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Recent Scientific Developments That Affect the Assessment of Risk Posed by Trichloroethylene and Perchloroethylene

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ABSTRACT: Trichloroethylene (TRI) and perchloroethylene (PER) are chlorinated hydrocarbons with similar chemical and toxicological properties. Cancer bioassay results with TRI and PER have shown increased incidence of liver tumors in $B_6C_3F_1$ mice. Though the exact mechanism of tumor induction caused by TRI or PER is unknown, metabolic activation is strongly implicated. The major metabolite, trichloroacetic acid (TCA), induces peroxisomal proliferation (PP) in livers of rodents. Evidence suggests that PP in the liver is linked to the development of hepatic carcinomas. Whether PP is causative or just a by-product of liver cancer is unknown, but results establish that human cells do not react to TCA as rodent cells do. The current information on pharmacokinetics and mechanism-of-action for TRI and PER do not support a concern for carcinogenicity of exposed persons, based on findings of cancer in rodents. Moreover, the findings do not suggest a need for quantitative risk assessment.

KEY WORDS: trichloroethylene, perchloroethylene, peroxisomal proliferation, pharmacokinetics

Trichloroethylene (TRI) and perchloroethylene (PER) are chlorinated hydrocarbons which have similar chemical and toxicological properties. Both compounds have been employed since the 1920s as solvents, with TRI being used widely today as a vapor degreaser and PER as a solvent in dry cleaning. Results with TRI and PER from cancer bioassay studies have shown positive findings for rodents. In particular, both TRI and PER have increased the incidence of liver tumors in $B_6C_3F_1$ mice. In this paper we suggest a perspective on these studies for public health purposes and contrast our news with those of the federal regulatory agencies [*1-3*].

Bioassay Findings

TRI administered by inhalation to NMRI mice showed no increase in the incidence of cancer ascribed to treatment [*4*]. While the authors of this study reported an accelerated appearance of lymphomas in the treated female mice, this response was perhaps related to increased stress. Swiss mice given TRI via corn oil gavage showed no significant increases in tumors [*5*]. ICR mice treated by inhalation with TRI had no increased cancer incidence in males, though females showed some increase in lung cancers but not total lung tumors [*6*]. Studies in rats have been negative [*1,4,6*], inconclusive [*7-9*], or in one case positive for Leydig cell tumors, although with some reservations [*10*]. One other study using Syrian hamsters administered TRI via inhalation was negative [*4*].

PER administered by gavage or inhalation to rats has not increased the incidence of tumors [*3,11*]. However, PER given by inhalation in a recent National Toxicology Program (NTP) study [*2*] was reported to increase the incidence of mononuclear cell leukemia in both sexes and kidney tumors in males. The spontaneous incidence of mononuclear cell leukemias in the NTP study was higher than historical background levels, and the pathology of this leukemia, which often is seen in aged rats, has been controversial. The increase in kidney tumors in the NTP study was not statistically significant. Recent reviews by the Science Advisory Board indicated that the study does not provide a basis for associating either the leukemias or the kidney tumors with exposure to PER [*12,13*]. In our opinion further research will be necessary before either endpoint can be utilized in a risk assessment.

Using "upper-bound" risk assessment models, EPA has calculated potencies for both TRI and PER as potential carcinogens [*14-16*]. However, when the cancer response in the mouse, plus recent metabolism and pharmacokinetic data are examined, a different opinion emerges. These two chlorinated solvents probably do not present a significant risk of cancer to man.

Though the exact mechanism of tumor induction caused by TRI or PER is still unknown, various authors have strongly implicated metabolic activation for these compounds to exert their carcinogenic effect in mice as described below.

Metabolism and Pharmacokinetics

In evaluating whether it is biologically plausible that a test chemical shown to produce tumors in experimental rodents would be likely to produce the same response in humans, it is important to integrate both mechanistic considerations and known species-specific differences in the pharmacokinetics and metabolism of the agent. Trichloroacetic acid (TCA) has been reported to be a major metabolite of TRI and PER in mice, rats, and man [*17,18*]. However, there is significantly less metabolism of TRI and PER in man than in either rats or mice, strongly suggesting that substantially lower blood levels of TCA would be formed in man than in rodents.

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The major documented pathway for TRI and PER metabolism occurs in the cytochrome P_{450} monooxygenase system and probably involves the formation, first of a transitory epoxide, followed by a rearrangement to trichloroethanol (reduction) or TCA (oxidation) [*19,20*]. Details of each metabolic pathway are shown in Fig. 1 (TRI) and Fig. 2 (PER). Alternative structures to the epoxide have been proposed for a transient intermediate, but these lead to the same products demonstrated to occur in the intact animal in the appropriate kinetic sequence. Following exposure to TRI or PER, blood levels of TCA are greater in mice than in rats [*21*]. Monster has shown that humans metabolize TRI at 20-fold lower rates than rats [*22*]. In cell culture experiments Elcombe has shown that mouse hepatocytes produce 30-fold more TCA than rat hepatocytes, which in turn produce 3-fold more TCA than human hepatocytes [*23*].

The rat undergoes biochemical responses to TCA *in vitro* that are similar to those observed in the mouse, when isolated hepatocytes from the two species are exposed in cell culture experiments. Thus absence of a carcinogenic effect in the rat liver would appear to be a function of its lower rate of production of TCA.

When animals are dosed with TRI or PER, the rate of metabolism directly affects the amount of metabolite (or the effective dose of the postulated toxicant) reaching the target organ and thus the amount of chemical leaving the body. Therefore mice with a metabolic rate for TRI and PER which is significantly greater than the rat will have a greater amount of metabolite (TCA) reaching the target site. Two points should be noted: (1) TCA induces PP in livers of both rats and mice, and (2) TCA itself has been shown to be carcinogenic in $B_6C_3F_1$ mice.

The most significant finding to come out of the many long-term animal carcinogenicity studies of TRI and PER is that the enhanced incidence of liver tumors in mice is not seen in rats or hamsters. The differences between rodent species apparently is explained by quantitative differences in the production of TCA.

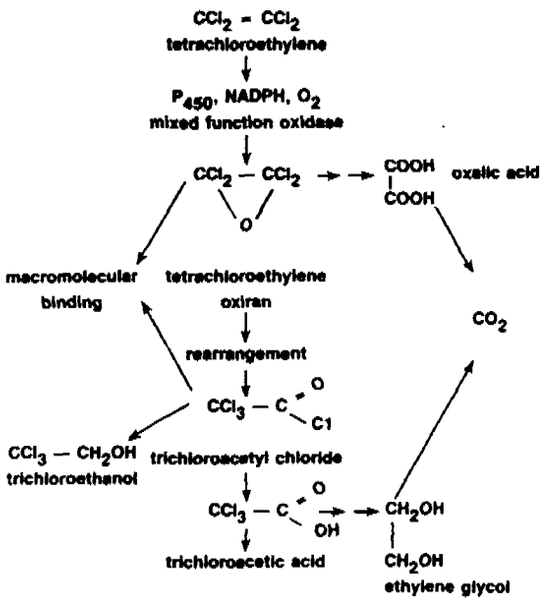

FIG. 1—*Possible metabolic pathways of tetrachloroethylene in animals and man.*

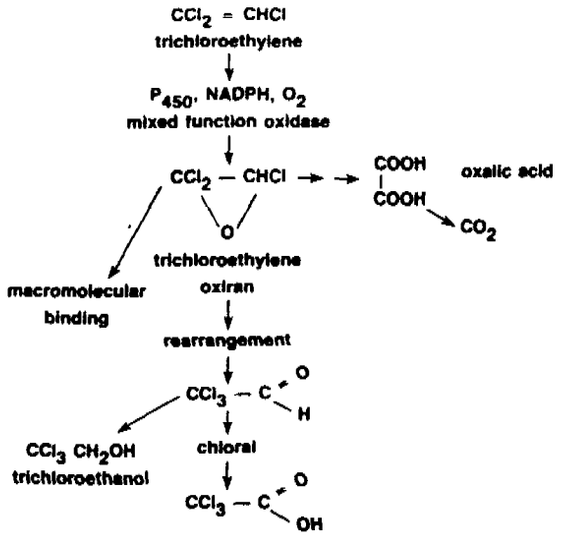

FIG. 2—*Possible metabolic pathways of trichloroethylene in animals and man.*

Mechanism of Action

Mechanism studies, described below, have shown that liver tumors arise by a mechanism specific to rodents. Thus humans are unlikely to be at risk from TRI or PER induced liver cancer. The incidence of spontaneous liver tumors in untreated $B_6C_3F_1$ mice is high. The Board of Scientific Counselors for NTP recommended that this strain of mice be replaced with another species not having this problem. Many toxicologists believe that the livers of the $B_6C_3F_1$ mouse are "pre-initiated"; that is, they respond to substances that merely accelerate the appearance of spontaneously arising tumors. If so, such substances, called "promotors," are thought to have practical thresholds, unlike initiating carcinogens, which may present greater hazards.

Mouse liver tumor formation is associated with PP. This proliferation is due to a metabolite, TCA, which is the so-called "proximal carcinogen." TCA alone can cause PP in mouse liver cells in culture or in the intact mouse. The level of PP in the mouse (and the rat) corresponds to the level of TCA production. The difference in toxicity between rodent species apparently is explained by quantitative differences in the production of TCA. Herren-Freund and co-workers have shown that TCA alone acts to induce mouse liver tumors in the $B_6C_3F_1$ mouse [*8*]. It is not yet known whether PP causes liver cancer in rodents or is caused by the carcinogenic process as an independent event.

Elcombe has shown that PP does not occur in human hepatocytes following *in vitro* exposure to TCA, whereas it does occur in rodent hepatocytes [*23*]. Whether PP is causative of liver cancer or just a by-product, these studies establish that human cells do not react to TCA as do rodent cells. Thus humans are unlikely to show a carcinogenic response to PER, because they fail to demonstrate the biochemically critical response, PP [*24*].

Risk Assessment

Current federal guidelines for carcinogen risk assessment call for the development of a biologically motivated model to estimate quantitative risk, even when this calculation is carried out as a "what-if" exercise. (That is, *what* might the risk be *if* this substance is a carcinogen.) EPA has not made such an effort in the case of TRI or PER. Instead, the Agency has used "default" procedures developed from general theories of carcinogenesis. An appealing alternative to the default model is within reach of Agency scientists.

The Federal agencies' current methodology for quantitative risk assessment is dominated by two policy assumptions: (1) that carcinogens do not have practical thresholds, and (2) that carcinogenic risk is a linear function of dose even at very low doses [*25*]. Given these policy choices, the agencies have chosen a mathematical model that performs well in estimating a maximum linear slope consistent with bioassay data. The model, sometimes referred to as the "linearized multistage" or "Crump" model, takes incidence data obtained at all doses into account, whereas "straight-line" or "single-hit" (Poisson) models have difficulty accepting more than one data point [*26*]. The Crump model operates with the data from a bioassay as follows:

- A version of the multistage model is developed that mathematically resembles a true multistage model, with the number of stages constrained by the number of non-zero doses used in the bioassay.
- A maximum likelihood fit of this specific model to the bioassay data is developed with the exponential values for each stage constrained to give only positive risks (shorter times between stages).
- All exponential coefficients higher than the single-hit (linear) component are held fixed and the magnitude of the single-hit exponent is enlarged in the direction of increasing risk to obtain a maximum value compatible with the data in a 95% confidence limit sense. The value of the linear exponent of the slope is used for risk estimation purposes.

However, the Crump model is not without difficulties. It is changed sufficiently from the original model of Armitage and Doll that it no longer retains a biological rationale [*27*]. The stages in the Crump model do not relate to discrete modifications of a cell line in the pathway to an observable tumor, and the number of stages is not related to the number of stages in the carcinogenic process. The exponents do not relate to the times between these discrete cell variants, and the overall set of exponential coefficients do not relate to the time to tumor. The constraint on non-negative exponents means that models in which a substance lengthens the time of one stage are forbidden. However, this biological effect has been observed experimentally. In short, a Crump model for a substance is not derived from an underlying biological theory of carcinogenesis or from knowledge of relevant biological effects of the substance in question. Instead, this model is a curve-fitting device.

The curve-fitting exercise is not without its costs. Point values are produced which tend to be insensitive to changes in the shape of the dose-response curve [*28*]. The confidence limit-driven slope is more sensitive to the number of animals the investigator may choose for the bioassay than to the tumorigenic response. The number of animals used, however, is an irrelevant variable for a model of the carcinogenic effect of a substance on which regulations will be based. A Crump model accepts pharmacokinetic or time-to-tumor data only with difficulty. Mathematical curve-fitting ignores metabolic features such as alternative pathways, competing pathways, saturation, and so forth. Information on age-specific cancer incidence, background rates, including cell-turnover or cell population kinetics, and lack of mutagenicity cannot be used at all unless the model maker arbitrarily alters the parameters.

Instead of a Crump model for TRI or PER, an agency could develop a Moolgavkar-Knudson model [*29*]. A Moolgavkar-Knudson model describes cancer induction as a filtered Poisson process with deterministic and stochastic elements that account for the dynamics of a cell population that is intermediate between two stages, transition from normal cells and transition to malignant cells. Biologically, these two transitions are characterized as rare and irreversible in practice. Use of a Moolgavkar-Knudson model for TRI or PER offers many advantages for scientists [*30*]. Moolgavkar-Knudson models do have a biological rationale and suggest research directions to improve risk estimates. A Moolgavkar-Knudson model can be constructed that fits the data and that does not contradict major policy assumptions of no practical threshold and low dose linearity. For example, a Moolgavkar-Knudson model can account for an unusual age-specific age period and then declines, such as childhood or hormonally dependent cancers. Further, one can model some of the pharmacodynamic factors involved in dose adjustment between species and relate human background rates and age-specific incidence to those of the rodents used as bioassay subjects. Pharmacokinetic data, suggested mechanisms (e.g., promotion versus initiation), and time-to-tumor are scientifically usable to modify the parameters of the model.

Many of the advantages of the Moolgavkar-Knudson model over the Crump model are directly relevant to the specific properties of TRI or PER: (1) shape of the dose-response curve; (2) low incidence at maximal response doses; (3) high background tumor rates in the mouse strains used as bioassay subjects; (4) strong suggestions of action by a promotional, non-genotoxic mechanism; (5) pharmacokinetics and mechanism-of-action data that have strong nonlinearities; (6) lack of genotoxicity; and (7) species differences.

The Moolgavkar-Knudson model is not necessarily the best description of carcinogenic risk from TRI or PER (or indeed any other chemical). In many cases, metabolic differences between species strongly suggest that, despite rodent carcinogenicity, there may be no human hazard. Further, Moolgavkar-Knudson models require intense biological data to have scientific credibility and, in fairness to the federal agencies, such data are not yet available. The OSTP guidelines advise that pharmacokinetic data should, when available, be incorporated into a risk assessment. In such cases, an agency might need to abandon the two policy assumptions of no threshold and low-dose linearity. Recognizing that such a state-of-the-art scientific approach may need time to gain general acceptance, as an interim measure an agency can use a Moolgavkar-Knudson model as a biologically more appropriate description that does not require an agency to abandon the two traditional policy assumptions.

Should the federal agencies persist with the use of a Crump model to estimate the "what-if" risks for TRI or PER, a better choice of dose adjustment factor also is available than body surface area. Optimally, the agencies would use a physiological-pharmacokinetic model for purposes of dose adjustment. Failing this, dose conversion should be carried out by body weight, which provides a better basis for dose adjustment between species.

Two kinds of data are available that have crucial impact on the best choice of a "default" value, as defined by the National Academy of Sciences Committee on Institutional Means for Risk Assessment [*31*]. Firstly, EPA recently co-sponsored a comparison of carcinogenic potency of various substances in humans and rodents. While the correlation between human and rodent potencies obtained with body weight as the dose adjustment basis was similar to that with body surface area (0.70 versus 0.71), for prediction of the potency value, body weight proved far superior to body surface area [*32*]. Secondly, two groups of investigators have tested the ability of the mouse to predict the rat and vice versa. Both Wilson, Crouch, and co-workers [*33–35*] and Gaylor and Chen [*36,37*] found that body weight proved superior to body surface area in predicting potency.

Epidemiology Findings

A number of epidemiology studies [*38–44*] have investigated the incidence of cancer mortality among dry cleaner workers. Only the National Institute for Occupational Safety and Health (NIOSH) studies, however, have attempted to identify persons exposed to PER exclusively. This study was conducted for NIOSH, completed in 1980 [*40*] and updated in 1985 [*41*]. Initially, it examined the health records of 1600 dry cleaner workers employed for at least one year prior to 1960 in metropolitan shops where PER was the primary solvent. The study found no deaths caused by liver cancer, but did find a small increase in mortality due to colon cancer. These results were confounded, however, by possible exposure to other substances and the lack of complete health records for a significant number of workers. Based on this study, EPA has concluded that the overall epidemiological data for PER was "inadequate" for purposes of interpreting possible human carcinogenicity [*14*].

In 1985, NIOSH subsequently completed a follow-up [*38*] to the 1980 study which involved a more detailed examination of an increased number of dry cleaners (1690 workers). The new study found the overall cancer mortality rate to be higher than, but not significantly different from, that predicted using U.S. mortality rates. The relative number of cancer deaths among the workers studied was reduced when compared to the higher cancer mortality rates in the metropolitan areas investigated. Among the site-specific cancer mortalities, urinary tract cancer (particularly in the bladder) was the only one found to have a significant increase. To eliminate the possible effects of exposure to other dry cleaning solvents, the researchers identified a subcohort of 615 workers with no known exposure to these other solvents. Within this subcohort of workers exposed to only PER, the incidence of mortality from urinary tract cancer (and from cancer in general) was lower than that expected from overall U.S. mortality rates.

A number of studies also have been carried out with the specific objective of investigating any possible association between TRI exposure and human liver [*45–51*] cancer. These studies show a weak to no correlation between TRI exposure and human liver cancer. A number of more general studies have been reported on workers potentially exposed to TRI. Although most of these studies have limitations (e.g., insufficient information on levels of TRI exposure), none present evidence to suggest that exposure to TRI is associated with an increased incidence of cancer in humans. A recent study [*50*] has added considerably to the epidemiological data base on TRI. This study of over 2600 exposed workers with an average exposure of over six years found no increase in cancer-related deaths compared with the expected result among unexposed white males (the largest group used for purposes of comparison).

Summary

In this paper we have suggested that current information on the pharmacokinetics and carcinogenic mechanism-of-action of TRI and PER in rodents do not support a concern for the safety of exposed persons. Neither do our conclusions suggest a need for a quantitative risk assessment, as supported by human epidemiological studies. However, if federal agencies feel compelled to develop such estimates for public policy reasons, we also have outlined how the agencies might develop risk estimates that incorporate more of the pharmacokinetic and mechanism-of-action data.

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