

Attachment IV

SHORT COMMUNICATIONS

Carcinogenic Risk Assessment: Ethylene Dibromide

Carcinogenic Risk Assessment: Ethylene Dibromide. RANNEY, J. C., PARK, C. B., OTT, M. G., AND GEHRING, P. J. (1979). *Toxicol. Appl. Pharmacol.* 47, 411-414. Ethylene dibromide has been shown to result in an increased incidence of gastric tumors in rats following inhalation at 40 mg/kg/day. The U.S. Environmental Protection Agency (EPA) has used a one-hit carcinogenic model with parameters derived from this bioassay in rats to estimate the risk of cancer in humans arising from inhalation exposure to ethylene dibromide. The EPA estimated an almost 100% lifetime incidence of cancer to be expected in workers exposed to 0.4 ppm of ethylene dibromide at citrus fumigation centers. This communication reports a test of the validity of that prediction based on a comparison of the incidence of cancer predicted by the method used by the EPA with that observed in a group of 156 workers employed in the production of ethylene dibromide. The one-hit model as used by the EPA predicted a total of 85 tumors above the normal background incidence in this group of employees. A total of eight tumors has been observed. Therefore, use of this model to predict carcinogenic response in humans appears to result in highly exaggerated risk estimates.

Ethylene dibromide (EDB) is a chemical used extensively as a gasoline additive and to a lesser extent as a grain and citrus fumigant. It has been shown to result in an increased incidence of gastric tumors in rats when administered by gavage (Olson *et al.*, 1973; Powers *et al.*, 1975). The Carcinogen Assessment Group (CAG) of the U.S. Environmental Protection Agency has recently used data from this carcinogenic bioassay in rats to estimate the risk of increased cancer in humans arising from exposure to EDB. The CAG has estimated an almost 100% lifetime incidence of cancer to be expected in humans exposed to a concentration of 0.4 ppm (3.1 mg/m³) of EDB for 40 years (Pesticide and Toxic Chemical News, 1977). The reliability of this alarming prediction is dependent upon the validity of the carcinogenesis model as well as its extrapolation from rats to a human population. To test these hypotheses, we have compared the incidence of cancer predicted by the CAG carcinogenesis model with that observed in a group of workers employed in the production of EDB.

METHODS

The model used by the CAG to obtain the risk estimate quoted above is a one-hit model in which the probability (p) of tumor formation is given by

$$p(x, t) = 1 - \exp(-\beta x t^{\lambda}) \quad (1)$$

The parameter x is the exposure to EDB expressed as milligrams per kilograms per day averaged over the entire lifetime. The time span for which the risk is estimated is represented by t , expressed as a fraction of the total lifetime (115 weeks for rats, 70

years for man). The parameters β and γ are estimated from the experimental data. β reflects the potency of the carcinogenic agent (with dimensions of reciprocal dose), while γ is a dimensionless parameter which reflects the observed time to tumor formation. When the risk is estimated for an entire lifetime, $t = 1$ and Eq. (1) reduces to

$$p(x) = 1 - \exp(-\beta x). \quad (2)$$

The parameter estimates used were those derived by the CAG from the age-specific incidence of tumor formation in male rats presented with EDB by gavage in corn oil at a dose level of 40 mg/kg/day. The resulting values were $\beta = 31.73 \text{ kg} \cdot \text{day}/\text{mg}$ and $\gamma = 6.95$. The parameter β includes an adjustment to human dosage equivalents on a milligram per surface area basis.

The epidemiologic study which provided the basis for this comparison was reported in detail by Ott and Scharnweber (1977). The study included a cohort of 156 employees from two EDB production facilities, one located in Michigan and another in Texas. Fifty-seven of the employees were reactor and still operators from the Michigan facility, which operated continuously from the mid-1920s until 1976.

Industrial hygiene surveys conducted in 1950 showed airborne concentrations of EDB from 1.0 to 10.6 ppm in the breathing zone of still operators and in 1951 from 19 to 31 ppm between stills. Time-weighted average (TWA) concentrations of EDB in the breathing zone of reactor and still operators in 1971 and 1972 ranged from 2.9 to 4.0 ppm. The 99 employees from the Texas facility were comprised of reactor and still operators, foremen, and lead burners. No industrial hygiene data were available from this location. EDB was the only organic bromide product manufactured at the Texas facility, while employees at the Michigan location were exposed to other products (including carbon tetrachloride and chloroform) as well as EDB.

The one-hit carcinogenic model was applied to the two groups of employees as follows: The duration of exposure to EDB at both locations was determined by the work history records of each employee. Based on the industrial hygiene surveys at the Michigan location, the TWA concentration of EDB was conservatively assumed to be 3.0 ppm (23 mg/m³). To test the effect of a different exposure concentration on the predicted incidence of tumor formation, another analysis was conducted at an assumed TWA of 0.9 ppm (6.9 mg/m³). All computations were done in a manner identical to that used by the CAG. Thus, the daily dose of EDB in milligrams per kilogram per day was calculated by assuming the individual body weights were 70 kg, the inspiratory volume for an average work day was 14 m³, and all inhaled EDB was absorbed. All calculations were made on the basis of 250 working days per year. Age was taken as the age either at the date of death or at termination of the study in 1976 (with a maximum of 70 years). Using the CAG parameter estimates from the carcinogenic bioassay in rats mentioned previously, the probability of tumor formation for each individual was then calculated as

$$p = 1 - \exp[-(31.73)(\text{daily dose})(250/365)(\text{years exposed})\text{age}^{-6.95}].$$

The individual probabilities were then accumulated to yield the total probability for tumor formation within each group of employees.

The employees working with arsenical compounds in addition to EDB have been excluded in this study because of prior indications that arsenical compounds are an increased risk of developing hepatocellular carcinomas (Ott *et al.*, 1974).

RESULTS AND DISCUSSION

Table 1 shows the number of malignant neoplasms observed (up to January 1976) within each group of employees and the number predicted based on probabilities calculated with the one hit model. As reported by Ott and Scharnweber (1977), no increase in the incidence of malignancies was noted in workers at the Texas location. In the Michigan production unit there have been five deaths due to malignant neoplasms vs 2.2 expected based on a comparison with the United States white male mortality rates. The gross overprediction of the incidence of malignant neoplasms by the one hit model is apparent at either of the assumed TWA concentrations of EDB. Eight malignant

TABLE 1
OBSERVED AND PREDICTED MALIGNANT NEOPLASMS IN EDB PRODUCTION
WORKERS AT TWO LOCATIONS

Location	Number of employees	Number of malignant neoplasms	
		Observed	Predicted
			3.0 ppm 0.9 ppm
Michigan	57	5	32 19
Texas	99	3*	53 33
Total	156	8	85 52

* Number of neoplasms above the normal background incidence predicted with the one hit carcinogenic model used by CAG.

Assumed average TWA concentration of EDB.

Excludes one employee, one death of probable cardiovascular cause.

Includes one employee with reported cancer of unknown site, one of whom was dead was antineoplastic therapy.

neoplasms have been observed thus far in both employee groups combined, whereas either 85 or 52 neoplasms above the normal background incidence were predicted at TWA concentrations of EDB of 3.0 or 0.9 ppm, respectively, by the one hit model.

The limited number of employees in the study population indicates the need for caution in the interpretation of these results. There is also a need for a continuing follow-up of this group of employees. Up to January of 1976, there were a total of 76 deaths in the cohort of 156 men in both groups (seven due to malignant neoplasms), and the average age of the remaining population was 55 years (range, 31 to 76). The possibility exists that a portion of the remaining population may possess undetected neoplasms. However, the probabilities of tumor formation calculated by the one hit model are adjusted for the age of each individual. Therefore it is extremely unlikely that the dramatically high incidence of cancer estimated by this technique is a realistic prediction.

The apparent failure of the one hit model as used by the CAG to predict the incidence of malignant neoplasms may be the result of several factors. Since the basic model parameters were derived from data arising from a carcinogenic bioassay, it is

* This difference was not statistically significant at the 0.05 level assuming a Poisson distribution.

the extrapolation from an inbred strain of laboratory rats to a heterogeneous human population with diverse environment may be one of the basic deficiencies in the model. Furthermore, the excessively high dose level from which the parameters were derived, as well as differences in the route of exposure (intubation vs inhalation) may also contribute to failure of the predictive value of the model. EDB is metabolized in the rat by conjugation with hepatic glutathione (Nachtoni, 1970), a process which is known to be saturable at doses sufficiently high to deplete available glutathione concentrations. Thus, nonlinearities in the dose-response relationship at low dose levels may obviate the predictive value of data derived from higher dose levels (Cornfield, 1977; Gehring and Biau, 1977). The foregoing reasons, plus the fact that no provision is made for DNA repair, make suspect the biological plausibility of this model as used by the CAG.

Whatever the reasons for failure of this particular method in predicting carcinogenic response in humans, it is apparent that a great deal of caution must be used in the application of such methods in predicting the hazard to be expected from exposure to potential carcinogenic agents.

REFERENCES

- CORNFIELD, J. (1977) Carcinogenic risk assessment. *Science* **198**, 693-699.
- GEHRING, P. J. AND BLAU, G. E. (1977) Mechanisms of carcinogenesis. Dose response. *J. Environ. Pathol. Toxicol.* **1**, 163-179.
- NACHTONI, E. (1970) The metabolism of ethylene dibromide in the rat—The enzymic reaction with glutathione *in vitro* and *in vivo*. *Biochem. Pharmacol.* **19**, 2853-2860.
- OLSON, W. A., HABERMANN, R. T., WEISBURGER, E. K., WARD, J. M., AND WEISBURGER, J. H. (1973) Induction of stomach cancer in rats and mice by halogenated aliphatic fumigants. *J. Nat. Cancer Inst.* **31**, 1993-1995.
- OTT, M. G., HOLDER, B. B., AND GORDON, H. L. (1974) Respiratory cancer and occupational exposure to arsenicals. *Arch. Environ. Health* **29**, 250-255.
- OTT, M. G. AND SCHARWEBER, H. C. (1977) *The Mortality Experience of 161 Employees Exposed to Ethylene Dibromide in Two Production Units*. Corporate Medical Department, The Dow Chemical Company, Midland, Mich.
- Pesticide and Toxic Chemical News*, October 12, 1977, pp. 3-4.
- POWERS, M. B., VOELKER, R. W., PAGE, N. P., WEISBURGER, E. K., AND KRAYBILL, H. F. (1975) Carcinogenicity of ethylene dibromide (EDB) and 1,2 dibromo-3-chloropropane (DBCP) after oral administration in rats and mice. *Toxicol. Appl. Pharmacol.* **33**, 171-172.

J. C. RAMSEY
C. N. PARK
M. G. OTT
P. J. GEHRING

Toxicology Research Laboratory
Health and Environmental Research
Dow Chemical Co.
Midland, Michigan 48640

Received February 23, 1978; accepted August 5, 1978