-8. The citation for Gass and Allaben (1977) was incorrect; the citation should be IRCS Med. Sci.: Libr. Compend. 5: 477 (1977). For two chemicals reported earlier, aspertame and di(2-ethyhexyl)phthalate, the dose calculation was incorrect. Therefore, other values such as the TD_{50} were also incorrect. Below we report the corrected plot for these two chemicals.

Left Side of Plot

	Spe Strain Site Xpo+Xpt Sex Route Hist Notes		TD50 2Tailpvl DR AuOp
ASPARTAME	100ng..:..1ug....:..10.....:..100....:..1mg....:..10.....:..100....:..1g.....:..10		
1	R f sls eat bra tum 52w52 ekr	.>	no dre P=1.
2	R f sls eat bra mix 24m24 er		no dre P=1. -
3	R m sls eat bra tum 52w52 ekr	.>	no dre P=1.
4	R m sls eat bra mix 24m24 er		186.gm * P<.5 -
DI(2-ETHYLHEXYL)PHTHALATE	100ng..:..1ug....:..10.....:..100....:..1mg....:..10.....:..100....:..1g.....:..10		
5	M f b6c eat liv MXA 24m24	: + :	825.mg * P<.0005c
a	M f b6c eat liv hpc 24m24		1.05gm * P<.0005c
b	M f b6c eat TBA MXB 24m24		350.mg P<.003
c	M f b6c eat liv MXB 24m24		825.mg * P<.0005
d	M f b6c eat lun MXB 24m24		7.26gm * P<.07
6	M m b6c eat liv MXA 24m24	: ±	976.mg * P<.03 c
a	M m b6c eat liv hpc 24m24		1.82gm * P<.08 c
b	M m b6c eat TBA MXB 24m24		1.54gm * P<.4
c	M m b6c eat liv MXB 24m24		976.mg * P<.03
d	M m b6c eat lun MXB 24m24		no dre P=1.
7	R f f34 eat liv MXA 24m24	: + :	1.11gm * P<.0005c
a	R f f34 eat liv hpc 24m24		2.30gm * P<.002 c
b	R f f34 eat liv nnd 24m24		2.35gm * P<.02
c	R f f34 eat TBA MXB 24m24		1.67gm * P<.6
d	R f f34 eat liv MXB 24m24		1.11gm * P<.0005
8	R m f34 eat liv MXA 24m24	: ±	1.17gm * P<.03 c
a	R m f34 eat liv hpc 24m24		3.36gm * P<.2 c
b	R m f34 eat TBA MXB 24m24		no dre P=1.
c	R m f34 eat liv MXB 24m24		1.17gm * P<.03

Right Side of Plot

	RefNum	LoConf	UpConf	Cntrl	1Dose	1Inc	2Dose	2Inc			Citation or Pathology Brkly Code
ASPARTAME	22839-47-0										
1	1327m	471.mg	n.s.s.	0/16	1.00gm	0/16	2.00gm	0/16	4.00gm	0/16	Ishii;txlt,7,433-437;1981
2	1327n	45.8gm	n.s.s.	1/60	1.00gm	0/60	2.00gm	2/60	4.00gm	0/60	
3	1327m	471.mg	n.s.s.	0/16	1.00gm	0/16	2.00gm	0/16	4.00gm	0/16	
4	1327n	35.2gm	n.s.s.	0/59	1.00gm	1/59	2.00gm	0/60	4.00gm	1/60	
DI(2-ETHYLHEXYL)PHTHALATE	117-81-7										
5	c52733	513.mg	1.67gm	1/50	383.mg	12/50	765.mg	18/50			liv:hpa,hpc.
a	c52733	638.mg	1.89gm	0/50	383.mg	7/50	765.mg	17/50			
b	c52733	175.mg	2.07gm	20/50	383.mg	35/50	(765.mg	35/50)			
c	c52733	513.mg	1.67gm	1/50	383.mg	12/50	765.mg	18/50			liv:hpa,hpc,nnd.
d	c52733	2.20gm	n.s.s.	0/50	383.mg	1/50	765.mg	2/50			lun:a/a,a/c.
6	c52733	440.mg	n.s.s.	14/50	353.mg	25/49	713.mg	29/50			liv:hpa,hpc.
a	c52733	736.mg	n.s.s.	9/50	353.mg	14/49	713.mg	19/50			
b	c52733	413.mg	n.s.s.	29/50	353.mg	37/49	713.mg	38/50			
c	c52733	440.mg	n.s.s.	14/50	353.mg	25/49	713.mg	29/50			liv:hpa,hpc,nnd.
d	c52733	1.97gm	n.s.s.	10/50	353.mg	9/49	713.mg	7/50			lun:a/a,a/c.
7	c52733	644.mg	2.40gm	0/50	294.mg	6/50	589.mg	13/50			liv:hpc,nnd.
a	c52733	1.12gm	5.90gm	0/50	294.mg	2/50	589.mg	8/50			
b	c52733	1.11gm	n.s.s.	0/50	294.mg	4/50	589.mg	5/50			S
c	c52733	321.mg	n.s.s.	41/50	294.mg	43/50	589.mg	49/50			
d	c52733	644.mg	2.40gm	0/50	294.mg	6/50	589.mg	13/50			liv:hpa,hpc,nnd.
8	c52733	526.mg	n.s.s.	3/50	235.mg	6/50	475.mg	12/50			liv:hpc,nnd.
a	c52733	1.13gm	n.s.s.	1/50	235.mg	1/50	475.mg	5/50			
b	c52733	455.mg	n.s.s.	36/50	235.mg	35/50	475.mg	34/50			
c	c52733	526.mg	n.s.s.	3/50	235.mg	6/50	475.mg	12/50			liv:hpa,hpc,nnd.

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