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Letter to the editor

Chemical interactions affecting tumor incidence rates

Several errors in a recent article compromise the validity of the reported data and the interpretation of results. Gough (2002) reported on a large series of experiments involving thousands of rats that was conducted by the National Cancer Institute (NCI) in the 1970s. The study was designed to investigate chemical interactions affecting tumor incidence rates (synergistic, antagonistic, or no interaction) when two known rodent carcinogens are administered simultaneously rather than alone. Gough (1) was not aware that the results had already been published; (2) he reported different tumor incidence rates that were based only on gross pathology prior to histological examination; and (3) his evaluation of the possible interactions lacked a statistical method to determine synergism or antagonism. Details are presented below, indicating that the earlier, published papers on these experiments should be considered the valid analysis.

(1) *Publication:* In his paper, Gough states that the results of the NCI series had not been published, and he reports tumor incidence rates from a Final Report of the contract laboratory, SRI (Jones, 1978). In fact, detailed analyses of the experiments had been reported in the late 1980s by Elashoff, Fears, and Schneiderman (hereafter EFS), who designed the NCI series (Elashoff et al., 1987; Fears et al., 1988, 1989). Additionally, analyses of the results in those earlier NCI papers were included in the Carcinogenic Potency Database for the experiments with administration of a single compound (http://potency.berkeley.edu, Gold et al., 1997). For two chemicals, the single compound experiments had also been reported as Technical Reports by the National Cancer Institute (NCI, 1977, 1978).

(2) *Tumor incidence rates:* The tumor data reported by Gough are not adequate. Whereas EFS gave tumor incidence rates based on microscopic histopathology, the SRI Final Report was issued prior to histopathological exam (Jones, 1978). Thus, the tumor data used by Gough, as stated in the SRI report, "are for grossly detectable tumor induction" and "histopathologic evaluation is not included in this report" (Jones, 1978). Since EFS reported only malignant tumors in their papers, whereas Gough reported only grossly detectable tumors, exact comparisons are not possible except when Gough reports fewer tumors. The inadequacy of the Gough data is apparent in the following example: we compared tumor incidence rates in the NCI Technical Report of lasiocarpine with the results in Gough. An extreme result is the difference in liver tumor rates in female rats: the NCI reported 0 in controls and 8 in the mid dose, whereas Gough reported 5 in controls and 23 in the mid dose; the EFS results were consistent with the NTP. Apparently, some lesions listed as tumors in the Gough paper were not diagnosed as tumors when histological examination was performed.

(3) *Evaluation of synergism, antagonism, or lack of interaction*: This large series of experiments, with several hundred comparisons, requires rigorous statistical methods to assess possible interactions between chemicals. Gough used only a simple test of an approximate 50% increase or decrease in tumors among animals dosed with two chemicals vs. those dosed with each chemical alone; he excluded cases with decreased median survival time. In contrast, EFS used an index of additivity based on the independent action model and analyzed crude incidence rates using a test for statistical significance; EFS also reported results based on mortality and lethality of tumor.

Under the conditions of these experiments, EFS as well as Gough primarily found a lack of interaction. EFS evaluated 24 chemical pairs and found evidence of antagonism in two and synergism in one.

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References

Elashoff, R.M., Fears, T.R., Schneiderman, M.A., 1987. Statistical analysis of a carcinogen mixture experiment. I. Liver carcinogens. JNCI 79 (3), 509–526.

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doi:10.1016/S0273-2300(03)00044-8

Fears, T.R., Elashoff, R.M., Schneiderman, M.A., 1988. The Statistical Analysis of a Carcinogen Mixture Experiment. II. Carcinogens with different target organs, *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine, *N*-butyl-*N* -(4-hydroxybutyl)nitrosamine, dipentylnitrosamine, and nitrilotriacetic acid. Toxicol. Ind. Health 4 (2), 221–255.

Fears, T.R., Elashoff, R.M., Schneiderman, M.A., 1989. The statistical analysis of a carcinogen mixture experiment. III. Carcinogens with different target systems, aflatoxin B_1, *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine, lead acetate, and thiouracil. Toxicol. Ind. Health 5 (1), 1–22.

Gold, L.S., Slone, T.H., Ames, B.N., Manley, N.B., Garfinkel, G.B., Rohrbach, L., 1997. Carcinogenic potency database. In: Gold, L.S., Zeiger, E. (Eds.), Handbook of Carcinogenic Potency and Genotoxicity Databases. CRC Press, Boca Raton, FL, pp. 1–605. http://potency.berkeley.edu.

Gough, M., 2002. Antagonism-no synergism-in pairwise tests of carcinogens in rats. Regul. Toxicol. Pharmacol. 35, 383–392.

Jones, D.C.L., 1978. Combined Effects of Chemical Carcinogens and Other Chemicals. SRI Project LSD-3478, Final Report.

U.S. National Cancer Institute 1978. Bioassay of Lasiocarpine for Possible Carcinogencity. Technical Report 39 DHEW, Public Health Service, National Institutes of Health, Bethesda, MD.

U.S. National Cancer Institute 1977. Bioassays of Nitrilotriacetic Acid (NTA) and Nitrilotriacetic Acid, Trisodium Salt, Monohydrate ($Na_3NTA{\cdot}H_2O$) for Possible Carcinogenicity. Technical Report 6 CAS No. 139-13-9 (NTA), CAS No. 18662-53-8 ($NA_3NTA \cdot H_2O$). DHEW, Public Health Service, National Institutes of Health, Bethesda, MD.