Methods for Nonhuman Primates

The NCI Laboratory of Chemical Pathology has ended its 36-year project (1961-97) on lifetime carcinogenesis studies in cynomolgus and rhesus monkeys. The Bioassays of Carcinogenicity Database (BOC) includes final lifetable analyses on 25 chemicals including 17 that we reported earlier with interim control data (indicated with a "j" notecode on the BOC). [a]

We have relaxed some of the rules of the BOC in order to include these monkey experiments. The following methodology has been adopted:

(1) An experiment with fewer than 5 animals is considered inadequate and is not included in the BOC. In order to obtain at least 5 animals per group in these studies, results have been combined for both sexes of cynomolgus and separately for both sexes of rhesus monkeys. For some chemicals, fewer than 5 monkeys were on test even when both sexes were combined; no tumors occurred in those cases when the chemical was evaluated as not carcinogenic in the other species.

(2) Whereas experiments with surgical intervention are generally excluded from the BOC, in these monkey tests laparoscopic examination of the liver was performed every 3 to 6 months, followed by wedge or needle biopsies of observed liver lesions.

(3) A few positive experiments are included that are shorter than one-half the standard 20-year lifespan even though such tests are generally excluded from the BOC. (For cycasin, IQ, DPN, and DEN in bush babies, nearly all dosed animals had tumors in this short time. Some experiments on adriamycin were longer than 10 years and some were shorter; we have included them all for completeness.)

(4) Experiments on sodium arsenate and sterigmatocystin are included even though monkeys were put on test as adults, at 4 years of age.

(5) Control monkeys are from the colony at NCI, which included breeders, offspring, and a small number of feral monkeys. The age of control animals ranged from neonate to greater than 25 years at a given time. Control monkeys were included only if they lived to be older than 8 months, the age of the first tumor in any group. Concurrent, vehicle controls were used only for IQ.

Some colony control monkeys were not examined histologically, and they have been excluded from the analyses because tumors may not have been detected at necropsy: Control N=106 cynomolgus (11 unexamined excluded), 120 rhesus (36 unexamined excluded). We investigated whether results would be similar if the unexamined controls had been included, and we determined that they would be: For target sites, all results were significant ($p<0.001$) regardless of whether the unexamined were excluded or not.

(6) The dose rate for a group is calculated based on the average of dose-rates for individual monkeys. To obtain the daily dose-rate for each monkey, the cumulative dose in mg/kg reported by NCI, was divided by the number of days of its life. Dosing schedules ranged across chemicals from once every 4 weeks to 5 times per week; for most experiments the chemicals were administered in a vitamin sandwich 5 times per week.

(7) Dose-response curves and *p*-values are estimated using lifetable data and are reported for every site at which a tumor occurred, benign or malignant, in dosed animals.

(8) In experiments with multiple target sites, a composite tissue-tumor combination is reported on the BOC for all animals with tumors at any of the target sites ("MXB,MXB" on the plot, as with NCI/NTP bioassays in rodents).

(9) For monkey tumor incidence for a dose-group in the BOC, the total number of monkeys represents the number alive at the first tumor of the type in the tissue-tumor combination. For details, see the file Notecodes.rtf.

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[a] The 25 chemicals in monkeys are: 2-acetylaminofluorene, 2,7-acetylaminofluorene, adriamycin, aflatoxin B_1, sodium arsenate, azathioprine, cycasin and methylazoxymethanol acetate, sodium cyclamate, cyclophosphamide, DDT, *N*,*N*-dimethyl-4-aminoazobenzene, IQ, melphalan, 3´-methyl-4-dimethylaminoazobenzene, *N*-methyl-*N*´-nitro-*N*-nitrosoguanidine, 3-methylcholanthrene, *N*-nitroso-*N*-methylurea, *N*-nitrosodiethylamine, *N*-nitrosodimethylamine, *N*-nitrosodipropylamine, *N*-nitrosopiperidine, procarbazine.HCl, sodium saccharin, sterigmatocystin, and urethane. In future we will report final results of studies on MeIQx and PhIP, which were begun at NCI and will be completed under the auspices of the Japanese National Cancer Center Research Institute.