ADDITIONAL REFERENCES

ARMITAGE, P. and DOLL, R. (1954). The age distribution of cancer and a multistage theory of carcinogenesis. *British J. Cancer* **8** 1–12.

BROWN, K. G. and HOEL, D. G. (1986). Statistical modeling of animal bioassay data with variable dosing regimens: Example—vinyl chloride. *Risk Anal.* **6** 155–166.

DEDRICK, R. L. (1985). Application of model systems in pharmacokinetics in risk quantitation and regulatory policy. Banbury Report No. 19, 187–198. Cold Spring Harbor Laboratory, Cold Spring Harbor, N. Y.

KNUDSON, A. G. (1985). Hereditary cancer, oncogenes, and antioncogenes. *Cancer Res.* **45** 1435–1443.

KREWSKI, D., MURDOCH, D. J. and DEWANJI, A. (1986). Statistical modeling and extrapolation of carcinogenesis data. In *Modern Statistical Methods in Chronic Disease Epidemiology* (S. H. Moolgavkar and R. L. Prentice, eds.). Wiley, New York.

MOOLGAVKAR, S. H. (1978). The multistage theory of carcinogenesis and the age distribution of cancer in man. *J. Nat. Cancer Inst.* **61** 49–52.

MURDOCH, D. J., KREWSKI, D. and CRUMP, K. S. (1987). Mathematical models of carcinogenesis. In *Cancer Modelling* (J. R. Thompson and B. W. Brown, eds.). Dekker, New York.

THORSLUND, T. W., BROWN, C. C. and CHARNLEY, G. (1987). Biologically motivated cancer risk models. *Risk Anal.* **7** 109–119.

WILSON, J. D. (1986). Time for a change: Guest editorial. *Risk Anal.* **6** 111–112.

Comment: The Use of Animal Experiments in Cancer Risk Assessment

J. Kaldor and L. Tomatis

Among the agents which have been demonstrated to cause cancer in humans, environmental chemicals have been the major focus of public and regulatory concern over the past several decades. In the case of artificially synthesized compounds, particularly strong sentiments can be aroused: why should proven, or even suspected causes of cancer, be allowed to contaminate the human environment? The answer often given is that many manmade carcinogens have become of substantial economic benefit, and the risks which they represent are to be weighed against the costs of their removal from the environment. It has long been recognized that the quantification of both risk and benefit presents major difficulties, and Freedman and Zeisel are only the most recent commentators to conclude that, in particular, the quantitative assessment of cancer risk entails a number of biological assumptions that have not been verified empirically. In reaching this conclusion, with which we are in general agreement, Freedman and Zeisel sidestep into areas where they appear to be out of their depth, and manage to distort several important issues concerning the use of animal experiments as indicators of potential human hazard.

The sine qua non for establishing a chemical as a human carcinogen is undoubtedly the epidemiological finding that, after eliminating as far as possible the effects of bias, confounding or chance, those exposed to the chemical have a higher risk of cancer than those unexposed. Although laboratory experiments and information on chemical structure, metabolism and pharmacokinetics all play an important role in the evaluation process, some grounds can always be found to challenge their relevance if epidemiological data are absent.

The current reality, however, is that for most environmental chemicals, studies of cancer risk in exposed humans are not available. In a few cases, this can be attributed to a lack of resources for studying an appropriate, exposed population. For the overwhelming number of chemicals, however, such a population does not exist, either because it is too difficult to define who is exposed, because when exposure does occur it is in conjunction with other chemicals or because not enough time has elapsed to be able to evaluate the cancer risk in exposed populations. For a number of major classes of chemicals such as the N-nitrosamines, which are both animal carcinogens and widespread in the human environment, direct epidemiological evidence of carcinogenicity is still lacking.

In this situation, the process of cancer risk assessment, whether qualitative or quantitative, must rely entirely on experimental data, perhaps combined with some information on human metabolism or other relevant parameters. Although each chemical should be evaluated independently, it is only on examination of results across chemicals that one can evaluate the validity and long term performance of experimental data in predicting human risk. In their critique of risk

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