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Health Risk Assessment of Environmental Exposure to Trichloroethylene[1]

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A review of the animal data showed trichloroethylene (TRI) to be of low acute toxicity. Repeated exposure showed that the target organs were the liver and, to a lesser extent, the kidney. TRI is not mutagenic or only marginally mutagenic. There is no evidence of fetotoxicity or teratogenicity. TRI is judged not to exhibit chronic neurotoxicity. Lifetime bioassays resulted in tumors in both the mouse and the rat. However, because of qualitative and quantitative metabolic differences between rodent and human, no one suitable tumor site can be chosen for human health risk assessment. In addition, of the several epidemiology studies, none has demonstrated a positive association for increased tumor incidence. A review of the health effects in humans shows TRI to be of low acute toxicity and, following chronic high doses, to be hepatotoxic. Environmental exposure to TRI is mainly via the atmosphere, while the contribution from exposure to drinking water and foodstuffs is negligible. The total body burden was calculated as 22 μg/day. The safety margin approach based on human health effects showed that TRI levels are well within the safety margin for the human no-observable-effect level (10,000 times lower). The total body burden represents a risk of 1.4×10^{-5} by linearized multistage modeling. Therefore, by either methodological approach to risk assessment, the environmental occurrence of TRI does not represent a significant health risk to the general population or to the population in areas close to industrial activities.

[1] This report was conducted under the auspices of the European Chlorinated Solvents Association (part of CEFIC) as a group further consisting of Paul A. Herbert, ICI Chemicals & Polymers Ltd., Cheshire, England; Fred H. van Mensch, AKZO Salt and Basic Chemicals, Hengelo, The Netherlands; and Harry G. Verschuuren and John Place, Dow Europe, Horgen, Switzerland.

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INTRODUCTION

A survey of the environmental occurrence of trichloroethylene (TRI) in ambient air and in ground and surface water has recently been published by CEFIC (1986). This survey shows that members of the general population are exposed to minute, yet measurable, quantities of the chlorinated solvent in their drinking water, in food, and in ambient air.

It is known that high, chronic exposure to TRI can cause a range of health effects (Fielder *et al.*, 1982). The present article briefly reviews the choice of the toxicological basis for the risk assessment and selects the relevant figures for environmental exposure. An assessment of the potential risk for human health resulting from such exposure, using a biological no-observable-effect level and safety factors, was calculated.

Alternative quantitative risk assessments have been published by the U.S. Environmental Protection Agency (EPA) on the basis of carcinogenicity as an endpoint and using linearized multistage modeling to predict unit risk (U.S. EPA 1984). The results of a safety factor approach using human health effects as an endpoint are reported and compared with the approach adopted by EPA.

REVIEW OF HEALTH EFFECTS

I. Animal Data

1. Acute Toxicity

Trichloroethylene is well absorbed after oral administration and on inhalation. It is of low acute toxicity. The principal effects seen in animal studies following exposure to TRI are central nervous system (CNS) depression, ventricular arrythmias, hepatotoxicity, and renal toxicity (Fielder *et al.*, 1982). The most sensitive of the effects appears to be on the CNS, the effects having been described by Grandjean (1955) as decreased swimming ability in rats exposed to 400 ppm TRI for 6 hr.

2. Subchronic and Chronic Toxicity

The primary target organs for the subchronic and chronic toxicity of TRI are the liver and kidney. An increase in liver weight and associated histopathological and biological changes have been reported in rats and mice exposed to TRI at relatively low concentrations for periods up to 14 weeks [e.g.: Kjellstrand *et al.* (1983a,b) exposed mice continuously to more than 37 ppm for 30 days, Kimmerle and Eben (1972) exposed rats to 55 ppm TRI, 8 hr/day, 5 days/week, for 14 weeks].

There is no evidence to suggest chronic neurotoxic effects in rodents. Acute effects are well described (above); however, minimal changes in CNS activity have been observed in rats exposed to TRI at levels as low as 200 ppm (Savolainen *et al.*, 1977).

Effects described in the kidney include increased kidney weight in mice exposed continuously to more than 75 ppm for 30 days (Kjellstrand *et al.*, 1983a,b) and renal dysfunction (in the absence of marked pathological changes) in rats continuously exposed to more than 50 ppm for 12 weeks (Nomiyama *et al.*, 1986).

3. *Effects on Reproduction and Development*

The reproductive and developmental toxicity of TRI has been explored in a number of studies in the rat, the mouse, and the rabbit by both oral and inhalation exposure. Male and female rats received up to 1000 mg/kg daily for 6 weeks by oral administration and were allowed to mate. Males receiving 1000 mg/kg, although showing an initial decrease in copulatory behavior, showed no evidence of altered sperm motility, morphology, or count. No other effects were reported. The females, who were also exposed to TRI during their pregnancy, showed no impairment in reproductive performance or its outcome (Zenick *et al.*, 1984).

No teratogenic effects have been observed in the offspring of rats or mice exposed to 300 ppm (gestational days 6–15) (Schwetz *et al.*, 1975). In a study in the rat, pregnant females were exposed to 1800 ppm TRI throughout gestation (Days 0–20). There was no evidence of teratogenicity, but there were signs of fetotoxicity (delayed development of the skeletal system) (Dorfmueller *et al.*, 1979). There are no reports of adverse reproductive effects in humans associated with exposure to TRI.

4. *Mutagenicity*

The mutagenic potential of TRI has been studied widely. In many of the reported studies the purity of the sample tested is not stated, although the potentially mutagenic epoxide stabilizers were almost certainly present. Therefore the relevance of the various studies to the mutagenicity of TRI itself is confounded.

The literature contains a number of reports of positive findings relating to *in vitro* assays with *Salmonella typhimurium, Saccharomyces pombe, Escherichia coli,* and *Aspergillus nidulans.* A similar number of studies reporting no activities are also described (Fielder *et al.*, 1982).

In *in vivo* assays TRI was without effect in a dominant lethal study in both rats and mice (Slacik-Erben *et al.*, 1980), in a mouse liver unscheduled DNA synthesis study (Mirsalis *et al.*, 1985), and in a mouse bone marrow chromosome aberration study (Loprieno and Abbandandolo, 1980). Positive effects have been suggested in the mouse micronucleus assay (Duprat and Gradiski, 1980). Finally, somatic mutations in TRI-treated mice similar in magnitude to spontaneous changes have been observed in a spot test, although the author suggested that there was a positive effect (Fahrig, 1977).

Covalent binding of TRI or its metabolites to microsomal protein, RNA, and DNA has been demonstrated *in vitro* (Bolt *et al.*, 1977), although this effect has not been satisfactorily demonstrated *in vivo* (Parchman and Magee, 1982; Stott *et al.*, 1982).

TRI has been found to be nonmutagenic or only marginally mutagenic. A contribution from the presence of mutagenic epoxide stabilizers contained in the TRI samples cannot be ruled out in some positive assays. Many reports are inadequate to allow a final conclusion to be drawn with respect to mutagenicity. This view is shared by several authors and international agencies (Henschler *et al.*, 1980; Elcombe, 1985; IARC, 1982, 1988; Dutch Criteria Document, 1984).

It is concluded that TRI itself does not appear to be a classic genotoxin and probably exerts its carcinogenic potential via an epigenetic mechanism; therefore, mutagenicity is not a suitable endpoint for human health risk assessment.

5. Carcinogenicity

Evidence from animal carcinogenicity data on TRI has been judged to be limited (IARC, 1988). However, TRI has been shown to increase tumor incidence in the mouse and to a lesser extent the rat. These data are summarized in Table 1. The principal tumor sites in the mouse are the liver and the lung (separate studies), and in the rat, the kidney.

i. Mouse liver tumors. The occurrence of mouse liver tumors (hepatocellular carcinomas and adenomas) is the most frequently reported and significant observation in lifetime cancer bioassays. These tumors have been observed in both sexes in Swiss and B6C3FI strains following both inhalation and gavage exposure to TRI. Liver tumors have not been reported in other strains of mice, for example, NMRI (Henschler *et al.*, 1980, 1984) and ICR (Fukuda *et al.*, 1983), nor have they been reported in other species, for example, rat and hamster (Henschler *et al.*, 1980; Maltoni *et al.*, 1986).

This response is considered to be of no significance to human risk assessment because of (a) quantitative differences between species in the metabolism of TRI to trichloroacetic acid (TCA), the proximal mouse liver carcinogen (Green and Prout, 1985; Prout *et al.*, 1985); and (b) qualitative differences between rodent and human in the biochemical response of the liver i.e. peroxisome proliferation (Elcombe, 1985).

TCA is the most significant metabolite of TRI in all species studied. This metabolite has also been shown to cause liver cancer in the mouse (Herren-Freund *et al.*, 1987). It is, therefore, reasonable to conclude that TCA is the proximal carcinogen in the mouse following exposure to TRI. The mouse has been shown to metabolize TRI to TCA via the cytochrome P450 pathway. The kinetics of this reaction are linear. However, in the rat and the human, this pathway is saturable (Stott *et al.*, 1982; Monster *et al.*, 1976). Thus, a maximum blood level of TCA can be demonstrated in the latter two species.

TRI causes peroxisome proliferation in mouse liver cells, an event associated with cancer induction in this species with a wide range of chemicals (Reddy *et al.*, 1980). This effect can be demonstrated both *in vitro* and *in vivo*. It is not observed in rat liver (Elcombe *et al.*, 1985). TCA has also been shown to cause peroxisome proliferation in mouse liver, but, unlike TRI, it also has this effect in rat liver cells. No such response is seen in human liver cells exposed to TCA *in vitro* (Elcombe *et al.*, 1985).

These data lead to the conclusion that liver cancer in the mouse is due to an effect associated with peroxisome proliferation, a mechanism believed not to be relevant to human cancer risk assessment. The difference between the rat and the mouse in this respect is due to the differences in metabolism between the species such that the maximal blood levels of TCA achieved in the rat are below the threshold required to trigger peroxisome proliferation. Thus, no carcinogenic response is observed in the liver of this species. The human behaves like the rat in this respect; human hepatocytes produce TCA at an even lower rate than the rat (Elcombe, 1985).

ii. Mouse lung. An increased incidence of lung adenocarcinomas in female ICR mice was observed by Fukuda *et al.* (1983) following exposure to TRI by inhalation. The effects were statistically significant at the two higher concentrations (incidence: control, 1/49; 50 ppm, 3/50; 150 ppm, 8/50; 450 ppm, 7/46), although the incidence of total lung tumors (benign and malignant) was not significantly increased above control levels. The sample of TRI tested contained 0.02% epichlorohydrin.

TABLE 1

SUMMARY OF KEY ANIMAL CARCINOGENICITY STUDIES ON TRICHLOROETHYLENE

	Dose	Exposure duration	Effects and comments
Mouse—oral/gavage			
U.S. NTP, 1982 (B6C3FI)	1000 mg/kg/day	104 weeks	Hepatocellular adenomas and carcinomas
Henschler *et al.*, 1984 (NMRI)	♀ 1.8 g/kg/day (adjusted to TWA 1.4 g/kg/day); ♂ 2.4 g/kg/day (adjusted to TWA 1.9 g/kg/day)	78 weeks; observation up to 104 weeks	Forestomach tumors with TRI stabilized with >0.25% epichlorohydrin; pure TRI, no tumors
Mouse—inhalation			
Henschler *et al.*, 1980 (NMRI)	100 and 500 ppm	78 weeks; observation for 130 weeks	Lymphomas in females only; no significant increases in tumor incidence at any other sites; poor survival in all groups
Maltoni *et al.*, 1986 (Swiss and B6C3FI)	100, 300, and 600 ppm	78 weeks; observation for lifetime	Hepatocellular adenomas and carcinomas; some benign lung tumors and adenocarcinomas in B6C3FI ♀ only
Fukuda *et al.*, 1983 (ICR)	50, 150, and 450 ppm	104 weeks; 3 weeks of observation	Only female mice tested; lung adenocarcinomas
Rat—oral/gavage			
U.S. NTP, 1982 (F344/N)	500 and 1000 mg/kg/day	104 weeks	Kidney adenocarcinomas in ♂ high-dose group only; study judged inadequate by NTP
Maltoni *et al.*, 1986 (Sprague–Dawley)	50 and 250 mg/kg/day	52 weeks; observation for lifetime	No significant increase in tumor incidence at any site
U.S. NTP, 1988 (August, ACI, Osborne Mendel, Marshall)	500 and 1000 mg/kg/dy	104 weeks	Kidney adenocarcinomas in ♂ Osborne Mendel; study judged inadequate by NTP
Rat—inhalation			
Henschler *et al.*, 1980 (Wistar)	100 and 500 ppm	78 weeks; observed for 156 weeks	No significant increase in tumor incidence at any site
Maltoni *et al.*, 1986 (Sprague–Dawley)	100, 300, and 600 ppm	104 weeks; observation for lifetime	Kidney adenocarcinomas in ♂ in 600-ppm group; some Leydig cell tumors and immunoblastic lymphosarcomas

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A small increase in the incidence of lung adenomas was observed in female B6C3F1 mice exposed to TRI by inhalation for 78 weeks and observed for lifetime (incidence: controls, 2%; 100 ppm, 7%; 300 ppm, 8%; 600 ppm, 16%). The effect was statistically significant only at the highest concentration. No increase in lung tumors was observed in male mice in the same study, nor in Swiss mice of either sex exposed to TRI using the same dosing regimen and the same laboratories (Maltoni *et al.*, 1986). Furthermore, lung tumors were not observed in a fourth study, reported by Henschler *et al.* (1980) with NMRI mice exposed to TRI by inhalation (100 and 500 ppm) for 78 weeks and observed for life; however, this study had a poor survival rate.

In summary the effect has been observed in the female ICR mouse and the female B6C3F1 mouse. It was not observed in the Swiss mouse nor in males of any of the mouse strains tested. The effect also appears to be species specific. In conclusion, it may be premature to conduct a human risk assessment on this effect. While the hazard of lung adenomas and adenocarcinomas may or may not be a valid basis for conducting quantitative risk assessment the relevance of the effect awaits further biochemical and mechanistic research.

iii. Rat kidney. A numerically small increase in the incidence of renal tubular adenocarcinomas has been observed in male Sprague–Dawley rats exposed to 600 ppm TRI by inhalation for 104 weeks (Maltoni *et al.*, 1986). The increase, 3% (incidence: control, 0/95, 600 ppm, 3/90), was termed borderline evidence by the authors. This effect has also been observed as a small, but statistically significant increase, 6% (incidence: control, 0/48; test group, 3/49) in the Fisher 344 male rat following gavage administration of TRI at 1000 mg/kg/day for 103 weeks (U.S. NTP, 1982). TRI administered at the same dosing regimen to four different strains of male and female rats—ACI, August, Osborne–Mendel, and Marshall—did not show any species or sex selectivity and resulted in small but statistically nonsignificant increases in renal cell adenocarcinomas (U.S. NTP, 1988). However, TRI caused tubular cell cytomegaly in 82–100% of all dosed animals and may be judged as nephrotoxic. These gavage studies in the rat are judged to be inadequate by the NTP because of insufficient survival and significant nontumor renal pathology.

The mechanism of renal tubular adenocarcinoma formation and its relevance to humans is unclear. Recent studies have provided evidence that the tumors may be the result of hepatic metabolism of TRI by glutathione-*S*-transferase (Dekant *et al.*, 1986) leading to activation of the resulting conjugate by renal β-lyase to a nephrotoxic and genotoxic entity (Green and Odum, 1985). However, since the kidney tumors appeared only in conjunction with tubular cell cytomegaly (U.S. NTP, 1988), the tumors may be the result of nephrotoxicity. The kidney tumors are therefore likely to be due to either a specific route of metabolic activation or renal cytotoxicity or a combination of both and are probably a high-dose phenomenon. The relevance of this observation to environmental risk assessment (i.e., very low levels) is therefore discounted.

iv. Other tumors. Isolated findings of tumors at other sites in rodents have been reported. For example, an increased incidence (statistically nonsignificant) of benign testicular Leydig cell tumours was observed following inhalation of TRI in male Sprague–Dawley rats (Maltoni *et al.*, 1986).

An apparent increase in immunoblastic lymphosarcomas was observed in both male and female rats exposed to TRI by inhalation (Maltoni *et al.*, 1986). However, the effect was unlikely to be related to exposure to TRI because it was not dose related

some Leydig cell tumors and immunoblastic lymphosarcomas

and the absolute incidence was small. This tumor type is known historically to have a variable incidence in groups of historical control Sprague–Dawley rats, the strain used.

Finally, forestomach tumors have been reported in mice receiving high doses of TRI by gavage stabilized with epichlorohydrin (>0.25%), a known genotoxic carcinogen causing tumors at the site of application (Henschler *et al.*, 1984). In the same study a sample of TRI stabilized with butylene oxide and a sample which was not stabilized did not cause an increase in forestomach tumors. Increases in the incidence of forestomach tumors in mice receiving TRI by inhalation, a study without stabilizers (Maltoni *et al.*, 1986), did not reach statistical significance.

None of these other tumors reported in rodents exposed to TRI can be considered to be of substantial significance to human health.

Summary. TRI-induced mouse liver tumors are the result of metabolism to TCA and peroxisome proliferation and therefore mechanistically are of no relevance to humans. The mouse lung tumors, at the present time, are of uncertain relevance to humans and await further biochemical and mechanistic research. Rat kidney tumors, while representing a hazard at high (nephrotoxic) doses, do not represent a risk at environmental levels of exposure. No relevant or suitable tumor sites are available to conduct a sensible human risk assessment on TRI with cancer as the endpoint. A further endpoint is therefore required for this analysis. Other authors, however, have proceeded to conduct risk assessments on TRI using mouse hepatocellular carcinomas as the endpoint (see the Appendix). Their conclusions are summarised later and compared with our own assessment using a noncancer endpoint.

II. Human Data

1. Neurotoxic Effects

Groups of three volunteers were exposed to 0, 27, 81, and 201 ppm TRI for 4 hr. No symptoms of significant CNS depression were reported in those exposed to 27 ppm TRI. Headaches occurred in individuals exposed to 81 and 201 ppm TRI (Nomiyama and Nomiyama, 1977).

Exposure to 110 ppm TRI for two 4-hr periods, separated by a 1.5-hr period without exposure, resulted in decreased performance in perception, memory, reaction time, and dexterity tests (Salvini *et al.*, 1971). Several other investigations using a similar range of neurological tests have failed to show any adverse effects on performance in individuals exposed to TRI at 100–300 ppm for up to 2 hr. In none of these studies were significant symptoms of CNS toxicity noted at 300 ppm or below (Fielder *et al.*, 1982).

The available data, therefore, suggest that the threshold for CNS effects in humans is in the range 81–110 ppm TRI, although the effects observed at these exposure levels reflected only mild symptoms of CNS depression.

2. Cancer Epidemiology

i. Cohort studies. Axelson *et al.* (1978) reported the results of a cohort consisting of 518 men that was based on a register of individuals occupationally exposed to TRI

as demonstrated by urinary determinations of TCA. This study was updated in 1984 (Axelson *et al.*, 1984; Axelson, 1986) to encompass a total of 1424 men, with more than 90% of the cohort having low-level exposure to TRI (<100 mg TCA/liter urine). Analyses have shown a deficit in total cancer mortality but a significant excess in the incidence of urinogenital tract cancers (11 cases observed versus 4.85 expected). For hematolymphatic malignancies, 5 cases were observed versus 1.20 expected. The author, however, does not think that these excesses are compound related (personal communication).

A study of Tola *et al.* (1980), also based on a cohort of individuals in which TCA levels in the urine were known, consisted of 1148 males and 969 females. Ninety-one percent of this cohort had low exposures (<100 mg TCA/liter urine) and no excess deaths from cancer or any other cause was observed.

Shindall and Ulrich (1985) described a cohort of 2646 men who had worked at least 3 months in a TRI-producing plant between 1957 and 1983. This cohort also included some office workers and people not directly involved with TRI production. The study also showed a lower-than-expected rate for cancer mortality and mortality from other causes.

ii. Case–control studies. In a study of 95 individuals with primary liver cancer living in the vicinity of a TRI production plant, no association with TRI exposure was found (Paddle, 1983). Novotna *et al.* (1979) studied 63 men with liver cancer and found that none had a history of occupational exposure to TRI.

Summary. Although some of the epidemiological studies of occupational exposure to TRI are open to criticism, as a whole, they lead to the conclusion that there is no association between increased cancer mortality rates and exposure to TRI. No positive epidemiologic findings of cancer in humans following exposure to TRI have been reported, although it has been manufactured and used over several decades.

3. *Hepatotoxicity*

The hepatotoxic effects of TRI in humans have been well documented following chronic, high exposures (Fielder *et al.*, 1982). A study of Japanese workers using TRI for degreasing in a communication machine factory has been reported (Takamatsu, 1962). The rationale for choosing this latter study as the database for a human health risk assessment is that there was relatively precise concurrent exposure data (groups of high, medium, and low exposure) and the health assessment showed a dose-related hepatotoxic effect. The degree of hepatotoxicity was assessed by clinical hematology; blood serum albumin levels were found to decrease and blood serum globulin levels were found to increase with severity of exposure. Both these trends in serum level changes are indicative of liver damage. (There was no control group in this study but clinical hematology values were compared to national averages.) The high-exposure group (150–250 ppm) showed marked blood protein changes, the medium-exposure (50–100 ppm) group showed mild changes, and the low-exposure group (<50 ppm) was within normal population values for blood protein changes and showed no significant clinical symptoms.

All 50 employees working in the degreasing area and the adjacent rooms were included. Most had been employed for 2 years at the time of the initial survey of the plant. Levels in the degreasing room ranged from 100 to 600 ppm and the concentra-

tions in the adjacent rooms, 50 to 100 ppm. A second study was carried out at the same factory 10 months later. The men were divided into three groups on the basis of their TRI exposure. There were 8 workers from the degreasing room, average exposure 150–250 ppm, 14 workers from the adjacent room, average exposure 50–100 ppm, and 16 workers from another assembly room, exposure below 50 ppm. The average urinary TCA levels at the end of the work week were 311 ± 119, 141 ± 53, and 50 ± 24 mg/liter, respectively. The urinary TCA level in the low-exposure group (50 ppm, 50 ± 24 mg/liter urine) corresponds to exposure to less than 50 ppm but greater than 20 ppm TRI (Monster, 1984).

III. Selection of the Biological Basis for Risk Assessment

While TRI has been shown to produce tumors at various sites in animal studies, primarily the liver, the lung, and the kidney, the fact that there is no evidence that TRI causes cancer in humans suggests that this effect is not a valid basis on which to carry out a human health assessment. This conclusion is supported by the fact that TRI itself is not mutagenic or is marginally mutagenic, and that its animal carcinogenicity is due to nongenotoxic mechanisms that are likely to be of minimal relevance to human exposure (Elcombe, 1985).

Consequently, it is concluded that the most appropriate effect upon which to conduct a human health risk assessment is hepatotoxicity, an effect that is well described in animal studies and in humans that have been occupationally exposed to TRI at well-defined atmospheric concentrations.

IV. Environmental Occurrence of Trichloroethylene

Environmental exposure of the general population to TRI occurs as a result of its presence in air, drinking water, and food. Atmospheric levels are highest in areas of concentrated industry and population, and decrease with movement to rural and remote areas. The general population can also be exposed to TRI by contact with and/or consumption of contaminated water and by the consumption of contaminated foodstuffs.

In the present study, exposure levels are used that cover a large proportion of the population (>95%), but do not take into account extreme cases.

i. Air. In studies conducted between 1980 and 1984 in several U.S. cities, ambient air concentrations of TRI of 0.04–0.71 ppb were measured (Ligocki *et al.*, 1985; Sullivan *et al.*, 1985; Singh *et al.*, 1982). Air monitoring in Germany, during 1980 gave an average of 0.5 ppb (range 0.02–1.0 ppb) (Hajimiragha *et al.*, 1986).

Locally high levels of TRI have been detected at landfill sites. For example, in New Jersey average values of 0.08–2.43 ppb with a peak of 12.3 ppb were measured (Harkov *et al.*, 1985). Also, emissions from industrial activities involving either production or use can result in high local atmospheric concentrations. In 1975, in a village close to a production plant in England, 12 to 64 ppb TRI was measured (Atri, 1985; Herbert *et al.*, 1986). An overall estimate of the exposure of the general population was presented in the Dutch Criteria Document on TRI (Besemer *et al.*, 1984). A theoretical calculation shows that only 0.1% of the population is exposed to 2 ppb and higher levels.

Thus, the general population in cities is mostly exposed to atmospheric levels below 2 ppb (10 $\mu g/m^3$). In exceptional cases (close to industrial activity), levels of 20 ppb may occur.

ii. Drinking water. TRI has been detected in drinking water originating either from groundwater or surface water supplies. In the United States, a recent EPA survey revealed that TRI was present in about 10% of the samples analyzed from groundwater supplies, a median level of positive samples being 1 ppb TRI; a single maximal level of 130 ppb was found (Westerick, 1984). In an earlier study of drinking water from 158 U.S. cities, those with surface water supplies had median concentrations ranging from 0 to 0.25 ppb, while those with groundwater supplies had an average concentration of 0.31 ppb (Coniglio *et al.*, 1980). In Germany, TRI concentrations in drinking water of about 0.2 ppb (Dusseldorf, 1980–1984) are quoted. It should, however, be pointed out that while, in general, groundwater wells showed concentrations less than 1 ppb TRI, some wells that were closed down showed levels up to 20 ppb (Hajimiragha *et al.*, 1986). Earlier data on drinking water contaminants in 50 German cities in the 1970s revealed levels of 0.1–82 ppb, with an average of 0.6 ppb (Atri, 1985).

From the data available, it is assumed that exposure of the general population to TRI through drinking water is mostly well below 2 ppb, but may be as high as 20 ppb in exceptional cases.

iii. Foodstuffs. Because TRI is present in the environment, contamination of foodstuffs occurs. Although the levels are generally low (comparable to those in drinking water), higher levels are found in foodstuffs when TRI has been used in processing (mainly as extraction fluid). Some examples are (Bauer, 1981) decaffinated coffee, 29.5 (10–92) ppb; sausage, 23.4 (2.5–192) ppb; and spices, 100 ppb. Furthermore, TRI is used in the preparation of certain types of meat and fruit juices. Fish and other seafood can contain from 10 to 30 ppb TRI (Atri, 1985). Because food-basket analyses on TRI are not available, an estimate of the exposure to TRI through foodstuffs must be made. Therefore, an average concentration of 2 ppb in foodstuffs is assumed.

V. *Risk Assessment*

1. *Estimate of No-Effect Level of Hepatotoxicity in Humans*

The following assumptions were made to calculate the total daily cumulative exposure in the Takamatsu (1962) study: (a) 1 ppm TRI is equivalent to 5.4 mg/m^3, and (b) 10 m^3 of air is breathed per 8-hr shift. Therefore, for a designated group from the study,

$$\text{total daily cumulative exposure} = \text{exposure (ppm)} \times 10\ m^3 \times 5.4\ mg/m^3$$
$$= \text{exposure (ppm)} \times 0.054\ g.$$

For the high-exposure group ($n = 8$)

$$\text{total daily cumulative exposure} = 150\text{–}250\ \text{ppm} \times 0.054\ g$$
$$= 8.1\text{–}13.5\ g.$$

For the medium-exposure group ($n = 14$)

$$\text{total daily cumulative exposure} = 50\text{–}100 \text{ ppm} \times 0.054 \text{ g}$$
$$= 2.7\text{–}5.4 \text{ g}.$$

For the low-exposure group ($n = 16$)

$$\text{total daily cumulative exposure} = <50 \text{ ppm} \times 0.054 \text{ g}$$
$$= <2.7 \text{ g}.$$

It is concluded from this study, that the no-observable-effect level in humans for TRI-induced hepatotoxicity is <2.7 g.

2. *Estimate of Uptake from Environmental Exposure*

i. Air. In general, urban populations are mostly exposed to atmospheric levels below 2 ppb (10 $\mu g/m^3$). Assuming that the average daily intake of air is 20 m^3,

$$\text{daily average cumulative exposure} = (2 \text{ ppb} \times 5.4 \text{ mg/m}^3 \times 20 \text{ m}^3/\text{day})$$
$$= 220 \ \mu g/\text{day}.$$

ii. Drinking water. From the data available, it is assumed that the exposure of the general population to TRI through drinking water is mostly well below 2 ppb. Assuming that the average daily intake of drinking water for an adult is 2 liters/day,

$$\text{daily average cumulative exposure} = (2 \ \mu g \times 2 \text{ liters/day})$$
$$= 4 \ \mu g/\text{day}.$$

iii. Foodstuffs. Assuming that the average daily food consumption is 1.5 kg,

$$\text{daily average cumulative exposure} = (2 \text{ ppb} \times 1.5 \text{ kg})$$
$$= 3 \ \mu g.$$

iv. Total exposure. From the data given it is clear that the main source of exposure of the general population to TRI is inhalation, 220 μg (by 2 ppb exposure when a 20-m^3 respiration volume per day is assumed). Contributions from foodstuffs and drinking water average 7 μg per day, thereby resulting in a total overall daily average cumulative exposure of 227 μg/day TRI.

Estimation of overall exposure to TRI can also be achieved by determining the body burden, through the measurement of TRI in blood or exhaled air, or alternatively by measuring its metabolite (trichloracetic acid) in the urine. In a study recently published, Hajimiragha *et al.* (1986) estimated the total body burden of TRI as 24.4 μg/day following individual exposure. Because this estimate is based on an internal dose a correction factor has to be applied to estimate exposure (10–50% absorption). Estimates of the average exposure of the general population to TRI have been given by Bauer (1981). He estimated a "theoretical possible total human load" of 51.2 μg. Lahl *et al.* (1981) and Von Duszeln *et al.* (1982) calculated an average daily burden from food, air, and drinking water for TRI of 0.24 μg/kg/day (including 6.0 μg from solid food and 1.2 μg from beverages).

TABLE 2

CALCULATED TOTAL DAILY CUMULATIVE EXPOSURES TO TRICHLOROETHYLENE

Experimental human exposure[a]	
High	13.5–8.1 g/day
Medium	5.4–2.7 g/day
Low	<2.7 g/day
Theoretical general population exposure[b]	
Air	220 μg/day
Drinking water	4 μg/day
Food	3 μg/day
Total body burden	227 μg/day

[a] Calculated from an occupationally exposed group (Takamatsu, 1962); see Section V.1 of text.
[b] Calculated from environmental contamination levels for the 95% general population exposure estimates; see Section V.2 of text.

3. *Safety Margins*

The safety margin approach to human health risk assessment involves direct comparison of a no-observed-effect level for a particular health effect with the calculated body burden. With TRI it was established above that hepatotoxicity is the most relevant base for a comparison. The Takumatsu (1962) study was chosen because of the human dose–response effect and the calculation of cumulative daily exposure.

The total daily average cumulative exposures for the three exposed groups in the Takamatsu study are tabulated in Table 2 and are compared with the possible total daily average cumulative exposures of the general population exposed to TRI by either contaminated air, drinking water, or foodstuffs and the estimate of total body burden from all three routes of exposure. Table 3 shows the margin-of-safety factors afforded by the human no-effect level from the Takamatsu low-exposure group (the no-observable-effect group) compared to the calculated total body burden from this document and other published papers.

IV. Comparison of Safety Factor Approach and Linearized Multistage Modeling

The concept and derivation of the EPA risk $q1^*$ values are discussed in the Appendix. The risk from atmospheric contamination (assuming the average man weighs 70 kg) is

$$\text{Risk} = \text{lifetime average daily dose} \times q1^*$$
$$= [(220\ \mu\text{g/day})/70\ \text{kg}] \times 4.6 \times 10^3/\text{mg/kg/day}$$
$$= 1.44 \times 10^{-5}\ (1.44 \text{ extra cancer deaths per } 100{,}000 \text{ population}).$$

The risk from oral exposure is

TABLE 3

SAFETY FACTORS ASSOCIATED WITH ENVIRONMENTAL EXPOSURE TO TRICHLOROETHYLENE BASED ON NO OBSERVABLE EFFECT (<2.7 g/day) FOR HUMAN HEPATOTOXICITY[a]

Contamination source/study	Contamination level (μg/day)	Magnitude of safety factor
Air (2 ppb)	220	0.12×10^5
Drinking water (2 ppb)	4	6.75×10^5
Food (2 ppb)	3	9.00×10^5
Total body burden	227	0.11×10^5
Hajimiragha *et al.* (1986)[b]	24.4	1.10×10^5
Bauer (1981)[c]	51.2	0.53×10^5
Von Duszeln *et al.* (1982),[d] Lahl *et al.* (1981)[d]	16.8[e]	1.60×10^5

[a] No-observable-effect level for human hepatotoxicity derived from Takamatsu (1962).
[b] Estimate of total body burden with internal dose correction factor incorporated.
[c] Average estimate of exposure.
[d] Average daily burden calculated as 0.24 μg/kg/day.
[e] Calculated for the average man, weight 70 kg.

$$\text{Risk} = \text{lifetime average daily dose} \times q1^*$$
$$= [(7\ \mu\text{g/day})/70\ \text{kg}] \times 1.1 \times 10^{-2}/\text{mg/kg/day}$$
$$= 1.1 \times 10^{-9}\ (1.1 \text{ extra cancer deaths per 1000 million population}).$$

Table 4 compares the risk estimates from mathematical models with those determined by the safety factor approach.

TABLE 4

COMPARISON OF SAFETY FACTOR APPROACH TO QUANTITATIVE MODELING APPROACH

Parameter	Safety factor approach	Linearized multistage model (EPA, 1984)
Species from which data are obtained for risk calculation	Human	Mouse
Endpoint	Human hepatotoxicity	Mouse hepatocellular carcinomas
No-observable-effect level	Not <2.7 g/day cumulative exposure (best estimate)	—
Inhalation risk estimate of 200 μg/day	Safety factor for exposure at least 0.12×10^5	Exposure causes 1.44 extra cancers per 100,000 population (1.4×10^{-5})
Oral risk estimate of 7 μg day (food and drinking water)	Safety factor for exposure at least 3.85×10^5	Exposure causes 1.1 extra cancers per 1000 million population (1.1×10^{-9})
Combined exposure risk; from inhalation and oral exposure	Safety factor for exposure at least 0.12×10^5	Exposure causes 1.44 extra cancers per 100,000 population (1.4×10^{-5})

DISCUSSION

It is estimated that members of the general population could be exposed to a total body burden of 227 μg of TRI/day, as a result of its environmental occurrence in ambient air, drinking water, and foodstuffs. The major route of exposure is via the atmosphere (220 μg/day from occurrence levels of 2 ppb). Contributions from both drinking water and foodstuffs (4 and 3 μg/day, respectively) are negligible. This estimated total daily body burden dose is at least 10,000 times less than that associated with an adverse health effect in humans. The resulting safety margin is extremely large. Furthermore, even for the small numbers of people living close to industrial activities, where exposure to TRI may be as high as 20 ppb, the margin of safety is still a factor of 1000.

There have been several reports of health risk assessments for TRI using cancer as the endpoint. Bogen (1988) recently applied a physiologically based pharmacokinetic model to TRI to more accurately reflect the interspecies variation in pharmacokinetics and metabolism. He estimated that exposure to 1 $\mu g/m^3$ TRI in the atmosphere and 1 μg/liter TRI in the drinking water (calculated as a lifetime weighted average) would result in an increased lifetime cancer risk of 3.9×10^{-8} to 1.1×10^{-5}. U.S. EPA (1984) also calculated that a lifetime weighted average exposure to TRI of 1 $\mu g/m^3$ would result in an increased lifetime cancer risk of 1.3×10^{-6}.

An increased lifetime cancer risk of 1×10^{-6} has been estimated as a result of exposure to 5 ppb TRI in drinking water (Fan, 1988). The author concluded that such exposure did not reflect a significant human health risk. This conclusion was supported in a further study of exposure to TRI in drinking water (Bogen *et al.*, 1988).

The use of cancer as an endpoint for quantitative health risk assessment is confounded by the fact that although tumors have been observed in animal studies their relevance to humans is uncertain and many of the studies were judged inadequate on the grounds of quality. However, those risk assessments that have been conducted on the basis of the cancer endpoint all conclude that the environmental occurrence of TRI does not represent a significant risk.

CONCLUSIONS

In conclusion, the estimates of environmental levels of TRI in either the atmosphere, drinking water, or foodstuffs present no appreciable risks to human health. A substantial margin of safety is present when comparing these levels to the human no-observable-effect level for hepatotoxicity, the most sensitive endpoint. Therefore, assuming that there is not a cancer risk, adventitious exposure to TRI in the environment is of no potential or practical significance to human health.

APPENDIX

EPA Approach to Risk Assessment

Since TRI has been shown to be carcinogenic by both inhalation and oral exposure in animals, EPA considered it inappropriate to conduct a risk assessment on the basis of an acceptable daily intake (subchronic or chronic). Instead they calculated carcino-

genic potency ($q1^*$) using the linearized multistage model of Crump, adopted by the EPA and modified in 1980. The model yields a "$q1^*$" term which is, or is assumed to be, a proportionality constant at low doses:

$$\text{dose} \times q1 = \text{risk}.$$

The $q1^*$ value is the upper 95% confidence limit on $q1$ based on unit-dose intake per kilogram per day. The risk assessments summarized in this paper are from U.S. EPA (1984).

Oral Exposure

The U.S. EPA (1984) risk assessment was based on male and female B6C3FI mice hepatocellular carcinomas induced by gavage in U.S. NCI (1976) and U.S. NTP (1982) bioassays. The geometric mean $q1^*$ for animals was determined to be 1×10^{-3} (per mg metabolized dose/kg/day). The human $q1^*$ value was determined using a surface area approximation (to extrapolate between species and converted from metabolized dose to exposure dosage) as 1.1×10^{-2} (per mg/kg/day). This means that there is an increased lifetime cancer risk to an individual who is continuously exposed orally to 1 mg/kg/day TRI from birth until death (assuming a 70-year lifespan) of 1.1×10^{-2}.

Inhalation Exposure

The same $q1^*$ values derived from mouse hepatocellular carcinoma incidence were used and modified by appropriate human pharmacokinetic data to estimate a human $q1^*$ value for inhalation exposure. The result was a calculated unit risk for TRI in air of 1.3×10^{-3}/mg/m^3.

Assuming 24-hr air intake of 20 m^3 and a body weight of 70 kg for humans, the unit risk could be converted to 4.6×10^{-3} (per mg/kg/day). This would result in an increased lifetime cancer risk from continuous inhalation exposure to 1 μg/m^3 TRI (approximately 2 ppm) of 4.6×10^{-3} (assuming 70-year lifespan).

The U.S. EPA has not yet published an evaluation of the data of Fukuda *et al.* (1983) in the context of developing a unit risk for inhalation exposure to TRI.

To perform a quantitative risk assessment on TRI, the following assumptions are made: (i) the animal tumors are likely to have direct relevance to humans; (ii) TRI is a potential human carcinogen; and (iii) since the models are linearized at low doses, that there is no practical threshold level (i.e., no no-observable-effect level). Previous arguments show that none of these assumptions are valid for TRI; see the text.

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