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Are Negative Toxicological Data Suspect: An Epilog[1]

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Curiously, the public and their leaders are requesting scientists to tell them what chemicals under what conditions are safe, while the scientists persist in equivocating whatever data or judgments they provide with very, if not overly, conservative caveats. A positive study is a priori deemed creditable; a negative is deemed suspect. While we complain that journals do not publish negative studies, the truth is none of us—toxicologists, epidemiologists, statisticians, etc.—feel comfortable with negative studies. We are driven to find evidence for disease caused by treatment. This is as it should be. However, the science of finding no untoward effects or defining under what conditions none will occur is in the end more important. If these issues are not decided in a scientific manner, they will be decided in a less desirable forum.

If one accepts the responsibility of our science to elucidate negative results, we must then accept the responsibility to communicate those results. Do not blame the journals for not publishing; journals publish what we want to read or hear.

The speakers today have addressed some of the problems inherent to current testing methods in animals and surveillance of human populations.

As Dr. Clayson demonstrated, use of the MTD in animal studies renders interpretation fuzzy at best. Using data from many of these studies requires extrapolation not only from animals to man but also from sick animals to man. There is good reason to believe that the latter is less creditable than the former.

Shown in Table 1 are some risk assessments for a few compounds, using the linearized multistage model. For perchloroethylene, trichloroethylene, acrylonitrile, and butadiene, exposure to $\frac{1}{2}$ the threshold limit value (TLV) for 20 years is predicted to cause an 8 to 26% increase in cancer. Although definitive epidemiological studies are not available, it is highly unlikely that such increases have occurred without recognition. For perchloroethylene and trichloroethylene, at least 8–10 small studies have been published, which indicate no increase in cancer of the liver. While not one of

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TABLE I

RISK ASSESSMENT BASED ON EXTRAPOLATION OF ANIMAL DATA[a]

Chemical	Exposure	Risk
Perchloroethylene	60 ppm for 20 years	0.23
Trichloroethylene	60 ppm for 20 years	0.08
Acrylonitrile	10 ppm for 20 years	0.13
Butadiene	500 ppm for 20 years	0.26
Vinyl chloride	200 ppm for 20 years	0.16
Bischlormethylether	0.01 ppm for	1.0
	10 years	0.45
	1 year	
Ethylene dibromide	3 ppm for	0.65
	20 years	0.41
	10 years	0.20
	4.2 years	
Aflatoxin	Average U.S consumption	789/100,000

[a] Risk calculated from cancer assessment group potency estimates published in methylene chloride health assessment document EPA/600/8-82/004F, February 1985.

these studies is in itself indicative, their consistency is an indication that the incidence of liver cancer is well below that predicted.

Vinyl chloride has been predicted to produce a 0.16 risk of cancer. However, two large interindustry studies indicate no increase in cancer in vinyl chloride monomer or PVC polymer workers other than angiosarcoma of the liver (Fox and Collier, 1977; Tabershaw and Gaffey, 1974). The worldwide incidence of angiosarcoma, 108 cases from 1955 to 1983 (Forman *et al.*, unpublished data, 1985), is far less than that predicted by the risk models, considering that tens of thousands of workers have been exposed and that, historically, exposure to several hundred parts per million were common.

Exposure to concentrations of bischlormethylether reportedly sufficient to cause marked respiratory irritation (1 ppm and greater) caused cases of respiratory tract cancer; however, the incidence was not 100% or even 45% as predicted from linear models.

For ethylene dibromide, no increase in cancer was seen in 156 employees exposed to an average of 3 ppm for 4.2 years, while the predicted incidence is 20% (Ramsey *et al.*, 1978).

The probability of dying from liver cancer in the United States is 210/100,000, yet the risk predicted from the average exposure to aflatoxin alone is 789/100,000.

The lack or inadequacy of epidemiological evaluation weakens the foregoing superficial analysis. However, it is not likely that the magnitude and consistency of overprediction will be discounted by more intense evaluation. More rigorous comparison of predicted risk with epidemiological results is needed. Such comparisons are needed to define the boundaries for the preconceptions inherent to risk assessment models.

In addition to using risk assessment models to predict the incidence of cancer in man from chronic bioassay data, similar predictions of the incidence in the same or other species of animals exposed to lower doses in other experiments need to be made when feasible. For chloroform, such an assessment shows that the risk assessment

models fail miserably (Reitz *et al.*, 1980). At the very least, it is reasonable to expect such predictions to be more accurate than predictions for man.

Assessments such as the foregoing indicate toxicologists better get about assessing the credibility of their science. Many, including epidemiologists, criticize the lack of power in epidemiological studies. It is high time we critically assess and admit the lack of power in animal toxicology studies with respect to interpretations currently being made. As a start, extrapolation of carcinogenicity data using the linearized multistage model should be considered only for materials found positive in mutagenicity evaluations. Biological rationale for using this model for nongenetic carcinogens does not exist.

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