TO: Chloroform file (CAS # 67-66-3)

FROM: Gary Butterfield

SUBJECT: Review of chloroform slope factor

DATE: March 13, 2006

A review was conducted of the current 1991 AQD chloroform cancer potency value, to determine why that value is different than the current IRIS value, and is there new data that suggests the value be updated. In Feb 2006 it was observed that IRIS has started the process to update the inhalation slope factor. However, that update probably won't be finalized for at least another year. EPA updated the IRIS oral RFD and removed the oral slope factor for chloroform in 2002, saying that the RfD was protective for cancer concerns.

There is a one order of magnitude difference between the 1991 AQD inhalation slope factor (2.4e-6 $(ug/m^3)^{-1}$) and the inhalation slope factor in IRIS (2.3e-5 $(ug/m^3)^{-1}$). The AQD cancer inhalation slope factor for chloroform is based on geometric mean of two oral exposure studies. These studies include the male Osborne-Mendel rat kidney tumors from NCI 1976 (as calculated by CalEPA 0.026 $(mg/kg)^{-1}$) and the Jorgenson et al 1985 Osborne-Mendel male rat kidney tumors (0.0061 $(mg/kg)^{-1}$). The AQD slope factor was converted from 0.013 $(mg/kg)^{-1}$ to an inhalation value by adjusting by a 65% adsorption rate from air, and the normal 70 kg person inhaling $20m^3$. The IRIS slope factor is based on the geometric mean of the male B6C3F1 mice liver tumors (0.033 $(mg/kg)^{-1}$) and female B6C3F1 mice liver tumors (0.2 $(mg/kg)^{-1}$) from NCI 1976. The IRIS slope factor of 0.081 $(mg/kg)^{-1}$ was converted to inhalation by using the normal 70 kg person inhaling $20m^3$. The NCI study was a gavage study with chloroform administered in corn oil. The Jorgenson et al study was chloroform administered in drinking water. The mice liver tumor increases could possibly be attributed to the corn oil vehicle exposure, rather than the chloroform. Therefore, the geometric mean of rat kidney tumor increases was used by AQD in calculation of the inhalation slope factor of (2.4e-6 $(ug/m^3)^{-1}$).

There is a 2 year inhalation study with chloroform in F344 rats and BDF1 mice reported by Nagano et al (1998). The male mice had increased incidence of renal cell carcinomas (0/50, 1/50, 4/50, 11/48) at exposure concentrations of 0, 5, 30 and 90 ppm (0, 24, 146, and 439 mg/m^3) for 6/24 x 5/7 for 104 weeks. This Nagano et al report is very brief and does not give a great deal of details. Details that are not reported include: time to tumor; and, which specific animals had tumors – not able to combine renal cell carcinoma and adenoma incidence. The lack of details limits the use of this study for the usual analysis, however it can be used to determine an approximate potency factor for comparison to the existing AQD factor which is based on oral data. The time adjusted exposure (6/24 x 5/7) doses are 0, 4.3, 26, and 78 mg/m^3. Chloroform can be considered to be a category 3 gas with extra-respiratory effects (renal carcinomas). The air/blood partition coefficients for chloroform in mice (21.3) and humans (7.43) were reported by Corley et al (1990). In the use of dose adjustment factor (DAF) to convert mouse exposure to human exposure, when the animal air/blood coefficient is greater than the human coefficient, as it is in this case, the default ratio of one for animal to human is used. Therefore the mouse exposure dose is equivalent to the human

exposure, in other words there is no difference between the mouse q_1* and the human q_1*. The Global 82 potency (q_1*) for male mice renal cell carcinomas was determined to be 4.95e-3 $(mg/m^3)^{-1}$ which converts to 4.95e-6 $(ug/m^3)^{-1}$.

There is surprising little difference between the slope factors of 1991 AQD 2.4e-6 $(ug/m^3)^{-1}$ and more recent Nagano data 4.95e-6 $(ug/m^3)^{-1}$. These slope factors would lead to IRSL values of 0.4 and 0.2 ug/m^3 respectively. Due to the little difference between these IRSL values, the lack of details available from the study by Nagano et al, and the fact that EPA has the old IRIS inhalation slope factor under review with an expected completion date of late in 2006 or early 2007, it was decided to not change the current AQD screening levels for chloroform until EPA new IRIS values come out.

References:

Corley et al. 1990. Development of a physiologically based pharmacokinetic model for chloroform. Toxicol Appl Pharmacol 103:512-527

EPA IRIS. 2006. see the chloroform entry at the web page www.epa.gov/iris

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Michigan Department of Natural Resources

Response to the October 1990 Document on Chloroform Toxicity
Submitted by Champion International Corporation
March 27, 1991

Roy F. Weston, Inc. on behalf of Champion, established a Scientific Review Panel to review the risk assessment of chloroform. In the fall of 1990 Weston presented the conclusions of that group to the Michigan Department of Natural Resources (MDNR). In the presentation several modifications to the MDNR's previous risk assessment were proposed. Major proposed modifications included use of the animal bioassay reported by Jorgenson et al (1985) instead of the National Cancer Institute (1976) upon which to base the potency, use of body weight rather than surface area when conducting interspecies extrapolations, assuming chloroform caused cancer via an epigenetic mechanism, and finally, calculating the potency from the maximum likelihood estimate (MLE) rather than the 95% upper confidence limit.

Upon review of each of these items, the MDNR has determined that a mean potency value from the Jorgenson and National Cancer Institute (NCI) bioassays is appropriate, surface area is the more appropriate method of interspecies extrapolation, there is a sufficient amount of conflicting evidence to make a conclusion on the topic of genotoxic versus epigenetic mechanism of cancer impossible at this time, and the use of the 95% confidence level is most appropriate in calculating the potency value for chloroform. Therefore, the recommended cancer potency value for chloroform is 2.4 E-6 (ug/m3)-1. Based on the this potency, the air concentration of chloroform associated with an estimated increased cancer risk of one in a million (1 E-6) is 0.4 ug/m3. On the following pages are detailed discussions on these topics which provide the basis for these conclusions.

1. Most appropriate study upon which to base risk assessment for chloroform air concentrations.

a. Jorgenson et al (1985) v. NCI (1976):

The U.S. Environmental Protection Agency's (EPA) Office of Drinking Water (ODW) has used the Jorgenson drinking water study upon which to base the oral cancer risk potency, while the EPA's Office of Research and Development (ORD), which acts independently of ODW, has used the NCI study upon which to base the inhalation cancer risk value. This has resulted in significant controversy as to which study is more appropriate for airborne contaminant risk assessment. Table 1 provides a comparison of the two studies.

Renal tumor incidence was increased in both studies. A closer examination of the reported kidney nontumor pathology from both of these studies reveals no further significant information on treatment related effects. The Jorgenson study reported nontumor pathology as being high in all groups (90 to 100 %) regardless of treatment. In the NCI study an equal frequency in all dose groups of numerous inflammatory, degenerative

and proliferative lesions of the kidney as is commonly found in aging rats was observed. Again, no remarkable difference between treatment groups was observed in this study.

b. Corn oil v. water vehicle:

Both studies found increased incidences of renal tumors in male rats, leading to the conclusion of chloroform being a carcinogen. However the issue of which tumor incidence rate to use in risk assessment is complicated by the fact that the NCI bioassay also found an increased incidence of mouse liver tumors. These tumors were not observed in the Jorgenson study. The vehicles used in these two studies were different, corn oil in the NCI study and water in the Jorgenson study. This fact leads to the question of whether the mouse liver tumors were due to the corn oil vehicle or the chloroform administration. Some authors have faulted the use of corn oil (a fat) as a vehicle in toxicity studies due to the impact of fat on the liver. However, this argument has been criticized because the human diet is also high in fats, and the role of fats in the mechanism of liver tumor formation is unknown.

Other studies have been conducted that suggest corn oil used as a vehicle may influence the number of liver tumors observed. Moore et al (1982) administered chloroform in corn oil or in toothpaste to Swiss mice. The mice receiving the corn oil were reported to have increased kidney and liver abnormalities. However this study had very few animals, only 3 to 5 per dose group, making conclusions about the significance quite questionable. Bull et al (1986) reported chloroform in corn oil as being more hepatotoxic than chloroform in an aqueous solution. Evidence of the hepatotoxicity was presented as increased liver weight, clinical chemistry (increased SGOT and changes in triglyceride levels), and changes in histopathology (hepatocyte lipid accumulation, altered hepatocyte shape and early evidence of cirrhosis).

In a study examining the differences between blood chloroform concentrations following chloroform administered in corn oil and water, Withey et al (1983) administered an equivalent amount of chloroform via gavage in each of the vehicles. The measured blood chloroform concentrations indicated the water vehicle led to much higher blood concentrations than did the corn oil. However this study does not address the differences in blood concentrations following gavage when compared to drinking water.

c. Dosing schedule gavage v. drinking water:

Dose administration via drinking water would probably more closely approximate environmental air exposure than would a single daily gavage. The drinking water route allows many small doses per day instead of the one large dose per day from the gavage route of administration. However, mechanistic data are not available to evaluate the influence on tumor incidence due to these different routes of exposure.

Conclusion: It is most desirable to use an inhalation study when determining an inhalation potency factor. Unfortunately there are no long term inhalation studies available. The Jorgenson et al and the NCI

studies are the best long term oral studies available upon which to base the inhalation potency, because both of these studies are of large size, with multiple species, and multiple dose groups with dose scheduling covering the majority of the test animals lifespan.

There is some evidence from other studies that suggest the corn oil vehicle may have an influence on the incidence of liver tumors in mice as reported in the NCI study. Because of this concern, quantitative risk assessment may more appropriately be based on kidney tumor response.

Kidney tumors were observed in both the NCI and the Jorgenson study. Both are considered valid bioassays upon which to base the cancer potency. Although the Jorgenson's drinking water route of administration delivers multiple small doses which more closely simulates continuous inhalation rather than a single large gavage dose, the Jorgenson study administered chloroform for a slightly greater portion of the test animal's lifetime with a greater number of dose levels covering the same dosage range as the NCI study, and Jorgenson had larger groups of animals in the more critical low doses, there appears to be no valid reason to ignore the rat kidney tumors observed in the also well conducted NCI study. Since rat kidney tumors were observed in both studies, and mechanistic data are not available to evaluate the influence on tumor incidence due to the different routes of exposure, it is recommended that an average of the slope factors from the Jorgenson study rat kidney tumors and the NCI male rat kidney tumors be used in the calculation of a cancer potency factor.

2. Absorption rates oral v. inhalation:

Absorption of any vapor or gas via the pulmonary route is affected by 1) vapor concentration, 2) duration of exposure, 3) blood/air solubility coefficient, 4) total body weight and tissue volumes available to distribute the amounts of absorbed material, and 5) physical activity which affects ventilation rate and cardiac output. As can be expected, the initial retention rate is much greater than the rate at equilibrium. From the limited published data that is available, humans appear to absorb chloroform from inhaled air with between 49 and 77 percent efficiency at equilibrium, while absorption from oral administration is nearly 100%. EPA (1985) and the State of California used 100% and 98% absorption efficiency via oral routes, and estimated 65% and 67% absorption efficiency via inhalation, respectively.

Conclusion: An approximate inhalation absorption factor of 65% appears to be reasonable when converting an oral dose to inhalation dose.

3. Interspecies extrapolations based on surface area v. body weight:

Basing the interspecies extrapolation on surface area accounts for several unquantified species differences that may include such things as sensitivity of target tissues, differences in distribution, detoxification and clearance, and differences in the numbers of target cells in exposed tissues, as well as differences in DNA repair and cell proliferation rates. Utilizing the surface area extrapolation affords some protection from differences that could increase human sensitivity

relative to the animals used in the bioassays. Additionally, chloroform has been shown to be metabolized at a rate proportional to surface area. EPA (1985) in their Health Assessment Document (HAD) performed an exercise in which they plotted body weight vs. metabolized chloroform (see graph attached). The resultant graph was a straight line with a slope of 0.65. This value, 0.65, is approximately the same as the 2/3 power used to adjust species dose from body weight based on surface area.

Conclusion: Surface area is the appropriate method for interspecies extrapolations.

4. Epigenetic v. genotoxic mechanism of cancer:

In vitro systems are used to isolate and study cellular, biochemical, and molecular mechanisms. There are numerous assay systems that can be used to evaluate a chemicals potential to be genotoxic. The weight or importance of the results for making regulatory decisions must relate to how relevant the conditions in the in vitro assay are to the conditions expected in vivo. The action of chloroform is complex and appears to depend on metabolic events. The complex nature of the interaction of chloroform and its metabolites within the cell makes the design of the assay system critical to the production of relevant results. The genotoxic potential of chloroform has been investigated in many different assay systems. Most results to date have been negative, however, most were not designed to address the action of chloroform. The following points are important to consider when evaluating in vitro assay results for chloroform.

*There is a body of evidence that suggests that chloroform is metabolized to phosgene and that phosgene is the species responsible for the toxicity associated with chloroform exposure. An assay system where the target cells can not metabolize the chloroform or where there is no exogenous metabolizing system will probably show negative results.

*Phosgene is a highly unstable and reactive compound and may bind protein and lipid immediately after it is produced. If the metabolizing system is exogenous to the cell (eg. S9 fraction added to bacterial system like the Ames Assay) the metabolite may bind with protein and lipid in the S9 or media components before it has contact with the genetic material. The active specie may be scavenged and the net result may have little or no contact with the genetic material. The assay may be negative, but the assay results may not be relevant to the in vivo situation where the microsomes occur within the eukaryotic cell membrane but outside the nuclear membrane.

*If the metabolism of chloroform occurs within the cell (as in vivo) the probability of the active specie contacting the genetic material is greatly increased because the cell membrane is no longer a barrier between the metabolites and the genetic material.

*A highly volatile compound like chloroform may not remain in solution long enough to allow a significant or controlled exposure.

*Enzymes other than those associated with the P450 system could be involved in the tumorigenic process. If chloroform or a metabolite could also be converted to an active specie by components in the nucleus, this again, would greatly enhance the probability of contact with the genetic material.

A small number of assays have given positive results and suggest that chloroform has the potential to be genotoxic (see Table 2).

Conclusion: Weston did not conduct a thorough review of the literature to support their statement that chloroform acts by an epigenetic mechanism. They did not discuss or consider the above points or assays. More data is needed before any conclusions can be reached as to whether chloroform acts via an epigenetic or genotoxic mechanism (ATSDR 1989, Probst 1981).

5. Issues concerning the potency calculation.

a. Usage of the MLE as an estimator of the upper bound on risk:

Weston proposed the use of the MLE instead of upper 95% confidence level when extrapolating to lower doses in the risk assessment process, citing the lack of genotoxicity as evidence supporting the unnecessary use of ultraconservativeness obtained when using the upper 95% confidence level. As described above, due to conflicting results and uncertainities in test systems, conclusions can not be made as to whether chloroform acts via an epigenetic or genotoxic mechanism.

In addition, the MDNR supports the use of the upper 95% confidence level in the risk assessment process due to the instability of the MLE. Small variations in the tumor response can cause large changes in the MLE, while use of the upper 95% confidence limit allows model responsiveness to data while modulating such fluctuations. This approach is consistant with the guidelines and practices of the EPA and other regulatory agencies.

b. Male rat kidney tumors are not applicable to humans:

The alpha-2u-globulin peculiar to male rats has been implicated as the cause of renal tumors following exposure to some materials. In these cases a distinctive pathology is usually observed consisting of cells with hyalin droplets, cortical tubular degeneration and necrosis occurring especially in the proximal convoluted tubules. However the details of the mechanism of renal tumors from chloroform exposure are not well enough understood at this time to dismiss the observed tumors in male rat kidney as irrelevant to other species. This issue was not a contention (i.e., to dismiss renal tumors from consideration) of Weston/Champion but was briefly discussed by them.

c. PBPK models:

Several authors have proposed models that describe the absorption, distribution, excretion and metabolism of chloroform. In a pair of related articles, Corley et al (1990) and Reitz et al (1990) described a physiologically based pharmacokinetic model (PBPK model) based on a model

originally developed by Ramsey and Anderson (1984). In their model, dose surrogates were derived. A dose surrogate can be described as an alternative dose to the administered dose. It is an estimate of dosage at the target tissue, in this case liver. The dose surrogates used in this model were based on the amount of macromolecular binding and cytotoxicity. The surrogate doses were then utilized in obtaining a virtual safe dose, when assuming a threshold effect, and a risk specific dose, when assuming a non-threshold. It is not clear how either of these dose surrogates are related to the carcinogenesis of chloroform. Also, this model has been faulted for concentrating on liver effects while the bioassays also found kidney tumors.

Bogen et al (1989) and Bogen (1990), developed a PBPK model known as the Cell Kinetic Multistage model (CKM). This model attempts to account for cell proliferation leading to tumor formation instead of using the generally used somatic mutation assumptions. Bioactivation is believed to be a necessary first step in the cytotoxicity/cell proliferation process. Therefore the metabolized dose can be used instead of the administered dose. The metabolized dose is estimated from enzyme activity. The metabolized dose was compared to published metabolism estimates for validation.

Currently data are not adequate to determine the appropriate PBPK model for chloroform. Additional validation is necessary before these models can be used in the regulatory process.

d. Comparison of potency calculations:

EPA's Integrated Risk Information System (IRIS) reports a potency of 8.1E-2 (mg/kg)-1 based on mice liver tumors (average of male and female) from the NCI (1976) data. In the past MDNR used this potency to arrive at an air potency of 2.3E-5 (ug/m3)-1. However the effects of the corn oil vehicle raises some questions concerning the applicability of the observed liver tumors for human risk assessment. However, there is no apparent reason to disregard the male rat kidney tumors from the NCI study.

Results of rat kidney tumors from the NCI study:

Administered Dose (mg/kg)	Animal Lifetime Average dose(mg/kg)	Tumor Incidence California
0	0	0/19
90	45	4/38
180	90	12/27

The risk assessment conducted by the State of California utilized procedures consistent with MDNR's and resulted in a potency that may be directly adopted by MDNR for the NCI study.

Results of rat kidney tumors from the Jorgenson study:

Administered Dose (mg/kg)	Animal Lifetime Average Dose (mg/kg)	Human Equivalent Dose (mg/kg)	Tumor Incidence	
			HAD	IRIS
0	0	0	4/301	1/50
19	17.8	3.43	4/313	6/313
38	35.6	6.9	4/148	7/148
81	75.9	14.8	3/48	3/48
160	150	28.9	7/50	7/50

The differences in the tumor incidences between HAD and IRIS are based on HAD's use of the large vehicle control group and IRIS's use of the smaller but more appropriate controls matched to the high dose water consumption rate. In addition HAD considered only renal tubular cell adenomas and adenocarcinomas while IRIS considered all renal tumors. The methodology employed by IRIS is more consistent with MDNR and results in a potency that can be directly adopted. EPA-IRIS reports the human potency from the Jorgenson study to be 6.1E-3 (mg/kg/d)-1. This value can be converted to 1.1E-6 (ug/m3)-1 by use of 20 m3/d inhalation rate, a body weight of 70 kg person, and assuming inhalation absorption efficiency of 65%.

Risk assessments conducted by other agencies provide supporting evidence of these potencies. Although the other agency's potencies are not exactly the same as those adopted by MDNR, the other potencies are quite close (see the following table). EPA-HAD reported a potency for the Jorgenson study of 4.4E-3 (mg/kg/d)-1. Using the same assumptions for conversion to an air concentration as in the above paragraph, the resultant inhalation potency is 8.2E-7 (ug/m3)-1 which is approximately the same as EPA IRIS. In Weston's documentation a GLOBAL printout identifies an animal potency of 8.2E-4 (mg/kg/d)-1. Adjusting that potency to a human potency by (70/.35) (1/3) results in the same potency as reported by HAD of 4.4E-3 (mg/kg/d)-1.

In their documentation Weston also calculated the potency for human equivalent dose. In that calculation Weston used a rat body weight of 0.2 kg for rats. A body weight of 0.35 kg is more appropriate for a full sized rat and will result in a larger equivalent human dose than what was reported in their documentation. The State of California also reported conducting a risk assessment of chloroform based on Jorgenson. The animal potency derived by them, 8.1E-4 (mg/kg/d)-1 is slightly different than EPA's and Weston's due to no adjustment for study length and the use of slightly different dosages (0, 18, 38, 79, 155 mg/kg). Another difference in their calculation was the use of a greater rat body weight, 0.5 kg. The resultant human potency, 4.2E-3 (mg/kg/d)-1 is still approximately the same as those derived by EPA IRIS and EPA HAD.

Study	Source	Potency (mg/kg/d)-1	Incidence and Doses
NCI m rat	California	2.6 E-2	0/19, 4/38, 12/27 0, 45, 90 mg/kg
	HAD	2.4 E-2	0/99, 4/50, 12/50 0, 90, 180 mg/kg
Jorgenson	California	4.2 E-3	4/301,4/313,4/148 3/48,7/50 0, 18, 38, 79, 155 mg/kg
	IRIS	6.1 E-3	1/50,6/313,7/148 3/48,7/50 0, 18, 38, 81, 160 mg/kg
	HAD/Weston	4.4 E-3	4/301,4/313,4/148 3/48,7/50 0, 18, 38, 81, 160 mg/kg

In evaluation of the risk assessment based on the NCI study that was performed by HAD, it can be found that the dose levels were not adjusted for a lifetime dosage as the dosing lasted for 78 wk which is much less than study length 111 wk. Also, HAD included animals that did not survive to the appearance of the first tumor, and HAD used the colony controls instead of the matched control group for comparison.

The recommended potency value is the geometric mean of the potencies derived from the Jorgernson and NCI studies. The risk assessment performed by California obtains the more appropriate potency for the NCI study (2.6E-2 (mg/kg/d)-1). The IRIS potency value for the Jorgenson study can be used in the averaging process (6.1 E-3 (mg/kg/d)-1). The resultant geometric average is 1.3 E-2 (mg.kg/d)-1 or 2.4 E-6 (ug/m3)-1 which results in a 10-6 risk value of 0.4 ug/m3.

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TABLE 1

Comparison of NCI and Jorgenson et al. Studies

	NCI (1976)	Jorgenson et al (1985)
Animals	m & f rats Osborne-Mendel m & f mice B6C3F1	m rats Osborne-Mendel f mice B6C3F1
Vehicle	corn oil	water
Dose Schedule	gavage 5d/wk for 78 wk plus obs period 15 wk for mice 33 wk for rats	in drinking water for 104 wk

Dose Levels (mg/kg)	NCI m rat	NCI f rat	NCI m mice	NCI f mice	Jorgenson m rat	Jorgenson f mice
	0	0	0	0	0	0
	90	100	138	238	18	34
	180	200	277	477	38	65
					81	130
					160	260

	NCI (1976)	Jorgenson et al (1985)
Number of Animals	20 control & 50/gr in dosed	50 to 330 /gr larger numbers in low dose gr to detect tumors at low doses
Significantly Increased Tumors	hepatocellular carcinoma f mice 0/20, 36/45, 39/41 m mice 1/18, 18/50, 44/45 renal epithelial tumors m rat 0/19, 4/38, 12/27	renal tubular cell adenoma/adenocarinoma m rat 1/50, 6/313, 7/148, 3/48, 7/50

TABLE 2

Summary of Positive Genotoxicity Assays

Author	Assay	Test System	Results
Callen, et. al. 1980	Mitotic recombination gene conversion, gene revision	in vitro Saccharomyces cerevisiae fungi	Positive
Paul, et. al. 1981	Morphologically abnormal spermatozoa	in vivo mice	Positive
DiRenzo, et. al. 1982	Binding of radio - labelled chloroform to calf thymus DNA	in vitro rat liver microsomes	Positive
Liang, el. al. 1983	Potent mitotic arrestant	in vitro grasshopper embryo	
Morimoto, et. al. 1983	Sister chromatid exhange	in vitro cultured human lymphocytes	Positive
Mitchell, et. al. 1988	Mouse lymphoma assay	in vitro +S9	Positive (small but significant increase in mutations)
Myhr, et. al. 1988	Mouse lymphoma assay	in vitro +S9	Positive

MICHIGAN DEPARTMENT OF NATURAL RESOURCES

INTEROFFICE COMMUNICATION

December 7, 1987

TO: Permit Engineers, Air Quality Division
District Supervisors, Air Quality Division

FROM: Catherine Simon, Air Quality Division

SUBJECT: Cancer Risk Assessments for Trichloroethylene and Chloroform

The cancer risk assessments for trichloroethylene and chloroform have been revised based upon new data and re-evaluation of previous risk assessments. The recommended unit risk values for these two compounds are as follows:

Chemical	Unit Risk Value
Trichloroethylene	1.7×10^{-6}
Chloroform	2.3×10^{-5}

The unit risk value is defined as the additional lifetime cancer risk that would result in a population in which all individuals were exposed for a lifetime to 1 ug/m^3 of the chemical . The unit risk values listed above are consistent with the most recent values determined by the Carcinogen Assessment Group of the U.S. Environmental Protection Agency.

Based upon the above unit risk values, the concentration in air resulting in an increased cancer risk of one in one million (1×10^{-6}) is 0.6 ug/m^3 for trichloroethylene and 0.04 ug/m^3 for chloroform.

CAS:mh

C. Simon