Appendix: Notecodes

Code	Definition
a	The exposure time reported on the plot is an average of the different exposure times of the individual dose groups in the experiment. For NCI/NTP, both exposure and experiment times have been averaged because of differential survival among the dose groups. (In the TD_{50} calculation for the NCI/NTP bioassays, full lifetable data have been used.)
A	Serial sacrifice experiments of aristolochic acid in the same paper were evaluated as positive at additional sites by the author but did not meet inclusion rules of the CPDB. Full data are reported in the Table at the end of this appendix.
b	Diet was specially prepared to be deficient in one or more vitamins.
C	Quantitative data are reported in the paper on cell division in this tissue in dosed and control animals (e.g., labeling index). C does not indicate whether or not there was an association between cell division and tumorigenesis.
c	Diet was specially prepared to be low in lipotropes.
d	A cyclic dosing schedule was followed for part of the exposure time, with at least one week between cycles, e.g., 3 weeks dosed, one week not dosed. (NCI only)
e	For the general literature we have used an effective number of animals in a group whenever possible. This effective number is either: (1) the number of animals alive at the time of appearance of the first tumor, or (2) if that is not reported, then the number of animals examined.
f	Diet was specially prepared to have a lower than average protein level.
g	Some or all of the animals were used as breeders during the course of the experiment.
I	Control and dosed animals received isocaloric diets.
i	Dosing in this test was intermittent; it was stopped for more than one week at some point in the experiment.
j	Data for this test have been previously published in the CPDB. The experimental results have been revised either because of a later publication by the same authors or because of a personal communication. In the CPDB, we give the same reference number to the experiment in all plot publications.
k	For interim and serial sacrifice experiments, we have reported, as a separate experiment with a k notecode, each sacrifice time that otherwise met the inclusion rules of the database. We have included unscheduled deaths with the terminal sacrifice data, and when this has been done, there is no k notecode for the terminal sacrifice experiment.
L	Female mouse strain was mammary tumor virus positive (MTV+) with a high spontaneous incidence of mammary tumors; histopathology was restricted to mammary gland. The study was designed to measure tumor latency, and no author's opinion about carcinogenicity is given in the CPDB.
m	The calculated dose rate for a group is an average of either (1) different doses administered to individual animals, or (2) a narrow range of doses administered.
n	NTP considered one dose group inadequate for detecting a carcinogenic response.
o	Chemical was administered as an aerosol.
r	Restricted site analysis; the authors either examined or reported results for only one or a couple of tissues.
s	Authors noted that survival was decreased due to toxicity, disease, or accidental death.
u	The NCI Technical Report indicated that tumors were "associated" with compound administration, and the NTP assigned a "positive" evaluation, while noting that "these experiments were particularly difficult to evaluate based on the wording in the Technical Report Summaries" (Haseman *et al., Environ. Health Perspect.* 74: 229-235, 1987).
v	Variable or irregular dosing schedules have been used, e.g. dose level changed during the experiment.
W	Tumors in control monkeys that lived longer than the last dosed animal in the experiment are deleted from the analysis. See Appendix 1 for details on monkey experiments.
w	For nonhuman primates, denominators for tumor incidence on the plot represent the number alive at the age of the first tumor of that type; since that age varies for different tumor types, denominators on the plot for control and dosed animals can vary widely from one site to another within an experiment. Only a few chemicals were tested at more than one dose level; we use the symbol "–/–" to indicate that for one of the dose groups all animals were dead before the occurrence of tumors of

that type in another group. The maximum number of animals used in any TD_{50} for an experiment is indicated by the denominator of the tumor incidence for "all tumor-bearing animals" ("tba" on the plot) and represents the number alive at the first tumor in any group.

x Exposure began before the animals were weaned.

y Animals were dosed for only 25 weeks; one week short of the standard criterion. Due to rounding, 6 months is reported as the exposure time on the plot.

z In a report of these vinyl chloride experiments (Maltoni, 1977), the author notes "All the animals exposed to the highest doses (30,000 and 10,000 ppm for 52 weeks), with or without tumors, were examined radiologically during treatment and/or at death; moreover, radiologic examinations have also been made on several animals bearing tumors even though these animals had been exposed to the lower doses." The experiment at the highest dose (30,000 ppm) is not included in the database. The reported data include the 10,000 ppm or lower doses.

For NTP bioassays evaluated as having no evidence of carcinogenicity, a statistically significant increase in tumors occurred in one or more sites ($p<0.05$). We have indicated this by placing a "–" in the opinion column and flagging the TD_{50} with a "#" sign in the plot just to the left of the TD_{50} value.

Notecode A: Aristolochic Acid

For the test of aristolochic acid (AA) in Wistar rats (Mengs, 1982), the CPDB includes only results of the chronic, 69 week experiment in which AA was administered at 0.1 mg/kg/day for 52 weeks (daily dose-rate in CPDB=0.075 mg/kg/day). Other groups of rats were administered 1.0 or 10 mg/kg/day for only 13 weeks and were sacrificed at various times shown in the table below; this short dosing period and the short times to sacrifice do not meet the inclusion rules of the CPDB (at least 26 weeks dosing and 52 weeks experiment length). In the 69-week experiment that meets the inclusion rules, the only target site was forestomach. Kidney and bladder were additional target sites in the groups that were administered higher doses for 13 weeks; tumor incidence data are given in the table below for each sacrifice time. The table reports the dose as administered for 13 weeks and not the CPDB daily dose-rate or a TD_{50} value, because the serial sacrifice experiments do not meet the CPDB inclusion rules.

Rat Sex	Tissue	Tumor	Weeks of Exposure duration	Weeks to Sacrifice	Administered dose by gavage (mg/kg/day)			
					0	0.1	1	10
f	Forestomach	sqp	13	13	0/9	0/9	8/9	10/10
		sqp,sqc	13	26	0/10	0/5	7/10	13/13
		sqp,sqc	13	39	0/7		9/11	4/4
		sqp,sqc	13	52	0/7	2/6		
		sqp,sqc	52 [a]	69 [a]	0/4	4/5		
	Kidney cortex	coc	13	26	0/10	0/5	0/10	2/13
		coa	13	39	0/7		0/11	4/4
	Urinary bladder	tpp,tcc	13	26	0/10	0/5	0/10	2/13
		tpp	13	39	0/7		0/11	1/4
m	Forestomach	sqp	13	13	0/9	0/9	7/9	10/10
		sqp,sqc	13	26	0/10	0/5	9/11	18/18
		sqp,sqc	13	39	0/6		9/9	
		sqp,sqc	13	52	0/6	4/7		
		sqc	52 [a]	69 [a]	0/5	4/4		
	Kidney/pelvis	tcc	13	26	0/10	0/5	0/11	8/18
	Kidney cortex	coa	13	39	0/6		1/9	
	Urinary bladder	tpp,tcc	13	26	0/10	0/5	0/11	6/18

[a] Experiment is included in CPDB since exposure and experiment length meet inclusion rules.