Supplement to the Carcinogenic Potency Database (CPDB): Results of Animal Bioassays Published in the General Literature in 1993 to 1994 and by the National Toxicology Program in 1995 to 1996

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The Carcinogenic Potency Database (CPDB) is a systematic and unifying analysis of results of chronic, long-term cancer tests. This paper presents a supplemental plot of the CPDB, including 513 experiments on 157 test compounds published in the general literature in 1993 and 1994 and in Technical Reports of the National Toxicology Program in 1995 and 1996. The plot standardizes the experimental results (whether positive or negative for carcinogenicity), including qualitative data on strain, sex, route of compound administration, target organ, histopathology, and author's opinion and reference to the published paper, as well as quantitative data on carcinogenic potency, statistical significance, tumor incidence, dose–response curve shape, length of experiment, duration of dosing, and dose rate. A numerical description of carcinogenic potency, the TD_{50}, is estimated for each set of tumor incidence data reported. When added to the data published earlier, the CPDB now includes results of 5,620 experiments on 1,372 chemicals that have been reported in 1,250 published papers and 414 National Cancer Institute/National Toxicology Program Technical Reports. The plot presented here includes detailed analyses of 25 chemicals tested in monkeys for up to 32 years by the National Cancer Institute. Half the rodent carcinogens that were tested in monkeys were not carcinogenic, despite usually strong evidence of carcinogenicity in rodents and/or humans. Our analysis of possible explanatory factors indicates that this result is due in part to the fact that the monkey studies lacked power to detect an effect compared to standard rodent bioassays. Factors that contributed to the lack of power are the small number of animals on test; a stop-exposure protocol for model rodent carcinogens; in a few cases, toxic doses that resulted in stoppage of dosing or termination of the experiment; and in a few cases, low doses administered to monkeys or early termination of the experiment even though the doses were not toxic. Among chemicals carcinogenic in both monkeys and rodents, there is some support for target site concordance, but it is primarily restricted to liver tumors. Potency values are highly correlated between rodents and monkeys. The plot in this paper can be used in conjunction with the earlier results published in the *CRC Handbook of Carcinogenic Potency and Genotoxicity Databases* [Gold LS, Zeiger E, eds. Boca Raton FL:CRC Press, 1997] and with our web site (*http://potency.berkeley.edu*), which includes a guide to the plot of the database, a complete description of the numerical index of carcinogenic potency (TD_{50}), 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. Two summary tables permit easy access to the literature of animal cancer tests by target organ and by chemical. For readers using the CPDB extensively, a combined plot on diskette or other format is available from the first author. It includes all results published earlier and in this paper, ordered alphabetically by chemical. A SAS database is also available. *Key words*: animal cancer test, carcinogenic potency, database, human carcinogen, monkey neoplasm, TD_{50}. — *Environ Health Perspect* 107(suppl 4):527–600 (1999).
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Background

The Carcinogenic Potency Database (CPDB) is a systematic and unifying analysis of the published results of the diverse literature of chronic, long-term animal cancer tests on individual chemicals. The CPDB standardizes the experimental results and creates an accessible resource widely used to address a variety of research and regulatory issues in carcinogenesis. All results in the CPDB prior to this paper are presented in an easily readable plot format in the 1997 *Handbook of Carcinogenic Potency and Genotoxicity Databases* (*1*), which includes all experimental results published in several papers in *Environmental Health Perspectives* beginning in 1984 (*2–7*). This paper is a supplement to the CPDB, reporting bioassay results published in the general literature in 1993 to 1994 and in Technical Reports of the National Toxicology Program (NTP) in 1995 to 1996. Our analyses are presented in the same plot format as the earlier plots in *Environmental Health Perspectives* (*2–7*) and in the CRC handbook (*1*). Data are reported for 513 new experiments on 157 chemicals. When added to the data published earlier, the CPDB now includes results of 5,620 experiments on 1,372 chemicals that have been reported in 1,250 published papers and 414 National Cancer Institute (NCI)/NTP Technical Reports.

In the CPDB, detailed information and analyses important in the interpretation of bioassays are reported on each experiment (whether positive or negative for carcinogenicity), including qualitative data on strain, sex, target organ, histopathology, and author's opinion, as well as quantitative information on carcinogenic potency, statistical significance, tumor incidence, dose–response curve shape, length of experiment, dose rate, and duration of dosing. Each set of experimental results references the original published paper, and a series of appendices defines the codes in the plot. A numerical description of carcinogenic potency, the TD_{50} (*8*), is estimated for each set of tumor incidence data reported in the CPDB, thus providing a standardized quantitative measure for comparisons. In a simplified way, TD_{50} may be defined as that dose rate in mg/kg body wt/day which, if administered chronically for the standard life span of the species, will halve the probability of remaining tumorless throughout that period. Stated differently, TD_{50} is the daily dose that will induce tumors in half of the test animals that would have remained tumor free at zero dose. We estimate TD_{50} using a one-hit model (*8*). TD_{50} is analogous to LD_{50}, and a low value of TD_{50} indicates a potent carcinogen, whereas a high value indicates a weak one. TD_{50} is often within the range of doses tested and does not indicate anything about carcinogenic effects at low doses because bioassays are usually conducted at or near the maximum tolerated dose (MTD). The range of TD_{50} values is at least 10 millionfold for carcinogens in each sex of rat or mouse (*1,9*).

The CPDB is exhaustive in that it includes all published results of experiments that meet a set of inclusion criteria designed to measure potency; however, because many tests do not

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We thank the many researchers who provided additional experimental results for the CPDB, sometimes by having to go back to early pathology reports. U. Thorgeirsson, D. Dalgard, and S. Sieber have provided us with information for many years about the bioassays of nonhuman primates. We also thank B.N. Ames, J. Ward, L. Bernstein, and D. Freedman for their many years of advice on the CPDB project. This work was supported through the University of California, Berkeley, by National Institute of Environmental Health Sciences Center grant ESO1896 and through the Lawrence Berkeley Laboratory by U.S. Department of Energy contract DE-AC-03-76SFO0098.

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meet the criteria, not all cancer tests are included. No attempt has been made to perform an evaluation of whether a compound induced tumors in any given experiment; rather, the opinion of the published authors is presented as well as the statistical significance of the TD_{50} calculated from their results.

In presenting this supplement to the CPDB, our intention is that the material be used as follows, in conjunction with the *CRC Handbook of Carcinogenic Potency and Genotoxicity Databases* (*10*) and/or with our fully searchable, 100-page web site on the World Wide Web (*http://potency.berkeley.edu*), which has been accessed by individuals from 111 countries:

- Complete results for each experiment in the CPDB to date are obtainable by using the plots in the CRC handbook (*1*) and the present paper.
- Detailed descriptions of the methods used to develop the CPDB and a guide on how to read the plot format are given in the CRC handbook and on the web site. The methods page (*http://potency.berkeley.edu/text/methods.html*) describes inclusion rules, sources of data, statistical methods on estimate TD_{50}, selection of tissue and tumor types to include, estimation of the average daily dose rate, and extrapolation of TD_{50} to the standard life span of each species. The guide to the plot (*http://potency.berkeley.edu/text/guide.html*) uses a sample experiment to describe each field of the plot format; special analysis and standardization methods for the NCI/NTP bioassays are also reported.
- A complete list of references that are the source of bioassay results in the CPDB is provided on the web site, including papers in the plot in this present paper (*http://potency.berkeley.edu/text/CPDBreferences.html*).
- Two summary tables on our web site have been updated to include the experimental results presented in this paper. The Summary Table by Chemicals in the CPDB (*http://potency.berkeley.edu/chemicalsummary.html*) is organized alphabetically by chemical name and summarizes results for each sex–species group of rats, mice, hamsters, dogs, and monkeys on positivity, target organ, and potency (TD_{50}). Chemicals with no evidence of carcinogenicity are included. Information is reported on each chemical about mutagenicity in *Salmonella*, whether potency values vary greatly within a species, and whether there is more than one positive test in each species in the CPDB. The Summary Table of Target Organs in the CPDB (*http://potency.berkeley.edu/pathology.html*) organizes results from the CPDB by target organ so that researchers can quickly determine all chemicals that induce tumors in each species at a given site, e.g., mammary gland or liver. This table includes only positive chemicals; results are organized by target organ, species, and mutagenicity in *Salmonella*. The table indicates whether each carcinogen has tests in another species in the CPDB and whether the chemical is positive in another species. In combination with the plots of the CPDB, these two tables provide a comprehensive summary of the field of long-term chronic bioassays and give full citations to each publication on each chemical and each target site.
- For readers using the CPDB extensively, a combined plot on diskette or other format is available from the first author that includes all results published earlier and in this paper, ordered alphabetically by chemical. A SAS database is also available (see *http://potency.berkeley.edu/orderform.html*).

CPDB Plot in This Supplement

This plot of the CPDB analyzes results of 513 long-term, chronic experiments on 157 chemicals, including tests in rats, mice, hamsters, and monkeys. Many chemical classes and compounds with a variety of uses are included: *a*) drugs, e.g., fluvastatin, codeine, ritalin, phenolphthalein, tamoxifen, dehydroepiandrosterone (DHEA), and potassium bicarbonate; *b*) industrial chemicals, e.g., acetonitrile, methyl *tert*-butyl ether (MTBE), nickel sulfate hexahydrate, sodium dichromate, and isoprene; *c*) pesticides and food additives, e.g., captan, captafol, piperonyl butoxide, ethyl acrylate, citric acid; and *d*) naturally occurring components of food, e.g., phenethyl isothiocyanate, 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP), catechol, L-ascorbic acid, and ethyl alcohol. Eighty-three of the 157 chemicals were already included in the database, and we have flagged these names in the plot with triple asterisks (***). The TD_{50} values for the compounds in this plot fall within the 10 millionfold range reported earlier. The positivity rate among chemicals reported here, based on the original author's evaluation, is 94/157 (60%), which is similar to the rate for the database as a whole.

The experimental results reported here reflect recent changes in the field of animal cancer testing. For NTP bioassays, for example, the standard bioassay protocol now includes three dose groups and a control; in contrast, in NCI/NTP Technical Reports published before 1994, only 8% of the experiments had more than two dose groups. In the general literature, over time fewer experiments have only one dose group, and in this plot 42% of the experiments have more than two dose groups and a control. In the 1990s there has also been an increase in the proportion of experiments that restrict histopathology to known target sites, indicating investigation of cocarcinogenic effects in parallel studies or of mechanisms of carcinogenesis. Of the 139 papers in this plot, 16 include data on cell division rates (indicated by the notecode "C" on the plot). We have consulted with nearly half the published authors and have received clarification of results or data in addition to that which appeared in their published papers; these citations are marked in the plot with "pers.comm." to indicate personal communication. For some literature papers we have been able to obtain from the authors full lifetable data and have used those results to estimate TD_{50} values, e.g., tamoxifen, MTBE.

Analyses That Use the CPDB

During the past 15 years we have published many papers based on results in the CPDB, including investigations of methodologic issues such as reproducibility of bioassay results and constraints on potency estimation, questions about extrapolation of carcinogenicity between species, estimation of regulatory risk, and providing a broad perspective on cancer risk estimates by ranking possible hazards at typical and average human exposures to rodent carcinogens. A variety of exposures are ranked, including natural chemicals in the diet, pharmaceuticals, workplace exposures, pesticide residues, and synthetic pollutants. Recently, we presented an overview of those results and included the principal findings in tabular form (*9,11*). We have now updated each of the analyses to include the experimental results presented in this paper. The findings in all cases are similar to the earlier published results, and we therefore refer the reader to the earlier overviews (*9,11,12; http://potency.berkeley.edu*), which also provide citations to the original papers on each topic. We continue to find that about half of all chemicals tested are carcinogenic in at least one experiment; about half are also positive for several subsets of the data, including naturally occurring and synthetic chemicals (Table 1). We have discussed in several papers the

Table 1. Proportion of chemicals evaluated as carcinogenic[a] for several data sets in the CPDB.

Chemicals tested in both rats and mice	
Chemicals in the CPDB	350/590 (59%)
Naturally occurring chemicals	79/139 (57%)
Synthetic chemicals	271/451 (60%)
Chemicals tested in rats and/or mice	
Chemicals in the CPDB	702/1348 (52%)
Natural pesticides	37/71 (52%)
Mold toxins	14/23 (61%)
Chemicals in roasted coffee	21/30 (70%)

CPDB, Carcinogenic Potency Database.
[a]A chemical is classified as positive if the author of at least one published experiment evaluated results as evidence that the compound is carcinogenic.

plausible explanations for the high positivity rate, including various high-dose effects (*9,11; http://potency.berkeley.edu*).

Comparison of Carcinogenicity in Monkeys and Rodents

This plot includes analyses of 25 NCI carcinogenicity studies in rhesus and cynomolgus monkeys, which lasted up to 32 years. Some of the experimental results were reported in earlier plots of the CPDB (these are marked on the plot with a "j" notecode); however, we have performed new lifetable analyses using the final control data that have recently become available (*13*). Results for eight chemicals tested in monkeys by NCI are reported for the first time. Some of the inclusion rules and methods of the CPDB have been relaxed for these monkey tests; they are described in Appendix 1.

Comparison of Positivity

As assessment of human cancer risk is usually based on studies in rodents, one ideally wants to know whether rodent carcinogens are human carcinogens; however, human data are rarely available. One major goal of this series of experiments in monkeys was to determine whether rodent carcinogens would also be carcinogenic in nonhuman primates (as monkeys are more closely related to humans than are rodents) and thus provide evidence in support of interspecies extrapolation in carcinogenesis (*14*). Conversely, if rodents and monkeys are different with respect to carcinogenicity under laboratory conditions, then this casts doubt on the validity of extrapolations from rodents to humans. The chemicals selected by NCI for use in monkey studies primarily have strong evidence of carcinogenicity in rodents, i.e., many positive rodent experiments with high tumor incidence rates, carcinogenic effects at doses below the MTD, or short latency periods for malignant tumor induction (*10,15,16*). The strong evidence in rodents for these chemicals suggests that when compared to other rodent carcinogens they would be likely to be carcinogenic in monkeys. Only one of these chemicals, arsenic, is not a rodent carcinogen in standard bioassays; however, it is a human carcinogen (*17*).

Table 2 describes positivity for the 25 chemicals tested in monkeys that are reported in detail in the plot presented here. Several of the test agents are model rodent carcinogens, some are nitrosamines or chemotherapeutic agents with strong evidence in rodents, and a few are synthetic food additives or pesticides. Two sweeteners, saccharin and cyclamate, have weaker evidence of carcinogenicity in rodents than the other chemicals tested. Several of the test agents have been evaluated by the International Agency for Research on Cancer (IARC) as human carcinogens (aflatoxin, arsenic, azathioprine, cyclophosphamide, melphalan) (*17*); of these, only aflatoxin and melphalan were evaluated as carcinogenic in these monkey studies.

Table 2 indicates that only 11 of 25 chemicals were evaluated by NCI as monkey carcinogens under the conditions of these studies; 3 had equivocal results, and 11 were not carcinogenic (*13,18*). The NCI evaluations are based on malignant tumors only. For monkey carcinogens the tumor yields were higher (see plot) and the latency period shorter than for chemicals that were not carcinogenic. For 8 of the 11 monkey carcinogens, the first tumor occurred in animals that died before 5 years on test and for the other 3 carcinogens by 13 years. Nearly all chemicals tested in monkeys are mutagens in *Salmonella* and about half are not carcinogenic in monkeys. A few chemicals were not mutagenic, and none of them were carcinogenic in monkeys, e.g., DDT, sodium saccharin, sodium cyclamate, sodium arsenate.

Possible explanatory factors for lack of evidence of carcinogenicity in monkeys for these rodent and human carcinogens include *a*) a true species difference including species-specific mechanism of action; *b*) a small number of monkeys on test, making it difficult to detect an effect; *c*) an experiment in only cynomolgus or rhesus monkeys but not both (Appendix 1); *d*) dose levels that may have been too low; *e*) dose levels that may have been too high (thus producing toxic effects that reduced life span and therefore the power to detect an effect); *f*) early termination of experiment before natural death; and *g*) other aspects of experimental design such as route of administration or length of dosing.

Table 2 indicates that experimental designs varied widely across this series of tests in monkeys with respect to whether both cynomolgus and rhesus were tested, number of monkeys on test, length of dosing and length of experiment, and average daily lifetime dose rate compared to rodent average daily lifetime dose rate. Detailed results on each experiment are given in the plot, including route of administration, dose rate, tumor types and incidence, TD_{50} and its confidence limits, and shape of the dose response.

We have investigated factors that might account for the lack of carcinogenic effects in monkeys, while noting that because of the small number of chemicals, the small number of animals, and the wide variation in protocols, it is difficult to conclude which factors may be most important. First, the number of dosed rhesus or dosed cynomolgus monkeys was generally fewer than 15 (Table 2). Thus one cannot rule out the possibility that a positive result might have been obtained with a larger number of animals. Second, the spontaneous tumor rate in the large colony control at NCI is low (*13,19*); thus, if a tumor occurred in even one or two of the small number of dosed animals, the results are difficult to interpret. Compared to rodents, which have a high spontaneous tumor rate, the lifetime spontaneous tumor rate in the NCI monkey colony is low: in rhesus controls, 19/120 (16%) had tumors (seven malignant), and in cynomolgus monkeys, 4/106 (4%) had tumors (three malignant). No type of tumor occurred spontaneously in more than two animals, except uterine leiomyoma, which occurred in 6 rhesus monkeys and 1 cynomolgus monkey.

For the model rodent carcinogens (*14*), the testing protocol used a short dosing period (5 years, i.e., one-fourth the standard life span of 20 years) (Table 2). Under these stop-exposure conditions only one chemical (urethane) was carcinogenic, even though the studies were continued for 20–32 years. In contrast, all of the model carcinogens induce tumors in rodent experiments lasting less than 6 months, i.e., less than one-fourth the standard life span of 2 years (*15,16*). Under the conditions of the 5-year dosing protocol, the following model rodent carcinogens were not carcinogenic in monkeys: 2-acetylaminofluorene, 2,7-acetylaminofluorene, *N,N*-dimethyl-4-aminoazobenzene, 3′-methyl-4-dimethylaminoazobenzene, 3-methylcholanthrene (*18*). Urethane had the weakest evidence of carcinogenicity among the monkey carcinogens: the latency period was longer than those of other monkey carcinogens, and only one tumor of any type was induced, i.e., no site was a target site for more than one animal in a monkey experiment. Thus, the stop-exposure design was less sensitive than the chronic dosing protocol (which also gives a higher total dose and higher average daily dose rate) that is used in standard rodent bioassays and in most of the monkey experiments. A true species difference cannot be ruled out, however, because monkeys were dosed for 5 years of a 20-year life span, i.e., one-fourth and this is the same proportion that produced carcinogenic effects in rodents for these chemicals, i.e., 6 months of a 2-year life span.

A difference in route of chemical administration between monkey tests and the positive tests in rodents does not appear to be important in explaining why many rodent carcinogens are not carcinogenic in monkeys. Routes of administration were more often different for the rodent carcinogens that were positive in monkeys than for the rodent carcinogens that were not carcinogenic in monkeys.

We examined whether the number of animals on test or the dose rate (mg/kg/day) may have been factors affecting positivity in monkeys. Our analysis first found the median value for the combination of negative and

Table 2. Protocol characteristics and carcinogenicity of 25 chemicals tested in monkeys by the National Cancer Institute.

Author's opinion of carcinogenicity in monkeys	Rhesus monkeys				Cynomolgus monkeys			
	Starting number	Exposure (years)	Experiment (years)	Dose ratio[a]	Starting number	Exposure (years)	Experiment (years)	Dose ratio[a]
NOT CARCINOGENIC								
2-Acetylaminofluorene	10	5	26	0.5 (R) 0.1 (M)				
2,7-Acetylaminofluorene	7	5	32	ND	7	5	29	ND
Arsenate, sodium					19	14	14	–[b]
Cyclamate, sodium	9	24	24	0.3 (M)	9	24	24	0.3 (M)
DDT	11	11	25	0.4 (R) 0.3 (M)	13	11	25	0.4 (R) 0.3 (M)
N,N-Dimethyl-4-aminoazobenzene	6	5	20	0.7 (R)				
3'-Methyl-4-dimethylaminoazobenzene	13	5	24	0.8 (R)				
3-Methylcholanthrene	9	5	26	0.9 (R)	5	5	27	0.7 (R)
N-Nitrosodimethylamine	6	10	10	0.4 (R) 2 (M)				
N-Methyl-*N'*-nitro-*N*-nitrosoguanidine	18	23	23	0.2 (R)				
Saccharin, sodium	7	23	23	0.009 (R)	6	23	23	0.009 (R)
EQUIVOCAL								
Adriamycin	6	2	9	ND				
	5	5	13	ND	5	5	15	ND
	6	10	16	ND	4	10	15	ND
Azathioprine	18	15	16	1 (M)	8	15	16	1 (M)
Cyclophosphamide	13	11	13	2 (R) 0.8 (M)	9	11	13	2 (R) 1 (M)
CARCINOGENIC								
Aflatoxin B_1	18	15	15	0.4 (R)	17	17	17	0.5 (R)
Cycasin mixture (diet)	10	18	24	ND[c]	6	18	24	ND[c]
(IPJ)	5	8	8	ND[c]				
IQ					36	9	9	1 (R) 0.4 (M)
Melphalan[d]	8	16	19	0.2 (R) 0.3 (M)	12	16	18	0.2 (R) 0.3 (M)
N-Nitroso-*N*-methylurea	19	18	22	25 (R) 0.7 (M)	19	18	22	20 (R) 0.6 (M)
N-Nitrosodiethylamine (diet)	14	22	22	6 (R)	16	16	16	7 (R)
(IPJ)	82	20	20	2 (R)	61	16	16	2 (R)
N-Nitrosodipropylamine	4	3	3	4 (R)				
N-Nitrosopiperidine (diet)	7	12	12	22 (R) 21 (M)	5	12	12	32 (R) 29 (M)
(IPJ)	6	20	20	0.6 (R) 0.5 (M)				
Procarbazine.HCl	22	16	23	0.4 (R) 0.7 (M)	17	16	19	0.4 (R) 0.8 (M)
Sterigmatocystin					30	17	17	0.09 (R) 0.07 (M)
Urethane	11	5	25	2 (R) 0.2 (M)	6	5	23	2 (R) 0.2 (M)

Abbreviations: CPDB, Carcinogenic Potency Database; IPJ, intraperitoneal injection; IQ, 2-amino-3-methylimidazo[4,5-*f*]quinoline; M, mice; ND, no rodent tests meet inclusion rules of the CPDB, but positive in other rodent test; R, rats.

[a]Ratio from CPDB of highest monkey daily lifetime dose rate (mg/kg/day)/highest rodent daily lifetime dose rate (mg/kg/day). [b]No positive rodent test. Ratio of the negative monkey dose in CPDB to the highest negative rodent dose is 0.0009 (rats). [c]Monkeys received a mixture of cycad flour, cycasin, and methylazoxymethanol acetate. There are no rodent tests of this mixture; cycad flour is carcinogenic in rats. [d]Melphalan was not carcinogenic in rhesus monkeys.

positive monkey experiments for the number of monkeys tested and for the ratio of the monkey dose rate compared to the positive rodent dose rate. For the number of animals we took the total number of monkeys that started on test for both monkey species combined, as the NCI evaluation of carcinogenicity for a chemical did not distinguish between the two species (*18*). The median value of the number of monkeys on test for the 24 rodent carcinogens in Table 2 was 19. We found a significant difference between the monkey positives and negatives. All of the chemicals in Table 2 that were NOT CARCINOGENIC in monkeys were below the median number of animals on test, except DDT. Only a few of the CARCINOGENIC chemicals were below the median. The three EQUIVOCAL chemicals were all above the median, thus suggesting that the greater power provided by more animals may be a factor in the evaluation of equivocal compared to not carcinogenic. All of the model rodent carcinogens had the stop-exposure protocol, and also had fewer than the median number of monkeys on test, thus providing a protocol with little power.

To assess whether the dose in monkeys (mg/kg/day) was low compared to the positive doses in rodents (mg/kg/day), we used the ratio (Table 2) of the average daily dose rate in monkeys to that in rodents, and again found the median for all chemicals regardless of carcinogenicity result in monkeys. For rodents, the dose was taken from a positive experiment with the same route of administration as the monkey experiment, wherever possible. Table 1 reports the ratio of the highest daily average lifetime dose rate in monkeys (mg/kg/day) to the highest in rats or in mice from the CPDB (mg/kg/day). The median for all chemicals was 0.4, indicating that for half the chemicals tested, the monkey dose

was about half the highest dose that induced tumors in rodents. The monkey doses were generally close to the rodent doses, even when they were lower. We repeated this analysis three ways, using the ratio in Table 2, the ratio using the lowest positive high dose in each rodent species, and the lowest dose at which tumors were significantly increased in each rodent species. These measures give increasing weight to how low a dose in rodents was tumorigenic, and therefore the second and third ones produce higher monkey-to-rodent ratios than the value of the first, which is presented in Table 2. Regardless of which dose ratio was selected, there was no difference between the chemicals that were carcinogenic in monkeys and those that were not carcinogenic. The overall difference in positivity between monkeys and rodents does not appear to be due to dose level, as the monkey doses (mg/kg/day) were generally not much below the doses that induced tumors in rodents. For the 5 human carcinogens the monkey doses were similar to the human carcinogenic doses even for the 3 chemicals that were not evaluated as carcinogenic in monkeys (arsenic, azathioprine, cyclophosphamide) (*20–22*).

Some aspects of the conduct of these monkey experiments contributed to a lack of sensitivity for some chemicals that were not carcinogenic in monkeys. All but one of the positive chemicals were tested in both rhesus and cynomolgus monkeys, i.e., there were at least five cynomolgus and five rhesus on test. For 6 of the chemicals that were not carcinogenic, however, only one monkey species had five animals on test. Among the 5 human carcinogens, only aflatoxin and melphalan were evaluated as carcinogenic in monkeys; however, for the others (azathioprine, cyclophosphamide and arsenic) the experiments lacked power to detect a carcinogenic effect because they were terminated early (by 16 years) even though the doses were not toxic.

Because the evaluations of carcinogenicity in monkeys were based on malignant tumors only, whereas evaluations in rodents usually consider both malignant and benign tumors, it is possible that if benign tumors had been considered, more monkey studies might have been evaluated as positive. This was not the case, however, as there were few benign tumors in tests of chemicals that were not carcinogenic, and nearly all were tumor types that also occur in control monkeys.

As a second general approach to understanding the discordance between rodents and monkeys, we searched on a case-by-case basis for idiosyncratic factors that may explain why some rodent carcinogens were not carcinogenic in monkeys. In a few cases, dosing was stopped or animals died because of toxicity, and this may be the reason for a negative result. For example, for DDT the dose was neurotoxic to rhesus monkeys and dosing had to be stopped at 10 years. In cynomolgus, however, the dose was not neurotoxic, thus providing a short exposure that may have been less effective than the exposures for most chemicals that were carcinogenic in monkeys.

Of the 4 nitrosamines that were positive in monkeys, all were tested at doses more than 3 times the rat carcinogenic dose (Table 2). Both nitrosamines that did not induce tumors in monkeys were tested at less than half the rat carcinogenic dose. For *N*-nitrosodimethylamine, which did not induce tumors, the administered doses produced toxic hepatitis, and all animals died by 10 years; thus, the animals may not have lived long enough to develop tumors. For *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG) a published study indicates that it is carcinogenic in cynomolgus monkeys (*23*). In that positive cynomolgus experiment (*23*), MNNG induced stomach tumors in just 1 year; MNNG was given by gavage 3 times per month at a 10-fold higher administered dose than the negative 23-year NCI rhesus experiment in which administration was by diet 5 times per week. Thus, a higher administered dose given less frequently by a different route to a different monkey species, induced tumors. One or a combination of these factors likely contributed to the difference in result from the NCI monkey test.

For the two sweeteners, sodium saccharin and sodium cyclamate, doses were selected on the basis of human consumption (*14*). The saccharin dose was equivalent to 5 cans of diet soda daily, and the cyclamate dose was equivalent to 30 cans daily (*18*). The average daily dose rate of sodium saccharin gave the lowest dose ratio of all chemicals (0.009) (Table 2), and sodium cyclamate was also relatively low (0.3). Neither chemical was carcinogenic in monkeys. In rats, induction of bladder tumors from sodium saccharin appears to require a high dose and is related to development of a calcium phosphate-containing precipitate in the urine (*24*). At the low dose administered to monkeys, there was no effect on the urine or urothelium, and no evidence of increased urothelial cell proliferation or of formation of solid material in the urine (*25*). Thus, one would not expect to find a carcinogenic effect under the conditions of the NCI study in monkeys. Additionally, however, there may be a true species difference, because primate urine has a low concentration of protein and is less concentrated (lower osmolality) than rat urine (*25*). Human urine is similar to monkey urine in this respect (*24*).

Six of the chemicals tested were antineoplastic and immunosuppressive drugs. Monkeys were administered doses within a factor of 2 of the human therapeutic doses, which are also similar to doses that induced tumors in rodents (Table 2). Three of these drugs were carcinogenic to monkeys (melphalan, *N*-methyl-*N*-nitrosourea, procarbazine), and three were evaluated as EQUIVOCAL (adriamycin, azathioprine, cyclophosphamide). Experiments with all three of the EQUIVOCAL drugs were less sensitive than a standard life span study because they were terminated by 16 years (adriamycin because of cardiotoxicity). For azathioprine and cyclophosphamide the doses were not toxic.

We note that most of the chemicals that are carcinogenic in monkeys are naturally occurring chemicals (Table 2). Among 12 natural chemicals tested in monkeys, 8 are positive (67%), whereas among 13 synthetic chemicals only 3 are positive (23%). Two chemicals, both naturally occurring, induced tumors rapidly in monkeys: *N*-nitrosodipropylamine (in 3 years) and 2-amino-3-methylimidazo[4,5-*f*]quinoline (IQ) (in 8 years). These results in monkeys are consistent with the finding that among the agents that IARC has evaluated as human carcinogens, 64% (35/55) are naturally occurring (*15,17*).

Comparison of Target Sites and Potency

Concordance in target sites according to the published author's opinion is reported in Table 3 for 11 chemicals that are positive in monkeys and rodents in the CPDB. This analysis is complicated by two facts: first, the evaluation of carcinogenicity for the monkey studies was based on malignant tumors only (*18*), whereas in rodents, evaluations of carcinogenicity often include benign tumors. We have indicated with an asterisk (*) in Table 3 those target sites for which the author's evaluation was based on a tumor increase that included benign tumors. A second complication of this analysis is the fact that there are frequently many positive experiments in rodents for a chemical; repeated testing provides an increased chance of finding a target site in common between monkeys and rodents.

The liver is the most common target site of chemically induced cancer in monkeys and rodents (Table 3), even among the chemicals that were noncarcinogenic in monkeys. Unlike rodents, monkeys had no spontaneous liver tumors in these lifetime studies (*13*). We note that among chemicals that are positive in both monkeys and rodents, there is a target site in common between monkeys and at least one rodent species for all chemicals except melphalan, which was evaluated as carcinogenic in monkeys on the basis of "all malignant tumors" (*13*). As expected, the liver is the most frequent site in common between monkeys and each rodent species. Only 3 carcinogens have a target site other than liver in common between rodents and monkeys

Table 3. Comparison of target sites[a] for eleven chemicals that are carcinogenic in monkeys and rodents.

Chemical agent	Rhesus monkeys	Cynomolgus monkeys	Rats	Mice
Aflatoxin B_1	*Liver*, gall bladder/bile duct, vascular[c]	*Liver*, gall bladder/bile duct, vascular[c]	*Liver*, *colon, kidney	
Cycasin mixture	*Liver*, kidney	*Liver*	*Liver*, large intestine[d]	
IQ		*Liver*	*Liver*, clitoral gland, large and small intestine, mammary gland, oral cavity, *pancreas, *preputial gland, *sebacious gland, skin, *urinary bladder, *vascular,[c] Zymbal's gland	*Liver*, *forestomach, *lung
Melphalan	–	"All malignant tumors"	Peritoneum	*Lung, lymphosarcoma
N-Nitrosodiethylamine	*Liver*	*Liver*	*Liver*, esophagus, *kidney, oral cavity, *stomach, vascular[c]	
N-Nitrosodipropylamine	*Liver*		*Liver*, *esophagus, nasal cavity	
N-Nitroso-*N*-methylurea	*Upper gastrointestinal tract*	*Upper gastrointestinal tract*	*Forestomach*, *lung, *nervous system	*Stomach*, vascular
N-Nitrosopiperidine[e]	*Liver*	*Liver*	*Liver*, esophagus, nasopharynx	**Liver*, forestomach, *lung
Procarbazine.HCl	*Leukemia*	*Leukemia*	*Leukemia*,[d] brain, lymphoma, mammary gland	*Leukemia*,[d] brain, *lung, lymphoma, lymphosarcoma, uterus
Sterigmatocystin		*Liver*	*Liver*, vascular[c]	Vascular
Urethane[b,e]	*Liver, vascular*,[c] jejunum	*Lung, vascular*,[c] pancreas	"All malignant tumors"	*Liver*, **lung, vascular*,[c] reticulum cell sarcoma

IQ, 2-amino-3-methylimidazo[4,5-*f*]quinoline.
[a]When tumors were induced in monkeys and rodents at the same target site, the site is listed first for each species and is italicized. In monkeys, opinions are based on malignant tumors. In rats and mice, asterisk (*) indicates that the author's opinion for a target site included benign tumors. [b]Only one monkey in each indicated species had a tumor at the target site. [c]Vascular tumors in the liver. [d]For cycasin, results in rats are from a bioassay of cycad flour (*15*). For procarbazine.HCl, leukemias were induced in bioassays that did not meet inclusion criteria in the Carcinogenic Potency Database (*15*). [e]*N*-Nitrosopiperidine and urethane were also tested in hamsters. For *N*-nitrosopiperidine, target sites in hamsters were similar to those in rats and mice (liver, digestive tract, respiratory system); for urethane, the sites in hamsters were different.

(Table 3): *N*-nitroso-*N*-methylurea (gastrointestinal), procarbazine.HCl (leukemia), and urethane (lung and liver hemangiosarcoma). Thus, while there is some support for target site concordance, it is primarily in liver.

The predominance of liver as a target site in laboratory studies in rodents and monkeys is noteworthy because in the United States, human liver cancer is rare. Chronic inflammation of the liver caused by Hepatitis B and C viruses is a common cause of liver cancer in Asia and Africa (*26*). The rodent liver may be a common site in carcinogenesis bioassays because the administered doses are high, and the liver is the primary site for detoxification. High doses can frequently cause increased liver cell proliferation by inducing cytotoxicity and regeneration This effect is similar to what is seen in the chronic hepatitis-induced inflammation in humans. High doses can also increase cell proliferation by other means such as peroxisome proliferation, inhibiting apoptosis with an accumulation of cells (especially in foci), inducing apoptosis with consequent regeneration, or by other mechanisms (*27*).

Carcinogenic potency values are highly correlated between monkeys and rodents for the chemicals that are carcinogenic to both (r = 0.79 for log TD_{50}). This result is expected, given the similarity in doses that were administered to rodents and monkeys (Table 2: "Dose ratio") and the fact that potency estimates are constrained to a narrow range about the high dose tested (*28,29*). Given the wide range of administered doses across chemicals, the correlation in potency follows statistically (*28*).

Half the 22 rodent carcinogens in the CPDB that have been tested by NCI in monkeys were not carcinogenic in monkeys, according to the published authors. This overall result does not provide strong evidence of the validity of extrapolation of carcinogenicity between species. Our analysis indicates, however, that this result is due at least in part to the fact that the monkey studies lacked power to detect an effect compared to standard rodent bioassays. Factors that contributed to the lack of power are the small number of animals on test, a stop-exposure protocol for model rodent carcinogens, in a few cases toxic doses that resulted in stoppage of dosing or termination of the experiment, and in a few cases low doses administered to monkeys or early termination of the experiment even though the doses were not toxic. Among chemicals carcinogenic in both monkeys and rodents, there is some support for target site concordance, but it is primarily restricted to liver tumors. Potency values are highly correlated as expected.

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