Appendix A. Health Effects Subcommittee Report

Appendix A. Health Effects Subcommittee Report – Table of Contents

Approach for Review of Existing Health-Based MCLs

Sources of Information

For each chemical for which the New Jersey Drinking Water Quality Institute has previously developed a Health-based MCL, the Health Effects Subcommittee conducted a review of the scientific literature and relevant risk assessment databases to determine whether a recommendation of revision was warranted. Sources of information which were reviewed include the USEPA Integrated Risk Information System (IRIS), National Toxicity Program (NTP), National Center for Environmental Assessment (NCEA), Agency for Toxic Substances and Disease Registry (ATSDR), International Agency for Research on Cancer (IARC), the National Institutes of Health/ National Institute of Environmental Health Sciences (NIH/NIEHS) Eleventh Report on Carcinogens, California Public Health Goals, and Toxline/Medline searches of the primary scientific literature.

For chemicals for which revision of the Health-based MCL was not necessary, a short summary of the basis for the current Health-based MCL, the results of the literature review, and the basis for the recommendation for no revision is provided. For chemicals for which revision of the Health-based MCL was recommended, a longer addendum to the original Health-based MCL Support Document was developed and is found below. Each of these documents was written by one or more members of the Health Effects Subcommittee, with input from other Subcommittee members. The addendum reviews the basis for the current New Jersey Health-based MCL, USEPA risk assessments for the chemical, results of the literature review, and any additional issues related to the risk assessment approach. Finally, it provides a recommendation for revision of the Health-based MCL.

Consideration of USEPA IRIS database

The Integrated Risk Information System (IRIS) risk assessments represent the agency-wide consensus of USEPA, and have been submitted to internal (EPA) peer review, and, in many cases, external peer review. For these reasons, particular attention was given to the risk assessments on IRIS during the review. However, IRIS does not contain up-to-date assessments for many of the chemicals that were reviewed, because, in many cases, the most recent IRIS review was conducted many years ago and thus does not reflect recent toxicity data. When a chemical is currently undergoing IRIS review, the existing risk assessment may be removed from the IRIS database and therefore no information is available on IRIS.

Within USEPA, programs such as the Office of Water may conduct their own risk assessments, which may or may not be incorporated into IRIS. Therefore, the basis for the MCLGs (human health-based Maximum Contaminant Level Goals) developed by the USEPA Office of Water is not included in IRIS for some chemicals. Additionally, some of the MCLGs developed by the Office of Water predate IRIS, and have not been updated to reflect the more recent risk assessment in IRIS.

Approach for Possible Human Carcinogens (Group C) and Suggestive Carcinogens

In 2000, NJDEP adopted a new risk assessment approach for chemicals considered Possible Human Carcinogens (Group C) under the USEPA Cancer Risk Assessment Guidelines (USEPA, 1986). The category Possible Human Carcinogen (Group C) under the 1986 USEPA guidelines is analogous to Carcinogenicity Category II in the New Jersey Health-based MCL development process (NJDWQI, 1987) and Suggestive Evidence of Human Carcinogens under the current USEPA Guidelines for Cancer Risk Assessment (USEPA, 2005). The new New Jersey approach is intended to harmonize the approaches for such chemicals that are used by the USEPA Office of Water and the USEPA Superfund program.

The earlier New Jersey approach for these chemicals, used by both NJDEP and NJDWQI, preferentially used the Reference Dose for non-carcinogenic effects, with incorporation of an additional uncertainty factor of 10 to account for possible carcinogenic effects. If no Reference Dose was available, a risk assessment based on the slope factor at a 10^{-5} risk level was used. This approach was based upon the approach used for Group C chemicals by the USEPA Office of Water.

The new approach for Possible Human Carcinogens adopted by NJDEP in 2000 preferentially utilizes a carcinogenic slope factor at the 10^{-6} risk level, if such a slope factor is available from USEPA and is not judged technically unsound by the NJDEP. The 10^{-6} risk level is specified in the A-280 Amendments to the New Jersey Safe Drinking Water Act (P.L.1983, c.443). The slope factors provided by USEPA on its IRIS database are generally technically sound, since, as discussed above, they represent USEPA consensus and those developed recently have been subjected to peer review. If such a slope factor is not available, the previous approach of using the Reference Dose with an additional uncertainty factor of 10 is followed. An exception is made if the risk assessment based upon the Reference Dose (without an additional uncertainty factor of 10) is more protective than the risk assessment based on the slope factor at the 10^{-6} risk level; in this case, the Reference Dose is used as the basis for the risk assessment.

This revised approach integrates the approaches used for Possible Human Carcinogens by the USEPA Office of Water, which has preferentially used the Reference Dose with an additional uncertainty factor, and the USEPA Superfund program, which has preferentially used the slope factor at a 10^{-6} risk level. This New Jersey approach is being used consistently by the New Jersey Drinking Water Quality Institute and throughout NJDEP for the development of health-based standards, criteria, and guidance for drinking water, ground water, surface water, soil, and air.

The Guidelines for Carcinogen Risk Assessment (USEPA, 2005), which supercede the 1986 USEPA cancer risk assessment guidelines, were used by NJDWQI in the reassessment of the New Jersey Health-based MCLs. These guidelines emphasize flexibility in approach as appropriate and consideration of all relevant data in development of a risk assessment. NJDEP evaluated the new Guidelines, and also consulted with USEPA scientists with expertise in cancer risk assessment and in drinking water risk assessment as to application of the Guidelines, particularly to chemicals classified as Suggestive Carcinogens. The approach adopted by NJDEP and DWQI (described above) for chemicals classified as Possible Human

Carcinogens under the previous guidelines is not inconsistent with the current (2005) Guidelines for Cancer Risk Assessment. Therefore, this approach was applied by NJDWQI and NJDEP to chemicals evaluated under the current (2005) Guidelines as it was to those evaluated under the previous (1986) Guidelines.

Reason for Recommendation of Revision of Health-based MCL

Some possible reasons for a recommendation of revision of Health-based MCLs include:

- New toxicology/epidemiology studies published since the Drinking Water Quality Institute's last review, which would indicate a change is warranted.
- Change in accepted risk assessment methodology, such as use of a threshold approach for carcinogenesis for chemicals which have sufficient evidence for such a threshold.
- New interpretation of existing toxicity data, such as kinetics of gavage versus bolus dosing.
- Data which indicates that the Relative Source Contribution factor or Uncertainty Factor should be revised for assessments based on a Reference Dose. It should be noted that, in most cases, adequate data to develop a chemical-specific Relative Source Contribution Factor is not available and the default Relative Source Contribution factor of 20% is used.
- Application of the revised New Jersey policy on chemicals classified in Carcinogenicity Group II (NJDWQI, 1987), equivalent to USEPA Possible Human Carcinogens (Group C) under the 1986 USEPA cancer risk assessment guidelines or Suggestive Evidence of Human Carcinogenicity under the current (2005) USEPA guidelines (see above).

Significant Figures for Health-based MCLs

Health-based MCLs include two significant figures. This is consistent with the previous NJDWQI Health-based MCL recommendations developed in 1987 and 1994.

References

NJDWQI (1987). New Jersey Drinking Water Quality Institute. Maximum Contaminant Level Recommendations for Hazardous Contaminants in Drinking Water. March 26, 1987.

USEPA (1986). United States Environmental Protection Agency. The Risk Assessment Guidelines of 1986. Washington, DC. EPA/600/8-87/045. August 1987.

USEPA (2005). United States Environmental Protection Agency. Guidelines for Carcinogen Risk Assessment. Risk Assessment Forum, USEPA, Washington, DC. EPA/630.P-03/001F, March 2005.

Contaminants for Which No Change in Health-Based MCL is Recommended

Carbon Tetrachloride:

Both New Jersey (NJDWQI, 1987) and USEPA IRIS classify carbon tetrachloride as a probable human carcinogen. The slope factor in USEPA IRIS (last revised in 1991) is 0.13 $(mg/kg/day)^{-1}$. It is based on the geometric mean of four studies. These were bioassays in male and female Syrian hamsters (Della Porta et al., 1961); in male and female mice (Edwards et al., 1942); in male and female B6C3F1 mice (NCI, 1976a,b; 1977), and in male and female Osborne-Mendel rats (NCI, 1976a,b; 1977).

The New Jersey slope factor is 0.091 $(mg/kg/day)^{-1}$. It is based on the study judged most appropriate, the combined data from male and female mice in the NCI (1976b) study, with time-to-death adjustment (NJDWQI, 1987). As discussed in NJDWQI (1987), the two older studies used by USEPA IRIS along with the NCI rat data were judged not suitable for quantitative risk assessment because they did not include concurrent controls.

A further literature search did not reveal any significant studies published since the New Jersey assessment was completed which indicate that the slope factor should be reevaluated. For these reasons, no change in the New Jersey slope factor is recommended.

References

Della Porta, G., B. Terracini and P. Shubik. 1961. Induction with carbon tetrachloride of liver cell carcinomas in hamsters. J. Natl. Cancer Inst. 26(4): 855-863.

Edwards, J.E., W.E. Heston and H.A. Dalton. 1942. Induction of the carbon tetrachloride hepatoma in strain L. mice. J. Natl. Cancer Inst. 3: 297-301.

NCI (National Cancer Institute). 1976a. Report on the Carcinogenesis Bioassay of Chloroform. National Cancer Institute, Bethesda, MD. March.

NCI (National Cancer Institute). 1976b. Carcinogenesis Bioassay of Trichloroethylene. National Cancer Institute Carcinogenesis Technical Report Series, No. 2. NCI-CG-TR-2. February.

NCI (National Cancer Institute). 1977. Bioassay of 1,1,1-Trichlorethane for Possible Carcinogenicity. National Cancer Institute Carcinogenesis Technical Report Series, No. 3. NCI-CG-TR-3. January 1977.

NJDWQI (New Jersey Drinking Water Quality Institute). 1987. Maximum Contaminant Level Recommendations for Hazardous Contaminants in Drinking Water. Appendix B: Health-based Maximum Contaminant Level Support Documents. March 26, 1987.

Chlordane

Both USEPA IRIS and New Jersey (NJDWQI, 1987) classify chlordane as a possible human carcinogen. The USEPA IRIS slope factor, 0.35 $(mg/kg/day)^{-1}$ (last updated in 1998), is based on the geometric mean of five data sets on hepatic carcinomas in three different strains of mice: B6C3F1 male and female mice (NCI, 1977); CD-1 male and female mice (IRDC, 1973), and ICR male mice (Khasawinah and Grusch. 1989). As discussed in the USEPA Toxicological Review of Chlordane (1997), only one of these studies (Khasawinah and Grutsch, 1989), which used male ICR mice, reported benign hepatocellular adenomas as well as carcinomas. In the Toxicological Review, a slope factor based on combined adenomas and carcinomas from this study of 2.34 $(mg/kg/day)^{-1}$ is derived.

The New Jersey slope factor, 2.7 $(mg/kg/day)^{-1}$ is based on hepatic adenomas in the male ICR mice (RIAST, 1983), as the data on carcinomas was not available at the time the slope factor was developed. It is very close to the slope factor of 2.34 $(mg/kg/day)^{-1}$ developed by USEPA for the combined benign and malignant tumors.

The USEPA Guidelines for Carcinogen Risk Assessment (2005) recommend that benign tumors be included in risk assessment analysis if they have the potential to progress to malignancy, as is believed to be the case for hepatic tumors. USEPA usually combines hepatic adenomas with carcinomas for slope factor development, and considering adenomas is consistent with USEPA policy (Dr. Robert McGaughy, USEPA chemical manager for chlordane, personal communication).

Because the difference in the USEPA slope factor for combined adenomas and carcinomas and the New Jersey slope factor for adenomas is very slight, the Health-based MCLs based on both slope factors is the same to two significant figures, 0.013 ug/L.

A further literature search did not reveal any significant studies published since the New Jersey assessment was completed which indicate that the slope factor should be reevaluated.

For these reasons, no change in the New Jersey slope factor is recommended.

References

IRDC (International Research and Development Corporation). 1973. Eighteen-month oral carcinogenic study of chlordane in mice. Unpublished report to Velsicol Chemical Corporation. MRID No. 00067568. Available from the U. S. Environmental Protection Agency.

Khasawinah, A.M. and J. Grutsch. 1989b. Chlordane: thirty-month tumorigenicity and chronic toxicity test in rats. Regul. Toxicol. Pharmacol. 10(2): 95-109.

NCI (National Cancer Institute). 1977. Bioassay of chlordane for possible carcinogenicity. Technical Report Series No. 8. U.S. Department of Health, Education and Welfare; National Institutes of Health. PB 271 977.

NJDWQI (New Jersey Drinking Water Quality Institute). 1987. Maximum Contaminant Level Recommendations for Hazardous Contaminants in Drinking Water. Appendix B: Health-based Maximum Contaminant Level Support Documents. March 26, 1987.

RIAST (1983). Research Institute for Animals Science in Biochemistry and Toxicology. Twenty-four month chronic toxicity and turmorogenicity test in mice by chlordane technical. Prepared for Velsicol Chemical Company.

US Environmental Protection Agency (2005). Guidelines for Carcinogen Risk Assessment. Risk Assessment Forum, USEPA, Washington, DC. EPA/630/P-03/001F, March 2005.

Chlorobenzene

Both USEPA IRIS and New Jersey (NJDWQI, 1994) classify chlorobenzene as a non-carcinogen. The USEPA IRIS Reference Dose (last revised, 1993) is 0.02 mg/kg/day, and the New Jersey Reference Dose (NJDWQI, 1987) is 0.0065 mg/kg/day. Both are based on the same No Observed Adverse Effect Level (NOAEL) from a subchronic dog study (Monsanto, 1967, 1977). The USEPA Reference Dose includes a total uncertainty factor of 1000, while the A-280 Reference Dose uses a total uncertainty factor of 3000, which includes an additional uncertainty factor of 3 for small sample size, since only four dogs were used in each dose group in the study. Such an additional uncertainty factor, which may also be called a "modifying factor", may be applied based on professional judgement to account for uncertainties in the study or data base which are not addressed by the other uncertainty factors (USEPA, 1993).

A further literature search did not reveal any significant studies published since the New Jersey assessment was completed which indicate that the Reference Dose should be reevaluated.

For these reasons, no change in the New Jersey Reference Dose is recommended.

References

Monsanto Company (1967). 13-week oral administration - dogs. Monochlorobenzene. Final report. Prepared by Hazelton Laboratories, Project No. 241-105, February 24.

Monsanto Company (1977). 13-Week oral administration – dogs, monochlorobenzene. USEPA. OPTS. Washington, DC. TSCA Sec. 8(e) Submission 8 DHQ-07798-0212 (3).

NJDWQI (New Jersey Drinking Water Quality Institute). 1987. Maximum Contaminant Level Recommendations for Hazardous Contaminants in Drinking Water. Appendix B: Health-based Maximum Contaminant Level Support Documents. March 26, 1987.

NJDWQI (New Jersey Drinking Water Quality Institute). 1994. Maximum Contaminant Level Recommendations for Hazardous Contaminants in Drinking Water. Appendix A: Health-based Maximum Contaminant Level Support Documents. September 26, 1994.

USEPA (1993). Reference Dose (RfD): Description and use in assessments. March 15, 1993. http://www.epa.gov/iris/rfd./htm.

1,2-Dichlorobenzene

Both USEPA IRIS and New Jersey (NJDWQI. 1987) classify 1,2-dichlorobenzene as a non-carcinogen. The New Jersey Reference Dose of 0.086 mg/kg/day (NJDWQI, 1994) is based on the same study as the USEPA IRIS Reference Dose, 0.09 mg/kg/day. The difference in two values is due to rounding to two significant figures by New Jersey versus one significant figure by USEPA.

A further literature search did not reveal any significant studies published since the New Jersey assessment was completed which indicate that the Reference Dose should be reevaluated.

For these reasons, no change in the New Jersey Reference Dose is recommended.

References

NJDWQI (New Jersey Drinking Water Quality Institute). 1987. Maximum Contaminant Level Recommendations for Hazardous Contaminants in Drinking Water. Appendix B: Health-based Maximum Contaminant Level Support Documents. March 26, 1987.

1,2-Dichloroethane

Both USEPA IRIS (last revised in 1991) and New Jersey (NJDWQI, 1987) classify 1,2-dichloroethane as a probable human carcinogen. The IRIS slope factor is 0.091 $(mg/kg/day)^{-1}$ and the New Jersey slope factor is 0.12 $(mg/kg/day)^{-1}$. Both slope factors are based on hemangiosarcomas in male Osborne-Mendel rats in the same study (NCI, 1978). The quantitative analysis of the data by USEPA and New Jersey differed slightly, resulting in the slight difference in slope factors.

A further literature search did not reveal any significant studies published since the New Jersey assessment was completed which indicate that the slope factor should be reevaluated.

For these reasons, no change in the New Jersey slope factor is recommended.

References

NCI (National Cancer Institute). 1978. Bioassay of 1,2-Dichloroethane for Possible Carcinogenicity. NCI Carcinogenesis Technical Report Series No. 55. DHEW Publ. No. (NIH) 78-1361, Washington DC.

NJDWQI (New Jersey Drinking Water Quality Institute). 1994. Maximum Contaminant Level Recommendations for Hazardous Contaminants in Drinking Water. Appendix A: Health-based Maximum Contaminant Level Support Documents. September 26, 1994.

cis-1,2-Dichloroethylene

Both USEPA IRIS and New Jersey (NJDWQI, 1994) classify cis-1,2-dichloroethylene as a non-carcinogen. IRIS has not provided toxicity factors for cis-1,2-dichloroethylene, but does provide a carcinogenicity classification of Group D, Not Classifiable as to Human Carcinogenicity. However, the USEPA Office of Water has developed a Reference Dose for this chemical, which is used as the health basis for its MCL. The New Jersey Reference Dose, 0.01 mg/kg/day, is identical to and has the same basis as the Reference Dose used by USEPA to set its MCL, as explained in NJDWQI (1994).

A further literature search did not reveal any significant studies published since the New Jersey assessment was completed which indicate that the Reference Dose should be reevaluated.

For these reasons, no change in the New Jersey Reference Dose is recommended.

References

NJDWQI (New Jersey Drinking Water Quality Institute). 1994. Maximum Contaminant Level Recommendations for Hazardous Contaminants in Drinking Water. Appendix A: Health-based Maximum Contaminant Level Support Documents. September 26, 1994.

trans –1,2-Dichloroethylene

Both USEPA IRIS and New Jersey (NJDWQI, 1994) classify trans-1,2-dichloroethylene as a non-carcinogen. The New Jersey Reference Dose, 0.017 mg/kg/day (NJDWQI, 1994), has the same basis, including study, choice of LOAEL, and uncertainty factors, as the USEPA IRIS Reference Dose, 0.02 mg/kg/day. The difference in the two values is due to rounding to two significant figures by New Jersey versus one significant figure by USEPA.

A further literature search did not reveal any significant studies published since the New Jersey assessment was completed which indicate that the Reference Dose should be reevaluated.

For these reasons, no change in the New Jersey Reference Dose is recommended.

References

NJDWQI (New Jersey Drinking Water Quality Institute). 1994. Maximum Contaminant Level Recommendations for Hazardous Contaminants in Drinking Water. Appendix A: Health-based Maximum Contaminant Level Support Documents. September 26, 1994.

Formaldehyde (New Jersey MCL has not currently been promulgated)

The New Jersey Reference Dose, 0.015 mg/kg/day (NJDWQI, 1994) and the USEPA IRIS Reference Dose, 0.2 mg/kg/day (last revised in 1990) are both based on a No Observed Adverse Effect Level in a chronic oral rat study (Til et al., 1989). The IRIS evaluation and Reference Dose were considered in the last A-280 review, and the A-280 and IRIS Reference Doses have the same toxicological basis. The difference between the A-280 and IRIS assessments is that A-280 classified formaldehyde as a possible human carcinogen (Group C) from oral exposure and incorporates an additional uncertainty factor of 10 to account for possible carcinogenic effects, while IRIS classifies it as Group D and treats it as a non-carcinogen.

A further literature search did not reveal any significant studies published since the New Jersey assessment was completed which indicate that the Reference Dose should be reevaluated.

For these reasons, no change in the New Jersey Reference Dose is recommended.

References

NJDWQI (New Jersey Drinking Water Quality Institute). 1994. Maximum Contaminant Level Recommendations for Hazardous Contaminants in Drinking Water. Appendix A: Health-based Maximum Contaminant Level Support Documents. September 26, 1994.

Til, H.P., R.A. Woutersen, V.J. Feron, V.H.M. Hollanders, H.E. Falke and J.J. Clary. 1989. Two-year drinking water study of formaldehyde in rats. Food Chem. Toxicol. 27(2): 77-87.

n-Hexane (New Jersey MCL has not currently been promulgated)

Both New Jersey (NJDWQI, 1987) and USEPA IRIS (last updated in 2005) treat n-hexane as a non-carcinogen for risk assessment purposes. The New Jersey Reference Dose is 0.0047 mg/kg/day. USEPA IRIS does not provide a Reference Dose for n-hexane.

A further literature search did not reveal any significant studies published since the New Jersey assessment was completed which indicate that the Reference Dose should be reevaluated.

For these reasons, no change in the New Jersey Reference Dose is recommended.

References

NJDWQI (New Jersey Drinking Water Quality Institute). 1987. Maximum Contaminant Level Recommendations for Hazardous Contaminants in Drinking Water. Appendix B: Health-based Maximum Contaminant Level Support Documents. March 26, 1987.

Methylene chloride

Both New Jersey (NJDWQI, 1987) and USEPA IRIS classify methylene chloride (dichloromethane) as a probable human carcinogen. The USEPA IRIS slope factor. 0.0075 $(mg/kg/day)^{-1}$ is the arithmetic mean of the slope factors from two chronic bioassays in mice: NCA (1983), which is an oral study, and NTP (1986), which is an inhalation study. Both of these studies were considered by New Jersey (NJDWQI, 1987), and the New Jersey slope factor, 0.014 $(mg/kg/day)^{-1}$, is based on NCA (1983), since oral studies are gnerally considered more appropriate for drinking water risk assessment than inhalation studies.

A further literature search did not reveal any significant studies published since the New Jersey assessment was completed which indicate that the slope factor should be reevaluated.

For these reasons, no change in the New Jersey slope factor is recommended.

References

NCA (National Coffee Association). 1983. Twenty-four month oncogenicity study of methylene chloride in mice. Final Report. Prepared by Hazleton Laboratories, America, Inc., Vienna, VA.

NJDWQI (New Jersey Drinking Water Quality Institute). 1987. Maximum Contaminant Level Recommendations for Hazardous Contaminants in Drinking Water. Appendix B: Health-based Maximum Contaminant Level Support Documents. March 26, 1987.

NTP (National Toxicology Program). 1986. Toxicology and carcinogenesis studies of dichloromethane (methylene chloride) (CAS No. 75-09-2) in F344/N rats and B6C3F1 mice (inhalation studies). NTP-TRS-306.

Methyl tertiary butyl ether (MTBE)

Neither USEPA IRIS or HEAST provides an oral toxicity factor or a carcinogenicity weight-of-evidence assessment for MTBE. New Jersey (NJDWQI, 1994) classifies MTBE as a possible human carcinogen, and has developed a Reference Dose of 0.01 mg/kg/day which incorporates an uncertainty factor of 10 to account for possible carcinogenicity.

A further literature search did not reveal any significant studies published since the New Jersey assessment was completed which indicate that the Reference Dose should be reevaluated.

For these reasons, no change in the New Jersey Reference Dose is recommended.

References

NJDWQI (New Jersey Drinking Water Quality Institute). 1994. Maximum Contaminant Level Recommendations for Hazardous Contaminants in Drinking Water. Appendix A: Health-based Maximum Contaminant Level Support Documents. September 26, 1994.

Naphthalene

Both USEPA IRIS (last updated in1998) and New Jersey (NJDWQI, 1994) classify naphthalene as a possible human carcinogen. The USEPA IRIS Reference Dose, 0.02 mg/kg/day, is based on a No Observed Adverse Effect Level of 100 mg/kg/day in an unpublished subchronic oral rat study (BCL, 1980) (incorporating an additional uncertainty factor for subchronic duration), while A-280 used an older chronic study. The New Jersey Reference Dose, 0.041 mg/kg/day, is based upon a chronic oral rat study (Schmahl, 1955) and incorporates an additional uncertainty factor of 10 to account for possible carcinogenic effects. Chronic studies, when available, are preferred to subchronic studies in Reference Dose derivation, and the Schmahl (1955) study is therefore preferable to the BCL (1980) study.

A further literature search did not reveal any significant studies published since the New Jersey assessment was completed which indicate that the Reference Dose should be reevaluated.

For these reasons, no change in the New Jersey Reference Dose is recommended.

References

BCL (1980). Battelle's Columbus Laboratories. Unpublished subchronic toxicity study: Naphthalene (C52904), Fischer 344 rats. Prepared by Battelle Laboratories under NTP Subcontract No. 76-34-106002.

NJDWQI (New Jersey Drinking Water Quality Institute). 1994. Maximum Contaminant Level Recommendations for Hazardous Contaminants in Drinking Water. Appendix A: Health-based Maximum Contaminant Level Support Documents. September 26, 1994.

Schmahl, D. (1955). Prufung von naphthalin und anthracen auf cancerogene wirkung an ratten [Testing of naphthalene and anthracene as carcinogenic agents in the rat]. Z. Krebsforsch 60: 697-710.

Polychlorinated biphenyls (PCBs)

PCBs are not commonly detected as drinking water contaminants, but are of major importance in other environmental media including soil, sediments, fish, and other aquatic life. For this reason, the New Jersey Drinking Water Quality Institute (NJDWQI, 1994) chose not to reassess PCBs, and recommended that the risk assessment for PCBs be reviewed by a NJDEP work group representing programs responsible for standards and guidance for several environmental media. In a 2000 letter to former New Jersey Drinking Water Quality Institute Chair Richard Sullivan, Leslie McGeorge, who was then Director of the NJDEP Division of Science, Research, and Technology, stated that the Department had reviewed the basis for the USEPA IRIS risk assessment and agreed with it.

Both New Jersey (NJDWQI, 1987) and USEPA IRIS classify PCBs as probable human carcinogens. USEPA IRIS (last updated 1997) recommends three slope factors for PCBs, based on degree of persistence of the PCB mixture (USEPA, 1996). These slope factors are

not based specifically on the particular Aroclor mixture or congener, but on the environmental medium in which the PCBs are found.

The slope factor for PCBs of high risk and persistence (2.0 $(mg/kg/day)^{-1}$) is recommended for PCBs found in the food chain (e.g. fish), ingestion of sediments and soils, inhalation of aerosols or dusts. It is also recommended for dermal exposures if an absorption factor has been applied, as well as for dioxin-like, tumor-promoting, or persistent congeners. This slope factor is recommended for early life exposure, regardless of the pathway or type of PCB mixture.

The slope factor for PCBs of low risk and persistence (0.4 $(mg/kg/day)^{-1}$) is recommended for PCBs when exposure is through ingestion of water soluble congeners and evaporated congeners, and for dermal exposure where no absorption factor has been applied.

The slope factor for PCBs of lowest risk and persistence (0.07 $(mg/kg/day)^{-1}$) is recommended for only for PCBs with a low degree of chlorination, when congeners with more than four chlorines are less than 0.5% of the total PCBs.

It was recommended that the slope factor for highly persistent PCBs, 2 $(mg/kg/day)^{-1}$, be used consistently by NJDEP in development of human health-based guidance and standards. As stated above, PCBs are rarely, if ever, detected in drinking water, but are detected in fish, soil, and sediments for which the slope factor for persistent PCBs is recommended. As a practical matter, for example, in the derivation of human health-based ambient water quality criteria for fresh waters, a single slope factor is used for exposure through both fish consumption and drinking water ingestion.

Additionally, the slope factor for highly persistent PCBs, 2 $(mg/kg/day)^{-1}$, is recommended for early life exposure, regardless of the environmental medium. Since the Health-based MCLs are intended to be protective for exposure throughout the lifetime, including during early life, the use of the slope factor for highly persistent PCBs is considered appropriate.

A further literature search did not reveal any significant studies published since the New Jersey assessment was completed which indicate that the slope factor should be reevaluated.

For these reasons, no change in the New Jersey slope factor is recommended.

References:

NJDWQI (New Jersey Drinking Water Quality Institute). 1987. Maximum Contaminant Level Recommendations for Hazardous Contaminants in Drinking Water. Appendix B: Health-based Maximum Contaminant Level Support Documents. March 26, 1987.

NJDWQI (New Jersey Drinking Water Quality Institute). 1994. Maximum Contaminant Level Recommendations for Hazardous Contaminants in Drinking Water. September 26, 1994.

USEPA (United States Environmental Protection Agency). PCBs: Cancer Dose-Response Assessment and Application to Environmental Mixtures. National Center for Environmental Assessment, Office of Research and Development, Washington, DC. EPA/600/P–96/001F, September 1996.

Tetrachloroethylene

USEPA IRIS does not provide an oral slope factor or a carcinogenicity weight-of-evidence assessment for tetrachloroethylene. New Jersey (NJDWQI, 1987) classifies tetrachloroethylene as a probable human carcinogen, and has developed a slope factor of 0.082 $(mg/kg/day)^{-1}$ (NJDWQI, 1987).

A further literature search did not reveal any significant studies published since the New Jersey assessment was completed which indicate that the slope factor should be reevaluated.

For these reasons, no change in the New Jersey slope factor is recommended.

References:
NJDWQI (New Jersey Drinking Water Quality Institute). 1987. Maximum Contaminant Level Recommendations for Hazardous Contaminants in Drinking Water. Appendix B: Health-based Maximum Contaminant Level Support Documents. March 26, 1987.

Trichloroethylene

USEPA IRIS does not provide a carcinogenicity weight-of-evidence assessment or toxicity factor for trichloroethylene. New Jersey (NJDWQI, 1987) classifies trichloroethylene as a probable human carcinogen, and has developed a slope factor of 0.031 $(mg/kg/day)^{-1}$ (NJDWQI, 1987).

A further literature search did not reveal any significant studies published since the New Jersey assessment was completed which indicate that the slope factor should be reevaluated.

For these reasons, no change in the New Jersey slope factor is recommended.

References:
NJDWQI (New Jersey Drinking Water Quality Institute). 1987. Maximum Contaminant Level Recommendations for Hazardous Contaminants in Drinking Water. Appendix B: Health-based Maximum Contaminant Level Support Documents. March 26, 1987.

Xylenes

Both New Jersey (NJDWQI, 1987; NJDWQI, 1994) and USEPA IRIS treat xylenes as non-carcinogenic for risk assessment purposes. The USEPA IRIS Reference Dose, 0.2 mg/kg/day, is based on the No Observed Adverse Effect Level, 250 mg/kg/day, in a chronic oral rat study (NTP, 1986). The New Jersey Reference Dose (NJDWQI, 1994), 0.15 mg/kg/day, is very close to the USEPA IRIS Reference Dose and is based on the Lowest Observed Adverse Effect Level, 150 mg/kg/day, for chronic nephropathy observed in female rats in a subchronic study (Condie et al., 1988) as well as consideration of the results of the chronic rat study (NTP, 1986).

A further literature search did not reveal any significant studies published since the New Jersey assessment was completed which indicate that the Reference Dose should be

reevaluated.

For these reasons, no change in the New Jersey Reference Dose is recommended.

References:
Condie, LW, Hill, JR, and Borzelleca, JF (1988). Oral toxicology studies with xylene isomers and mixed xylenes. Drug Chem. Tox. 11: 329-354.

NJDWQI (New Jersey Drinking Water Quality Institute). 1987. Maximum Contaminant Level Recommendations for Hazardous Contaminants in Drinking Water. Appendix B: Health-based Maximum Contaminant Level Support Documents. March 26, 1987.

NJDWQI (New Jersey Drinking Water Quality Institute). 1994. Maximum Contaminant Level Recommendations for Hazardous Contaminants in Drinking Water. Appendix A: Health-based Maximum Contaminant Level Support Documents. September 26, 1994.

NTP (National Toxicology Program). (1986) NTP technical report on the toxicology and carcinogenesis of xylenes (mixed) (60% m-xylene, 13.6% p-xylene, 17.0% ethylbenzene, and 9.1% o-xylene) in F344/N rats and B6C3F1 mice (gavage studies). Research Triangle Park, NC. NTP TR 327, NIH Publ. No. 86-2583.

Table: Summary of Health Effects Information for Contaminants with Recommended Revisions to Existing Health-based MCLs and Contaminants with New Health-based MCLs

Contaminant	Parameter	ug/L	Date	Key Study	Endpoint	Uncertainty Factor (For specifics of UFs, see footnotes. All UFs are 10 unless otherwise noted.)	Reference Dose and/or Slope Factor	NJ or USEPA Carcinogenicity Classification *(Cancer Risk Assessment Guidelines Used to Assess)*
Benzene	Proposed Health-based MCL	0.12	7/07	Rinsky (1987) update of Pliofilm cohort. Crump and Allen (1984) exposure assessment	Leukemia	NA	0.28 $(mg/kg/day)^{-1}$ (95% Upper Confidence Level)	NJ Category I – Carcinogenic to Humans *(2005 USEPA Guidelines)*
	Current Health-based MCL	0.15	1987	Pooled Ott (1978), Wong (1983), Rinsky (1981) occupational cohorts. Crump and Allen (1984) exposure assessment	Leukemia	NA	0.23 $(mg/kg/day)^{-1}$ (95% Upper Confidence Level)	NJ Category I – Known Human Carcinogen *(1986 USEPA Guidelines)*
	USEPA IRIS	NA	2000	Rinsky et al., 1981, 1987; Paustenbach et al., 1993; Crump 1994; U.S. EPA, 1998; U.S. EPA, 1999. Human occupational	Leukemia	NA	0.015 - 0.055 $(mg/kg/day)^{-1}$ (Maximum Likelihood Estimate)	USEPA Group A – Known Human Carcinogen *(1986 USEPA Guidelines)* Known Human Carcinogen *(1996 USEPA Guidelines)*

Contaminant	Parameter	ug/L	Date	Key Study	Endpoint	Uncertainty Factor (For specifics of UFs, see footnotes. All UFs are 10 unless otherwise noted.)	Reference Dose and/or Slope Factor	NJ or USEPA Carcinogenicity Classification *(Cancer Risk Assessment Guidelines Used to Assess)*
Benzene (continued)	USEPA MCLG	Zero*	1987	----	Leukemia	NA	-----	USEPA Group A – Known Human Carcinogen *(1986 USEPA Guidelines)*
	PQL	1 (current). 0.8 (new).	NA	NA	NA	NA	NA	NA
1,3-Dichloro-benzene	Proposed Health-based MCL	6.3	4/06	McCauley et al. (1995). Rat subchronic gavage.	LOAEL – 9 mg/kg/day Thyroid – male & female. Pituitary – male. Cholesterol, LDH – male.	10,000 UFs - A, B, C, D	0.0009 mg/kg/day (RfD)	NJ Category III – Inadequate information (Non-carcinogen) *(2005 USEPA Guidelines)*
	Current Health-based MCL	600	1987	NTP(1985). Mouse chronic gavage. (Based upon **1,2-DCB**, in absence of data for 1,3-DCB).	LOAEL – 43 mg/kg/day Kidney - Male (adjusted for 5/7 days)	500 UFs – A, B, C (5)	0.085 mg/kg/day (RfD)	NJ Category III – Not classifiable (Non-carcinogen) *(1986 USEPA Guidelines)*
	USEPA IRIS	NA	1992	NA	----	----	----	USEPA Group D– Not classifiable (Non-carcinogen) *(1986 USEPA Guidelines)*
	USEPA MCLG	----	----	----	----	----	-----	-----

Contaminant	Parameter	ug/L	Date	Key Study	Endpoint	Uncertainty Factor (For specifics of UFs, see footnotes. All UFs are 10 unless otherwise noted.)	Reference Dose and/or Slope Factor	NJ or USEPA Carcinogenicity Classification *(Cancer Risk Assessment Guidelines Used to Assess)*
1,3-Dichloro-benzene (continued)e	PQL	5 (current). 1 (new)	NA	NA	NA	NA	NA	NA
1,4-Dichloro-benzene	Proposed Health-based MCL	14	4/06	Naylor and Stout (1996). Dog chronic oral (capsule)	NOAEL – 7 mg/kg/day (adjusted for 5/7 days)	3000 UFs – A,B,E,F* UF of 3 for small # of animals and minimal time period (1 yr) in chornic study.	0.0023 mg/kg/day (RfD)	NJ Category II-Suggestive *(2005 USEPA Guidelines)*
	Current Health-based MCL	150	1994	NTP(1987). Mouse chronic gavage.	LOAEL – 214 mg/kg/day. Liver –Male and Female (adjusted for 5/7 days)	10,000 UFs – A,B,C,E	0.021 mg/kg/day (RfD)	NJ Category II– Possible *(1986 USEPA Guidelines)*
	USEPA IRIS	NA	----	----	----	----	----	----
	USEPA MCLG	75	1987	NTP(1987). Mouse subchronic gavage.	NOAEL – 107 mg/kg/day (adjusted for 5/7 days)	10,000 UFs – A,B,D,E	0.0107 mg/kg/day (RfD)	USEPA Group C – Possible *(1986 USEPA Guidelines)*
	PQL	5 (current). 1 (new).	NA	NA	NA	NA	NA	NA

Contaminant	Parameter	ug/L	Date	Key Study	Endpoint	Uncertainty Factor (For specifics of UFs, see footnotes. All UFs are 10 unless otherwise noted.)	Reference Dose and/or Slope Factor	NJ or USEPA Carcinogenicity Classification *(Cancer Risk Assessment Guidelines Used to Assess)*
1,1-Dichloro-ethane	Proposed Health-based MCL	23	4/06	Hofman et al. (1971). Cat subchronic inhalation.	NOAEL 32.5 mg/kg/day Kidney	10,000 UFs –A,B,D,E	0.0032 mg/kg/day (RfD)	NJ Category II-Suggestive *(2005 USEPA Guidelines)*
	Current Health-based MCL	46	1994	Hofman et al. (1971). Cat subchronic inhalation.	NOAEL 32.5 mg/kg/day Kidney	5000 UFs – A,B,D,F(5)	0.0065 mg/kg/day (RfD)	NJ Category III –Not classifiable (Non-carcinogen) (*1986 USEPA Guidelines)*
	USEPA IRIS	NA	----	----	----	----	----	USEPA Group C – Possible *(1986 USEPA Guidelines)*
	USEPA MCLG	----	----	----	----	----	----	----
	PQL	1	NA	NA	NA	NA	NA	NA

Contaminant	Parameter	ug/L	Date	Key Study	Endpoint	Uncertainty Factor (For specifics of UFs, see footnotes. All UFs are 10 unless otherwise noted.)	Reference Dose and/or Slope Factor	NJ or USEPA Carcinogenicity Classification *(Cancer Risk Assessment Guidelines Used to Assess)*
1,1-Dichloro-ethylene	Proposed Health-based MCL	63	4/06	Quast et al.(1983). Rat chronic drinking water.	NOAEL 9 mg/kg/day– females. Liver	1000 UFs – A,B,E	0.009 mg/kg/day (RfD)	NJ Category II-Suggestive *(2005 USEPA Guidelines)*
	Current Health-based MCL	1	1987	NTP(1982). Mouse chronic gavage.	LOAEL 1.4 mg/kg/day Liver (adjusted for 5/7 days)	10,000 UFs -A,B,C,E	0.00014 mg/k/gday (RfD)	NJ Category II– Possible *(1986 USEPA Guidelines)*
	USEPA IRIS	NA	2002	Quast et al.(1983). Rat chronic drinking water.	BMDL on NOAEL 4.6 mg/kg/day - females. Liver	100 A,B	0.05 mg/kg/day (RfD)	Inadequate information (non-carcinogen) by <u>oral</u> route. Suggestive by <u>inhalation</u> route. *(2005 USEPA Guidelines)*
	USEPA MCLG	7*	1987	Quast et al.(1983). Rat chronic drinking water.	LOAEL – 10 mg/kg/day (Apparent error in dose chosen for LOAEL– see Support Document)	10,000 UFs – A,B,C,E	0.001 mg/kg/day (RfD)	USEPA Group C – Possible (1986 USEPA Guidelines)
	PQL	2 (current). 0.9 (new).	NA	NA	NA	NA	NA	NA

Contaminant	Parameter	ug/L	Date	Key Study	Endpoint	Uncertainty Factor (For specifics of UFs, see footnotes. All UFs are 10 unless otherwise noted.)	Reference Dose and/or Slope Factor	NJ or USEPA Carcinogenicity Classification *(Cancer Risk Assessment Guidelines Used to Assess)*
Ethylene Glycol	Proposed Health-based MCL	10,000	9/07	DePass et al. (1986) Rat chronic diet Neeper-Bradley et al. (1995). Mouse developmental gavage	NOAEL 200 mg/kg/day. Renal toxicity NOAEL 150 mg/kg/day. Fetal malformations	100 A,B 100 A,B	2 mg/kg/day 1.5 mg/kg/day (Reference Dose)	NJ Category III – Inadequate information (Non-carcinogen) (*2005 USEPA Guidelines*)
	Current Health-based MCL	290	1987	Blood (1965) Rat chronic diet	NOAEL 42 mg/kg/day (estimated from 0.2% in diet). Renal oxalate deposition	1000 A,B,F	0.042 mg/kg/day (Reference Dose)	NJ Category III – Not classifiable (Non-carcinogen) *(1986 USEPA Guidelines)*
	USEPA IRIS	NA	1989	DePass et al. (1986) Rat chronic diet	NOAEL 200 mg/kg/day Renal toxicity	100 A,B	2 mg/kg/day (Reference Dose)	USEPA Group D – Not classifiable (Non-carcinogen) *(1986 USEPA Guidelines)*
	USEPA MCLG	------	------	----------	----------	----------	----------	----------
	PQL	10,000 (new)	NA	NA	NA	NA	NA	NA

Contaminant	Parameter	ug/L	Date	Key Study	Endpoint	Uncertainty Factor (For specifics of UFs, see footnotes. All UFs are 10 unless otherwise noted.)	Reference Dose and/or Slope Factor	NJ or USEPA Carcinogenicity Classification *(Cancer Risk Assessment Guidelines Used to Assess)*
Methyl Ethyl Ketone	Proposed Health-based MCL	4200	9/08	Cox et al. (1975) 2-generation rat reproductive and developmental study of MEK metabolite, 2-butanol	BMDL 657 mg/kg/day Weight loss in pups at postnatal day 21	1000 A,B,F F=use of 2-butanol as a surrogate for MEK, and lack of chronic data	0.6 mg/kg/day (Reference Dose)	NJ Category III – Inadequate information (Non-carcinogen) (*2005 USEPA Guidelines*)
	Current Health-based MCL	270	1987	Smith and Mayers (1944) Human occupational	LOAEL 870 mg/m^3 (Inhalation) Numbness of hands, fingers, and legs	1000 A,C,F F=To prevent MEK augmenation toxicity of other substances	0.039 mg/kg/day (Reference Dose)	NJ Category III – Not classifiable (Non-carcinogen) *(1986 USEPA Guidelines)*
	USEPA IRIS	NA	2003	Cox et al. (1975) 2-generation rat reproductive and developmental study of MEK metabolite, 2-butanol	BMDL 657 mg/kg/day Weight loss in pups at postnatal day 21	1000 A,B,F F=use of 2-butanol as a surrogate for MEK, and lack of chronic data	0.6 mg/kg/day (Reference Dose)	Data inadequate for assessment of human carcinogenic potential *(1999 USEPA Guidelines)*
	USEPA MCLG	------	------	----------	----------	----------	----------	----------
	PQL	2 (new)	NA	NA	NA	NA	NA	NA

Contaminant	Parameter	ug/L	Date	Key Study	Endpoint	Uncertainty Factor (For specifics of UFs, see footnotes. All UFs are 10 unless otherwise noted.)	Reference Dose and/or Slope Factor	NJ or USEPA Carcinogenicity Classification *(Cancer Risk Assessment Guidelines Used to Assess)*
1,1,2,2-Tetra-chloroethane	Proposed Health-based MCL	0.18	9/06	NTP (1978). Mouse chronic gavage.	Liver tumors in female mice	NA	0.2 $(mg/kg/day)^{-1}$ (Slope Factor)	NJ Category II- Suggestive *(2005 USEPA Guidelines)*
	Current Health-based MCL	1	1994	Gohlke et al. (1977). Rat chronic gavage. Schmidt et al. (1972). Rat chronic inhalation.	LOAEL – 3.2 mg/kg/day Histological changes in liver, kidney, testes, thyroid, adrenal. LOAEL – 1.34 mg/kg/day ↑ fat in liver, ACTH, and WBC. ↓ body weight.	10,000 UFs - A, B, C, E 10,000 UFs – A, B, C, E	0.00023 mg/kg/day (RfD) 0.000134 mg/kg/day (RfD)	NJ Category II– Possible *(1986 USEPA Guidelines)*
	USEPA IRIS	NA	1987	NTP (1978). Mouse chronic Gavage.	Liver tumors in female mice	NA	0.2 $(mg/kg/day)^{-1}$ (Slope Factor)	USEPA Group C – Possible *(1986 USEPA Guidelines)*
	USEPA MCLG	-----	NA	---------	----------	----------	----------	----------
	PQL	1 (current) 0.2 (new)	NA	NA	NA	NA	NA	NA

Contaminant	Parameter	ug/L	Date	Key Study	Endpoint	Uncertainty Factor (For specifics of UFs, see footnotes. All UFs are 10 unless otherwise noted.)	Reference Dose and/or Slope Factor	NJ or USEPA Carcinogenicity Classification *(Cancer Risk Assessment Guidelines Used to Assess)*
1,2,4-Tri-chlorobenzene	Proposed Health-based MCL	18	9/06	Hazleton - Washington (1994). Chronic mouse diet.	LOAEL – 26.3 mg/kg/day Distended abdomen and increased liver weight.	10,000 UFs – A, B, C, E	0.0026 mg/kg/day (RfD)	NJ Category II-Suggestive *(2005 USEPA Guidelines)*
	Current Health-based MCL	8.6	1987	Watanabe et al. (1978). Subchronic rat inhalation.	NOAEL – 1.2 mg/kg/day (extrapolated from 3 ppm in air). Increased urinary porphyrins.	1000 UFs – A, B, D	0.0012 mg/kg/day (RfD)	NJ Category III – Not classifiable (Non-carcinogen) *(1986 USEPA Guidelines)*
	USEPA IRIS	NA	1996	Robinson et al. (1981). Rat multigeneration reproductive drinking water.	NOAEL – 14.8 mg/kg/day (100 ppm in drinking water). Increased adrenal gland weight.	1000 UFs – A,B,D	0.01 mg/kg/day (RfD)	USEPA Group D – Not classifiable (Non-carcinogen) *(1986 USEPA Guidelines)*
	USEPA MCLG	70	1992	Robinson et al. (1981). Rat multigeneration reproductive drinking water.	NOAEL – 14.8 mg/kg/day (100 ppm in drinking water). Increased adrenal gland weight.	1000 UFs – A,B,D	0.01 mg/kg/day (RfD)	USEPA Group D – Not classifiable (Non-carcinogen) *(1986 USEPA Guidelines)*

Contaminant	Parameter	ug/L	Date	Key Study	Endpoint	Uncertainty Factor (For specifics of UFs, see footnotes. All UFs are 10 unless otherwise noted.)	Reference Dose and/or Slope Factor	NJ or USEPA Carcinogenicity Classification *(Cancer Risk Assessment Guidelines Used to Assess)*
1,2,4-Tri-chlorobenzene (continued)	PQL	5 (current). 1 (new).	NA	NA	NA	NA	NA	NA
1,1,1-Tri-chloroethane	Proposed Health-based MCL	2000	9/08	NTP (2000). Subchronic mouse microcapsule diet.	LOAEL – 850 mg/kg/day Weight loss in male mice.	3000 UFs – A, B, C*,D *UF of 3 used for LOAEL to NOAEL due to minimal nature of the effect	0.28 mg/kg/day (RfD)	NJ Category III – Inadequate information (Non-carcinogen) (*2005 USEPA Guidelines*)
	Current Health-based MCL	26	1987	McNutt et al. (1975). Subchronic rat inhalation.	LOAEL – 250 ppm (inhalation) mg/kg/day. Cytoplasmic changes in liver. Pharmaco-kinetic modeling used to body burden and equivalent drinking water concentration from inhalation data.	10,000 UFs – A, B,C,D	0.0037 mg/kg/day (RfD)	NJ Category III – Not classifiable (Non-carcinogen) *(1986 USEPA Guidelines)*

Contaminant	Parameter	ug/L	Date	Key Study	Endpoint	Uncertainty Factor (For specifics of UFs, see footnotes. All UFs are 10 unless otherwise noted.)	Reference Dose and/or Slope Factor	NJ or USEPA Carcinogenicity Classification *(Cancer Risk Assessment Guidelines Used to Assess)*
1,1,1-Tri-chloroethane (continued)	USEPA IRIS	NA	2007	NTP (2000), Subchronic mouse microcapsule diet.	BMDL –2155 mg/kg/day Weight loss in female mice.	1000 UFs – A,B,D,F* *UFs of 3 for D and F	2 mg/kg/day (RfD)	Inadequate information (Non-carcinogen) (*2005 USEPA Guidelines*)
	USEPA MCLG	200*	1987	McNutt et al. (1975). Subchronic rat inhalation.	LOAEL – 250 ppm (inhalation) equivalent to 35 mg/kg/day. Cytoplasmic changes in liver.	1000 UFs – A,B,C	0.035 mg/kg/day (RfD)	USEPA Group D – Not classifiable (Non-carcinogen) *(1986 USEPA Guidelines)*
	PQL	1 (current). 0.9 (new).	NA	NA	NA	NA	NA	NA
1,1,2-Tri-chloroethane	Proposed Health-based MCL	0.61	9/06	NCI (1978). Mouse chronic gavage.	Liver tumors in male mice	NA	0.057 $(mg/kg/day)^{-1}$ (Slope Factor)	NJ Category II-Suggestive *(2005 USEPA Guidelines)*
	Current Health-based MCL	3	1994	White et al. (1985) & Sanders et al. (1985). Mouse subchronic drinking water.	NOAEL – 3.9 mg/kg/day Changes in liver enzymes and decreased immune response	10,000 UFs – A,B,D,E	0.0039 mg/kg/day (Reference Dose)	NJ Category II– Possible *(1986 USEPA Guidelines)*

Contaminant	Parameter	ug/L	Date	Key Study	Endpoint	Uncertainty Factor (For specifics of UFs, see footnotes. All UFs are 10 unless otherwise noted.)	Reference Dose and/or Slope Factor	NJ or USEPA Carcinogenicity Classification *(Cancer Risk Assessment Guidelines Used to Assess)*
1,1,2-Tri-chloroethane (continued)	USEPA IRIS	NA	1988 (RfD) --- 1987 (slope factor)	White et al. (1985) & Sanders et al. (1985). Mouse subchronic drinking water. --- NCI (1978) Mouse chronic gavage.	NOAEL – 3.9 mg/kg/day Changes in liver enzymes and decreased immune response. --- Liver tumors in female mice	10,000 UFs – A,B,D,E --- NA	0.004 mg/kg/day (Reference Dose) --- 0.057 $(mg/kg/day)^{-1}$ (Slope Factor)	USEPA Group C – Possible *(1986 USEPA Guidelines)*
	USEPA MCLG	3	1989	White et al. (1985) & Sanders et al. (1985). Mouse subchronic drinking water.	NOAEL – 3.9 mg/kg/day Changes in liver enzymes and decreased immune response	10,000 UFs – A,B,D,E	0.0039 mg/kg/day (Reference Dose)	USEPA Group C – Possible *(1986 USEPA Guidelines)*
	PQL	2 (current) 1 (new)	NA	NA	NA	NA	NA	NA
2,4,6-Trichlorophenol	Proposed Health-based MCL	3.1	9/08	NCI (1979). Rat chronic diet	Leukemia in male rats.	NA	0.011 $(mg/kg/day)^{-1}$ (Slope Factor)	NJ Category I-Likely *(2005 USEPA Guidelines)*
	Current Health-based MCL	1	1994	NCI (1979). Mouse chronic diet.	Liver tumors in male mice	NA	0.026 $(mg/kg/day)^{-1}$ (Slope Factor)	NJ Category I-Probable Human Carcinogen *(2005 USEPA Guidelines)*

Contaminant	Parameter	ug/L	Date	Key Study	Endpoint	Uncertainty Factor (For specifics of UFs, see footnotes. All UFs are 10 unless otherwise noted.)	Reference Dose and/or Slope Factor	NJ or USEPA Carcinogenicity Classification *(Cancer Risk Assessment Guidelines Used to Assess)*
2,4,6-Trichlorophenol (continuted)	USEPA IRIS	NA	1990	NCI (1979). Rat chronic diet	Leukemia in male rats.	NA	0.011 $(mg/kg/day)^{-1}$ (Slope Factor)	USEPA Group B2 – Probable Human Carcinogen *(1986 USEPA Guidelines)*
	USEPA MCLG	---	---	----	---	---	---	---
	PQL		NA	NA	NA	NA	NA	NA
Vinyl Chloride	Proposed Health-based MCL	0.023	4/06	Feron et al. (1983). Rat chronic diet.	Liver tumors female rats. Pharmaco-kinetic and early childhood adjustments.	NA	1.5 $(mg/kg/day)^{-1}$ (Slope Factor)	NJ Category I Carcinogenic to Humans *(2005 USEPA Guidelines)*
	Current Health-based MCL	0.084	1987	Feron et al. (1983). Rat chronic diet.	Liver tumors female rats.	NA	0.42 $(mg/kg/day)^{-1}$ (Slope Factor)	New Jersey Category 1 USEPA Group A – Human Carcinogen *(1986 USEPA Guidelines)*
	USEPA IRIS	NA	2000	Feron et al. (1983). Rat chronic diet.	Liver tumors female rats. Pharmaco-kinetic and early childhood adjustments.	NA	1.5 $(mg/kg/day)^{-1}$ (Slope Factor)	Carcinogenic to Humans *(2005 USEPA Guidelines)*

Contaminant	Parameter	ug/L	Date	Key Study	Endpoint	Uncertainty Factor (For specifics of UFs, see footnotes. All UFs are 10 unless otherwise noted.)	Reference Dose and/or Slope Factor	NJ or USEPA Carcinogenicity Classification *(Cancer Risk Assessment Guidelines Used to Assess)*
Vinyl Chloride (continuted)	USEPA MCLG	Zero*	1987	NA	NA	NA		USEPA Group A – Human Carcinogen *(1986 USEPA Guidelines)*
	PQL	5 (1)** (current). 1 (new).	NA	NA	NA	NA	NA	NA
Dacthal (DCPA) and degradates	Proposed Health-based MCL	28	4/08	ISK Biotech Corp. (1993), Rat chronic diet	NOAEL 1 mg/kg/day Effects on the lungs, liver, kidney, thyroid and thyroid hormones in males and females and eyes of females	1000 A,B,E **NOTE: A Relative Source Contribution factor of 0.8, based on available exposure data, was used instead of the default value of 0.2**	0.001 mg/kg/day (Reference Dose)	NJ Category II-Suggestive *(2005 USEPA Guidelines)*
	Current Health-based MCL	---	----	----	----	----	-----	-----
	USEPA IRIS	NA	1994		NOAEL 1 mg/kg/day Effects on the lungs, liver, kidney, thyroid and thyroid hormones in males and females and eyes of females	100 A,B,E	0.01 mg/kg/day (Reference Dose)	------

Contaminant	Parameter	ug/L	Date	Key Study	Endpoint	Uncertainty Factor (For specifics of UFs, see footnotes. All UFs are 10 unless otherwise noted.)	Reference Dose and/or Slope Factor	NJ or USEPA Carcinogenicity Classification *(Cancer Risk Assessment Guidelines Used to Assess)*
Dacthal (DCPA) and degradates (continuted)	USEPA MCLG	------	------	----------	---------	----------	----------	----------
	PQL	2 (new).	NA	NA	NA	NA	NA	NA
1,2,3-Trichloro-propane	Proposed Health-based MCL	0.0014	3/09	NTP (1993). Chronic mouse gavage.	Forestomach tumors in female mice	NA	25 $(mg/kg/day)^{-1}$ (Slope Factor)	NJ Category I-Likely *(2005 USEPA Guidelines)*
	Current Health-based MCL	----	----	----	-----	-----	-----	-----
	USEPA IRIS	NA	1990	NTP (1983). Rat subchronic gavage.	NOAEL 5.71 mg/kg/day Clinical chemistry changes and reduced red blood cell mass	1000 A,B,D	0.006 mg/kg/day (Reference Dose)	------- **NOTE: IRIS has not been updated to reflect NTP (1993) chronic cancer bioassay results.**
	USEPA MCLG	---	----	---	---	---	---	---
	PQL	0.03 (new)	NA	NA	NA	NA	NA	NA

Uncertainty Factors: A –Intraspecies
B - Interspecies
C - Lowest Observed Adverse Effect Level (LOAEL) to No Observed Adverse Effect Level (NOAEL)
D - Subchronic to Chronic
E - Suggestive or Possible Carcinogenicity
F - Other (e.g. data deficiencies, small number of animals, or other uncertainties not accounted for by other UFs).

*USEPA MCLG is below Proposed NJ Health-based MCL.
**USEPA PQL lower than New Jersey PQL.
NA – Not Applicable
---- Information not available

Addenda to Support Document for Contaminants with Existing Health-Based MCLs

Addendum to Health-Based MCL Support Document:
Benzene

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For the New Jersey Drinking Water Quality Institute

July, 2007

Executive Summary

A thorough literature search and detailed evaluation of all available data was conducted as part of the effort to update the existing risk assessment for benzene. In summary, all of the risk assessment approaches for benzene discussed in this document are based on mortality from leukemia in studies of workers exposed by inhalation. A cancer slope factor is derived by mathematical modeling of the mortality data and individual exposure estimates. As discussed below, it is concluded that the most appropriate basis for the recommended cancer slope factor of 0.28 per mg/kg/day is an updated follow-up of the Pliofilm rubber worker cohort. This cohort is one of three pooled studies used as the basis for the original New Jersey cancer slope factor (NJDWQI, 1987) and also forms the basis for the USEPA (2000) Integrated Risk Information System (IRIS) assessment. The overall conclusion is that the recommended cancer slope factor represents only a small modification of the current New Jersey slope factor that was recommended twenty years ago.

The basis for the current New Jersey cancer slope factor and Health-based Maximum Contaminant Level (HBMCL), the USEPA IRIS cancer slope factor, and the New Jersey HBMCL recommendation developed in this document are shown in Table 1.

The current New Jersey Health-based Maximum Contaminant Level (1987) for benzene of 0.15 ug/L is based on a cancer slope factor of **0.23 per mg/kg/day** (see Table 1). This slope factor is based on the 95% upper confidence limit (95% UCL) of a linear multiplicative model of leukemia mortality data and benzene exposure in three pooled worker cohorts, including the initial follow-up (Rinsky et al., 1981) of the large Pliofilm rubber cohort. The Pliofilm worker exposure was based on the exposure assessment of Crump and Allen (1984), and was not adjusted for the shorter exposure period for workers compared to lifetime environmental exposure (45 years/70 years).

The USEPA (2000) IRIS database provides a range of slope factors from 0.015 to 0.055 per mg/kg/day calculated by Crump (1994). This range was based only on the Pliofilm cohort (updated by Rinsky et al., 1987), which is considered the most relevant and best characterized occupational cohort for benzene. In contrast to the New Jersey assessment, the maximum likelihood estimate of the slope, rather than the 95% UCL, was used by USEPA, and exposure was adjusted for 45 years/70 years to account for lifetime exposure duration. The low end and the high end of the range arise from the use of two different exposure assessments. The high end of the range uses the same Crump and Allen (1984) assessment used in the current New Jersey assessment, while the low end uses the exposure assessment of Paustenbach et al. (1992). Crump (1994) and USEPA (2000) did not include the Rinsky et al. (1981) exposure assessment, and use of the Rinsky et al. (1981) assessment would have resulted in a higher cancer slope

factor.

The cancer slope factor recommended herein is **0.28 per mg/kg/day**. This slope factor is based on information provided in the USEPA support document for the IRIS database for benzene (1998). The basis for this slope factor is identical to the higher end of the USEPA slope factor (0.055 per mg/kg/day) discussed above, except that it uses the 95% UCL rather than the maximum likelihood estimate. The 95% UCL was used as the basis for the current (1987) New Jersey slope factor for benzene, and the current USEPA Cancer Risk Assessment Guidelines (2005) suggest the use of the 95% UCL for extrapolating slope factors outside of the exposure range of epidemiological data.

The recommended Health-based MCL (set at the one-in-one-million lifetime risk level) based on a cancer slope factor of 0.28 per mg/kg/day is 0.12 ug/L. This represents a slight decrease from the current Health-based MCL of 0.15 ug/L.

Table 1. Summary of Current A-280, Current USEPA, and Recommended New Jersey Cancer Slope Factors for Benzene

#	Assessment	Cohort	Pliofilm Exposure Assessment	95% UCL or MLE[b]	Adjusted for 45/70 years	Slope Factor (per mg/kg/day)	Drinking Water Concentration[d] (ug/L)
1	Current NJ HBMCL (NJDWQI, 1987)	Pooled Ott-Wong-Rinsky cohorts[a]	Crump and Allen (1984)	95% UCL	No	0.23	0.15
2	USEPA IRIS (2000) Lower end of range	Rinsky (1987) update of Pliofilm cohort	Paustenbach et al. (1992)	MLE	Yes	0.015	2.2
3	USEPA IRIS (2000) Upper end of range	Rinsky (1987) update of Pliofilm cohort	Crump and Allen (1984)	MLE	Yes	0.055	0.6
4	**Recommended NJ HBMCL**	**Rinsky (1987) update of Pliofilm cohort**	**Crump and Allen (1984)**	**95%[c] UCL**	**Yes**	**0.28**	**0.12**

Row 4 (in bold) represents the recommended approach.

[a] Ott (1978) and Wong (1983) are chemical worker cohorts; Rinsky (1981) is the original follow-up of Pliofilm cohort

[b] 95% upper confidence level (95% UCL), maximum likelihood estimate (MLE) of the slope (i.e., the central estimate)

[c] Provided in USEPA (1998) IRIS Support Document

[d] Drinking water concentration equivalent to one-in-one-million lifetime cancer risk

NOTE: All assessments are based on a linear multiplicative model.

Technical Overview

The current New Jersey cancer slope factor for benzene is 0.23 per milligram per kilogram body weight per day $(mg/kg/day)^{-1}$ (NJDWQI, 1987). It represents the 95% upper confidence limit of the slope factor based on linear mathematical modeling of inhalation exposures and the risk of leukemia mortality in pooled data from the Pliofilm worker cohort (Rinsky et al., 1981) and two chemical worker cohorts (Ott et al., 1978; Wong et al., 1983). Exposure in the Pliofiolm cohort was assigned using the Crump and Allen (1984) exposure assessment matrix. The drinking water Health-based Maximum Contaminant Level (HBMCL), based on this slope factor at a one-in-one-million lifetime cancer risk and the default exposure factors of 70 kg adult body weight and 2 L daily adult tap water consumption is 0.15 ug/L.

The Rinsky et al. (1981), Ott et al. (1978), and Wong et al. (1983) studies were also the basis of the 1985 USEPA assessment, which developed a cancer slope of 0.026 $(mg/kg/day)^{-1}$ from the geometric mean of four maximum likelihood unit risk estimates generated from the three studies.

This USEPA oral cancer slope factor was updated in 1998 and was posted in IRIS in 2000, based on the next follow-up of the Pliofilm cohort (Rinsky et al., 1987). This cohort is the largest and has the best exposure assessment data of the several cohorts of benzene exposed workers which have been studied. Neither of the chemical worker studies has sufficient power for independent calculations, and the net result of discarding data from them had only a small effect on the unit risk estimate (USEPA, 2000). A range of values for the slope factor was developed (Crump, 1994), based upon the linear extrapolation of two (Crump and Allen, 1984; Paustenbach et al., 1992) of the three Pliofilm exposure assessments using competing workplace exposure matrices. The slope factor range (adjusted for continuous exposure between ages 20 and 65) is 0.014 – 0.055 $(mg/kg/day)^{-1}$, and the health-based drinking water concentrations based on them, at the one-in-one-million cancer risk level and the assumptions given above, are 0.6 -2.0 µg/L. The high end of the slope factor range is based on a linear-multiplicative model using the Crump and Allen (1984) exposure assessment. If the upper 95% confidence limit (95% UCL) for this model (USEPA, 1998) were used instead, the slope factor would be 0.28 $(mg/kg/day)^{=1}$ and the health-based drinking water level would be 0.1 µg/L.

In addition, a third exposure assessment (Rinsky et al., 1981, 1987) was not considered by USEPA (1998) in developing the range, because the USEPA (1998) range is based on analyses by Crump (1994), who chose not to include that assessment in his analyses. Because the estimated overall average cohort exposure in the Rinksy assessment is approximately half that of the Crump and Allen assessment, its use would have resulted in a cancer slope that is approximately twice as high as the slope based on Crump and Allen (1984), and thus a more stringent drinking water level. Use of the 95% UCL of the slope estimate would have resulted in a yet higher final slope and lower drinking water level.

Several approaches summarized below were used to develop estimates of drinking water concentrations of benzene resulting in 10^{-6} lifetime cancer risk. These estimates converge on a drinking water concentration of approximately 0.1 ug/L.

1) The USEPA (1998) IRIS support document utilizes a subsequent analysis by Crump (1994) of the Rinsky et al. (1987) update of the Pliofilm cohort. The 95% UCL of the linear multiplicative model of the cancer slope using the Crump and Allen (1984) exposure assessment was calculated (0.28 per mg/kg/day), but only the central estimate (0.055 $(mg/kg/day)^{-1}$) was used as the upper

bound of the cancer slope range currently presented in IRIS. Use of the 95% UCL yields a drinking water concentration of **0.12 ug/L**.

2) Although the Rinsky et al. (1981, 1987) exposure assessment was not included in Crump (1994), it can be approximated by increasing the estimated slope factor at the central estimate by a factor of 2 (from 0.055 to 0.11 $(mg/kg/day)^{-1}$), which reflects the observation that the overall exposure estimate by Rinsky et al. was half that of Crump and Allen (1984). An approximation of the 95% UCL, by assuming it is higher than the central estimate of the slope by a factor of 1.5 - 2, would yield a drinking water concentration of **0.15 – 0.2 ug/L.**

3) The Crump (1986) report to NJDEP included an analysis of the original follow-up of the Pliofilm cohort by itself, using the Crump and Allen (1984) exposure assessment. The 95% UCLs of linear slope factors were calculated by Crump, but an adjustment for occupational versus lifetime exposure was originally excluded from the final HBMCL calculation. The updated cancer slope factor (0.25 $(mg/kg/day)^{-1}$) yields a drinking water concentration of **0.14 ug/L.** Unfortunately, the Rinsky et al. (1981) exposure assessment was not examined by Crump (1986).

4) In addition, the recent report by Rinsky et al. (2002) on the follow-up of the Pliofilm cohort through 1996 found that the central estimate of the cancer slope factor was 0.18 $(mg/kg/day)^{-1}$, using a linear multiplicative model. A 95% UCL is 0.36 per mg/kg/day, which corresponds to a drinking water concentration of **0.12 ug/L**. Further adjustment from occupational exposure to lifetime exposure would increase the cancer slope and lower the HBMCL by approximately a factor of 7.

Thus several lines of evidence support the recommendation that the New Jersey cancer slope be based on the upper bound of the 95 percent confidence interval (USEPA 1998) of the linear-multiplicative model using the Crump and Allen (1984) exposure assessment of the Pliofilm cohort, as adjusted for incidence in the general population. The central estimate of the slope factor is 0.055 $(mg/kg/day)^{-1}$ and the upper 95 percent confidence limit is 0.28 $(mg/kg/day)^{-1}$, based on mortality. The HBMCL based on this slope factor and a one-in-one million lifetime cancer risk is 0.12 ug/L. This is a slight decrease from the current New Jersey HBMCL of 0.15 ug/L. The recommended slope factor is based on cancer mortality rather than cancer incidence. A slope factor based on cancer incidence would be approximately 60% more stringent than one based on mortality, since the incidence rate for leukemia is approximately 60% higher than mortality due to leukemia (Burger et al., 2000; Ries et al., 2006). Thus, the recommended slope factor is considered to be sufficiently protective, but not unreasonably conservative.

General Background

An extensive literature, reviewed in the original Health-based MCL Support Document (NJDWQI, 1987), reports a strong, consistent association between occupational benzene inhalation exposure and both hematotoxicity (bone marrow depression) and leukemia mortality. Of the many types of hematological neoplasms that have been linked to benzene exposure, acute non-lymphocytic leukemia (ANLL), primarily acute myeloid leukemia, has been most consistently linked. Since the original NJDWQI (1987) assessment, there have been additional occupational cohort studies and numerous laboratory animal and *in vitro* mechanistic studies of carcinogenesis, all of which support the original designation of benzene as a "known human carcinogen". The laboratory studies are well summarized by ATSDR (1998).

The current New Jersey cancer slope factor is 0.23 $(mg/kg/day)^{-1}$. It is based on linear modeling of grouped inhalation exposure (as parts per million, ppm, or the equivalent micrograms per cubic meter of air, ug/m^3) and the risk of leukemia mortality in pooled data from workers at the Pliofilm rubber hydrochloride facilities (Rinsky et al., 1981) and two chemical worker cohorts (Ott et al., 1978; Wong et al., 1983). The Crump and Allen (1984) exposure assessment was used to assign exposure in the Pliofilm cohort. The drinking water Health-based MCL, using this slope factor at a one-in-one-million lifetime cancer risk and the default exposure factors of 70 kg adult body weight and 2 L daily adult tap water consumption, is 0.15 ug/L.

Many risk assessments have been developed based on the Pliofilm Cohort, using various workplace exposure matrices and mathematical models, especially those based on workers directly involved with or close to processes involving benzene ("wetside"). These are reviewed in more detail below. The original epidemiological analyses focused on standardized mortality ratios (reviewed in NJDWQI, 1987), while the current analyses use relative rate ratios, as in Table 2. Rinsky et al. (1987) observed standardized mortality ratios (SMRs, shown as ratios rather than as percent) for leukemia which ranged from a nonsignificant 1.09 (2 observed, 1.83 expected) at cumulative exposures under 40 ppm-years to a statistically significant SMR of 23 (5 observed, 0.21 expected; $p < 0.05$) at 200 ppm-years or more of exposure. An update through 1996 (Rinsky et al., 2002) showed that for exposed white males, the SMR for total leukemia, based on 15 deaths, declined from 3.4 (Rinsky et al., 1987) to 2.6 (both statistically significant) because no new deaths were observed. Silver et al. (2002) documented the observed early peak of leukemia and the subsequent decline in mortality. For the highest category of exposure, >400 ppm-years, the SMR was 24 (3 cases), while the SMR for the lowest category, <31 ppm-years was 1.45 (not statistically significant, NS). A linear approach to the Cox proportional hazards model, based on all exposed workers, yielded a mortality risk of .023 - .025 per ppm-yr and 0.076 per ppm for the follow-up through 1996 (Rinsky et al., 2002).

In the recent USEPA (1998, 2000) assessment, the Pliofilm (rubber hydrochloride) workers studied by the National Institute of Occupational Science and Health (Rinsky et al., 1981, 1987) were deemed to provide the best published set of data to date for evaluating human cancer risks from exposure to benzene. Compared to the published studies of Ott et al. (1978), Bond et al. (1986), and Wong (1987), this cohort study has better exposure assessment and fewer reported co-exposures to other potentially carcinogenic substances in the workplace that might confound risk analysis. Other studies (Jakobsson et al., 1993; Fu et al., 1996; Schnatter et al., 1996; Lynge et al., 1997; Ireland et al., 1997) were also published since the earlier New Jersey assessment (NJDWQI, 1987), but were not as complete in their exposure assessments.

A range of values for the slope factor was developed (USEPA, 1998), based upon the linear extrapolation by Crump (1994) of two of the three competing Pliofilm exposure assessments (Crump and Allen, 1984; Paustenbach et al., 1992) using competing workplace exposure matrices. The slope factor range (adjusted for continuous exposure between ages 20 and 65) is $0.014 – 0.055$ $(mg/kg/day)^{-1}$, and the health-based drinking

Table 2. Summary information and relative risk estimates for leukemia mortality among white male Pliofilm workers[1] by exposure category

Exposure Matrix	Categories of cumulative exposure (ppm-years)	Mean	Person-years	Cases	Expected number of cases	Relative risk	95 % CI
'WETSIDE' WORKERS (N=1212)							
Rinsky	0-39	15.9	29648	5	2.228	2.24	0.73-5.24
	40-199	93.3	7209	4	0.677	5.91	1.61-15.13
	200-399	260.8	2476	2	0.232	8.64	1.03-31.12
	≥ 400	530.1	1059	3	0.086	34.76	7.21-101.98
Crump	0-39	15.5	24907	4	1.842	2.17	0.59-5.56
	40-199	108.0	9358	3	0.801	3.74	0.77-10.95
	200-399	279.0	3100	4	0.280	14.29	3.89-36.57
	≥ 400	808.4	3026	3	0.320	9.39	1.94-27.41
Paustenbach	0-39	16.7	20354	3	1.405	2.14	0.44-6.24
	40-199	108.9	9827	2	0.816	2.45	0.29-8.85
	200-399	290.9	3587	2	0.349	5.73	0.69-20.69
	≥ 400	745.3	6623	7	0.673	10.41	4.18-21.43
'WETSIDE' AND 'DRYSIDE' WORKERS (N=1717)							
Rinsky	0-39	13.3	41688	5	2.874	1.74	0.56-4.06
	40-199	92.9	7256	4	0.699	5.72	1.56-14.65
	200-399	260.8	2476	2	0.232	8.64	1.03-31.12
	≥ 400	530.1	1059	3	0.086	34.76	7.21-101.98
Crump	0-39	14.3	36261	4	2.441	1.64	0.45-4.20
	40-199	108.0	10041	3	0.847	3.54	0.73-10.35
	200-399	276.9	3151	4	0.283	14.11	3.85-36.18
	≥ 400	808.4	3026	3	0.320	9.39	1.94-27.41
Paustenbach	0-39	16.0	28461	3	1.810	1.66	0.34-4.85
	40-199	108.6	12072	2	0.938	2.13	0.26-7.70
	200-399	293.4	4042	2	0.373	5.36	0.64-19.36
	≥ 400	747.1	7905	7	0.770	9.09	3.65-18.73

[1] Non-black male 'wetside' workers (n=1212); person-years of risk from 1940 to 1987. Data from the National Institute of Occupational Science and Health analyzed by Office of Environmental Health Hazards, California Environmental Protection Agency.

water levels based on them, at the one-in-one-million cancer risk level and the assumptions given above, are 0.6 -2.0 µg/L. The high end of the slope factor range is based on a linear-multiplicative model using the Crump and Allen (1984) exposure assessment. However, a third exposure assessment (Rinsky et al., 1981) was not considered by USEPA in developing the range because Crump (1994) did not include that assessment. Crump (1994) reasoned that Cody et al. (1993) found that hematotoxicity in a subset of Pliofilm workers was correlated with exposure to benzene in the 1945-1948 period using the Crump and Allen (1984), but not the Rinsky et al. (1981) exposure matrix. However, more recent work found otherwise, as discussed in more detail in the next section.

Another major set of studies, completed since the current New Jersey slope factor was developed (NJDWQI, 1987), is the Chinese Worker Cohort (Dosemeci et al., 1994; Hayes et al., 1996, 1997, 2001; Yin et al., 1996), which provides a large data set in which exposures remained relatively constant for a large portion of the cohort. The National Cancer Institute, in cooperation with the Chinese Academy of Preventive Medicine, has been conducting a comprehensive study of 74,828 benzene-exposed workers employed from 1972 to 1987 in 672 factories in 12 cities of China. A comparison group of workers consisting of 35,805 employees was assembled from non-benzene-exposed units in 69 of the above factories and 40 factories elsewhere. A variety of job categories were studied in the painting, printing, footwear, rubber, and chemical industries. Workers in both groups were followed for an average of slightly less than 12 years. Less than 0.3% was lost to follow-up in both the exposed and the unexposed group. Work histories were utilized to link benzene exposure data to individual time-specific estimates for each worker (Dosemeci et al., 1994).

This study, one of the largest of its type ever undertaken, enabled its authors to claim detection of significantly elevated risks at lower levels of exposure than in previous studies. Their findings suggested that workers exposed to benzene at average levels of less than 10 ppm are subject to an increased risk of hematologic neoplasms (risk ratio, RR = 2.2, 95% C.I .= 1.1-4.2). A combination of ANLL and myelodysplastic syndrome (MDS) produced a relative risk of 3.2 (95% C. I. = 1.0-10.1). (MDS may be a precursor to ANLL and has not been systematically distinguished from ANLL in past epidemiological studies.) For exposure to a sustained concentration of 25 ppm benzene, the relative risk of ANLL and MDS increased to 7.1 (95% C.I. = 2.1- 23.7). These risks were associated with more recent exposure to benzene (less than 10 years). The risk of leukemias other than ANLL, including chronic myeloid and monocytic leukemia, was also elevated (RR = 2.0), although not significantly so. Additionally, the risk of non-Hodgkin's lymphoma was significantly elevated (RR = 4.2 with 95% C.I. = 1.1-15.9) for those with a sustained exposure to benzene that occurred 10 years prior to diagnosis.

However, the Chinese cohort suffers from some uncertainties and potential weaknesses, including concurrent exposures to many other chemicals, possible effects of lifestyle factors, and the fact that only 38% of the exposure estimates were based upon actual measurements of benzene concentrations (Dosemeci et al., 1994). During the earliest period, only 3% of the exposure estimates were based on actual measurements. Nevertheless, it is notable that the exposure estimates were indirectly validated by a study of hematological effects, such as low white blood cell and platelet levels (Dosemeci et al., 1996; Lan et al., 2004; Lan et al., 2006). The effects showed a clear dose-response relationship down to at least the 1 ppm exposure level.

Exposure Assessment Issues in the Pliofilm Cohort

The most important determinants of the magnitude of the cancer slope are the choice of the estimates of the exposures (primarily through the inhalation pathway) to which workers were subjected, the number of observed and expected cancers, and the choice of extrapolation model used to estimate risk at lower, environmentally relevant levels of exposure.

Three separate estimates of exposure by job category in the Pliofilm Cohort are available: (1) the Rinsky exposure matrix (Rinsky et al., 1981) which was developed for the National Institute of Occupational Safety and Health (NIOSH); (2) the Crump exposure matrix (Crump and Allen, 1984) which was developed for the Occupational Safety and Health Administration, and (3) the Paustenbach exposure matrix (Paustenbach et al., 1992). The average estimated exposure in the cohort was lowest for the Rinsky et al. exposure matrix, approximately half of that using the Crump and Allen exposure matrix, which was approximately half again as much using the Paustenbach et al. matrix (OEHHA, 2001). Paustenbach et al. (1992) attempted to improve on the Rinsky and Crump exposure matrices by including additional information such as extended work weeks, dermal exposure, and several other factors. However, the exposure estimates of Paustenbach et al. (1992) are likely to be unreasonably high and the methods used to generate them have been criticized (Utterback and Rinsky, 1995). Those authors explained that the exposure estimates of Paustenbach et al. (1992) were based upon worst-case assumptions and selected information, which was improperly cited, to inflate estimates of exposure and produce risk estimates that were incorrect by an order of magnitude. The Crump matrix adjusts the exposures when measurements are scarce by relating them to reductions in the Threshold Limit Values developed by the American Conference of Governmental Industrial Hygienists over time. However, Utterback and Rinsky (1995) noted that available information suggests that overhead ventilation systems were in place before 1942, that efficient benzene recovery systems were in place by the 1940s as economy measures, and that there is no evidence of significant improvements in these control systems through 1975 at which point the process was terminated. Williams and Paustenbach (2003) reviewed the exposure assessment data and the competing approaches, using a Monte Carlo statistical simulation method. Their conclusions indicated some validity in each of the three exposure assessment approaches, depending on job category, and that dermal exposure accounted for only minor exposure in some job categories and up to approximately 5 – 15% (and higher during 1975-1976) for others, increasing as installation of ventilation decreased inhalation exposure.

Comparison of the different exposure assessment matrices to hematopoietic toxicity (anemias) provides a validation of the Rinsky approach. As noted above, Cody et al. (1993) found that red and white blood cell counts in a subset of Pliofilm workers were correlated with exposure to benzene in the 1945-1948 period using the Crump and Allen (1984), but not the Rinsky exposure matrix. More recently Ward et al (1996) found that the Rinsky exposure matrix was indeed correlated with hematotoxicity by using a more appropriate analytical method. They used a nested case-control design utilizing the entire database while controlling for temporal trends in pre-employment hematotoxicity data. Temporal trends had a significant effect because pre-employment blood counts were increasing after World War II, perhaps because of improved nutrition. This increase acted as a confounder because it was correlated with the decreasing exposure estimates found in the Crump and Allen (1984) exposure matrix.

Based on two of these three exposure matrices, USEPA (2000) developed a range of slope factors. USEPA (2000) is quoted below:

The two most important determinants of the magnitude of the unit risk number are the choice of extrapolation model to be used to estimate risk at environmental levels of exposure and the choice of the exposure estimates to which the Pliofilm workers (Rinsky et al., 1981, 1987) were subjected. Crump (1992[not cited here], 1994) presented 96 unit risk calculation analyses by considering different combinations of the following factors: (1) different disease endpoints, (2) additive or multiplicative models, (3) linear/nonlinear exposure-response relationships, (4) two different sets of exposure measurements (Crump and Allen [1984] vs. exposure estimates by Paustenbach et al. [1993]) and (5) cumulative or weighted exposure measurements. The unit risk estimates range from 8.6 x 10^{-5} to 2.5 x 10^{-2} at 1 ppm (3200 µg/m^3) of benzene air concentration (Crump, 1994).

When a linear model was employed, the choice of cancer unit risk estimates narrows to a range between 7.1 x 10^{-3} and 2.5 x 10^{-2} at 1 ppm (2.2 x 10^{-6} to 7.8 x 10^{-6} at 1 µg/m^3 of benzene in air), depending on which exposure measurements were used, i.e., Crump and Allen (1984) or Paustenbach et al. (1993). The choice of these limits was dictated by the following considerations: (1) use of the (1981, 1987) Rinsky cohort, (2) use of Crump's (1994) analysis of the Crump and Allen (1984) and the Paustenbach (1992, 1993) exposure measurements. The range of risks nearly includes the 1985 EPA risk estimate of 2.6 x 10^{-2} at 1 ppm (8.1 x 10^{-6} at 1 µg/m^3).

The risk range of 7.1 x 10^{-3} to 2.5 x 10^{-2} per ppm in air (2.2 x 10^{-6} to 7.8 x 10^{-6} at 1 µg/m^3) is equivalent to 1.6 x 10^{-2} to 5.5 x 10^{-2} $(mg/kg/day)^{-1}$ by ingestion (see an example of the conversion calculation in the Appendix). These risk estimates included an adjustment to continuous exposure over a lifetime.

The USEPA rationale for not including the Rinsky exposure assessment matrix is not stated, other than that Crump (1994) chose not to include it. There is no scientific basis upon which to ignore the Rinsky exposure assessment, and it would have resulted in a higher upper bound of the cancer slope range.

Investigations by Crump (1994, 1996) indicated that linear models fit the Pliofilm data better than non-linear ones. There is insufficient information to determine the shape of the dose-response curve at environmentally relevant levels of exposure, in part because the mechanisms by which exposure to benzene and its metabolites exert their toxic and carcinogenic effects remain uncertain. Therefore, the use of a linear extrapolation model as a default approach is appropriate.

The USEPA Guidelines for Carcinogen Risk Assessment (2005) are silent on the issue of additive (absolute risk) versus multiplicative (relative risk) risk models, but most risk assessments based on epidemiological data use relative risk. The relative risk model was preferred by the BEIR V and BEIR VII committees for assessing radiation-induced leukemia (NRC, 1990, 2006), and has been more often used in setting regulatory standards than the absolute risk model. The Crump (1994) slope factors based on the linear multiplicative model alone were larger than the slope factors based on the linear additive model.

The 95% UCL of the central (maximum likelihood) cancer slope estimate is not presented in the IRIS website because it was not utilized by Crump (1994) to account for variability in susceptibility in the general population. However, the 95 percent confidence intervals were

computed by USEPA (1998). The upper bound of the linear multiplicative model based on Crump and Allen (1984) exposure assessment was 0.13 per ppm (0.28 per mg/kg/day). At the time when the IRIS (2000) benzene slope factor was developed, it was not necessarily USEPA policy to use the 95% UCL for human studies. However, the USEPA Guidelines for Carcinogen Risk Assessment (2005) suggest using the 95 % UCL in the development of cancer slope factors. There is a substantial literature on genetic susceptibility factors for benzene (Morgan and Smith, 2002). For example, a 7.6-fold difference was observed in relative risk of benzene-induced hematotoxicity among people with different phenotypes of the metabolic enzymes CYP2E1 and NQO1 (Rothman et al., 1997). Consideration of these uncertainties supports the use of the 95% UCL. Additionally, the current New Jersey slope factor for benzene (NJDWQI, 1987) is based on the 95% UCL estimate.

Cancer slope factors developed by California EPA (OEHHA, 2001; Table 28) from other cohorts (Fu et al., 1996; Lynge et al., 1997; Ott et al., 1978; Wong, 1987; Jakobsson et al., 1993; Ireland et al., 1996) range from minimally below to well above the USEPA IRIS (2000) range of slope factors of 0.014 to 0.055 $(mg/kg/day)^{-1}$. The 95% UCLs of these estimates are 0.0088, 0.070, 0.086, 0.13, 0.32 and 0.53 $(mg/kg/day)^{-1}$, respectively.

Additionally, the range of the 95% UCL of the cancer potency estimates developed by California EPA from the animal studies employing oral exposures, 0.04 to 0.2 $(mg/kg/day)^{-1}$ (OEHHA, 2001, Table 29), includes the upper end of the USEPA IRIS (2000) range of 0.014 to 0.055 $(mg/kg/day)^{-1}$.

Risk Assessment Conclusions

Several different approaches to the analysis of existing epidemiology data converge on the choice of a cancer slope factor that is somewhat more stringent than the current New Jersey cancer slope factor, resulting in a health-based drinking water concentration which is below the current HBMCL. (The details of converting inhalation dose to ingestion dose are discussed in the next section and the Appendix, but the results are shown here.)

A set of linear relative risk models, both additive and multiplicative (Crump, 1994) was employed by USEPA (1998, 2000) to analyze the complete set of Pliofilm Cohort data (with the full range of exposures and assessments). The 10^{-6} lifetime cancer risk estimates ranged between 7.1×10^{-3} and 2.5×10^{-2} per ppm (2.2×10^{-6} to 7.8×10^{-6} at 1 $\mu g/m^3$ of benzene in air), based on the Crump and Allen (1984) and Paustenbach et al., (1992) exposure assessments. The earlier USEPA (1985) risk estimate of 2.6×10^{-2} at 1 ppm (8.1×10^{-6} at 1 $\mu g/m^3$) is only slightly higher than the upper end of the USEPA (2000) range in IRIS. The range is equivalent to 0.014 – 0.055 per mg/kg/day, which corresponds to a range of drinking water unit risks of 4.4×10^{-7} to 1.6×10^{-6} per µg/L. The resulting range of drinking water concentrations at the 10^{-6} risk level is 0.6 – 2.2 ug/L (Appendix).

However, either inclusion of the more conservative Rinsky et al. (1981, 1987) exposure assessment or use of the upper bound of the 95 percent confidence interval of the risk estimate instead of the maximum likelihood estimate would have increased the range of the cancer slope values and thus resulted in lower health-based drinking water concentrations.

As summarized in Table 3, several approaches for estimation of the drinking water concentration resulting in 10^{-6} lifetime risk converge on a value of approximately 0.1 ug/L.

1) The Crump (1986) report to NJDEP included an analysis of the original follow-up of the Pliofilm cohort (Rinsky et al., 1981) by itself, as well as the pooled data from the two chemical worker cohorts and the Pliofilm cohort. Crump used the Crump and Allen (1984) exposure assessment and generated 95% UCLs of linear slopes. However, an adjustment for years of occupational exposure (age 20 through age 65 = 45 years) to lifetime exposure (70 years) was excluded from the original HBMCL calculation (NJDWQI, 1987). Including that correction in the original calculation (row 1), which used the pooled data, would have resulted in an HBMCL of 0.1 ug/L (row 2). The Pliofilm cohort alone yielded 0.16 per mg/kg/day for the 95% UCL of the cancer slope factor or 0.25 per mg/kg/day when adjusted as above for years of occupational exposure versus lifetime exposure, corresponding to a drinking water concentration of **0.14 ug/L** (row 3). Unfortunately, the Rinsky et al. (1981) exposure assessment was not examined by Crump.

2) The USEPA (1998) IRIS support document utilizes an analysis by Crump (1994) of the Rinsky et al. (1987) update of the Pliofilm cohort, which he had adjusted for lifetime exposure (rows 4 and 5). The 95% UCL of the linear multiplicative slope (0.28 per mg/kg/day) using the Crump and Allen (1984) exposure assessment was calculated, but the only the central (maximum likelihood) estimate was used as the upper bound of the cancer slope factor range currently presented in IRIS (USEPA, 2000). Use of the 95% UCL yields a drinking water concentration of **0.12 ug/L** (row 6).

3) Though the Rinsky et al. (1981) exposure assessment was not included in Crump (1994), it can be estimated by increasing the slope estimate by a factor of 2 (row 7), which reflects the observation that the overall exposure estimate by Rinsky et al. (1981) was approximately half that of Crump and Allen (1984). Including an estimate of the 95% UCL (by assuming it was a factor of 1.5 – 2.0 times the central estimate, based on the results given by Rinsky et al., 2002) results in a cancer slope factor of 0.16 – 0.22 per mg/kg/day, corresponding to a drinking water concentration of **0.15 – 0.2 ug/L** (row 8)**.**

In addition, the recent report by Rinsky et al. (2002) on the follow-up of the Pliofilm cohort through 1996 found that the central estimate of the cancer slope factor was 0.076 per ppm, equivalent to 0.17 per mg/kg/d orally (row 9). They used a linear multiplicative model. Though a 95% UCL was not included in the report, there was sufficient information for approximation, assuming that the slope factor is adequately characterized by a Wald chi-square statistic. The estimated 95% UCL is 0.15 per ppm (0.33 per mg/kg/d), which yields a drinking water concentration of 0.12 ug/L (row 10). Adjustment from occupational exposure to lifetime exposure would increase the cancer slope and lower the drinking water concentration by a factor of 4.7 (days per year adjustment was already included) to 0.025 ug/L (row 11).

All four approaches support an HBMCL that is below the range of drinking water concentrations at the 10^{-6} risk level presented in the IRIS database (USEPA, 2000). The drinking water concentrations based on these approaches are closer to the current New Jersey HBMCL of 0.15 ug/L. The second approach (row 6) is the best supported since the use of a 95% UCL of the cancer slope factor is suggested by the USEPA Guidelines for Carcinogen Risk Assessment (2005), and since the IRIS Toxicological Review (USEPA, 1998), which is the source of the 95% UCL, underwent extensive review.

The weight of evidence discussed above supports a cancer slope factor of 0.28 per mg/kg/day,

corresponding to a drinking water concentration based on a one-in-one million lifetime risk of 0.12 ug/L (Table 3, row 6). The more stringent result obtained from the most recent update of the Pliofilm cohort (Rinsky et al., 2002) for lifetime exposure (row 11) supports an even lower drinking water concentration, but is not by itself sufficient to recommend an HBMCL below 0.1 ug/L. It should be noted that adjustment of calculations in Table 3 for cancer incidence in the general population (Burger et al., 2005; Ries et al., 2006) instead of mortality (the metric used for the Pliofilm cohort and most occupational studies) would result in slope factors approximately 60% more stringent than those based on mortality. The resulting drinking water concentration in row 6 would be about 0.08 ug/L (0.12 ug/L / 1.6).

Table 3. Cancer Slope Factors and Health-based Drinking Water Concentrations for Benzene Exposures Based on Different Approaches

#	Assessment	Cohort	Source of Piofilm Exposure Assessment	95% UCL or MLE[b]	Adjusted for 45/70 years?	Slope Factor $(mg/kg/day)^{-1}$	Drinking Water Concentration[c] (ug/L)	Notes
1	Current NJ HBMCL (NJDWQI, 1987)	Pooled Ott-Wong-Rinsky cohorts[a]	Crump and Allen (1984)	95% UCL	No	0.23	0.15	Based on Crump (1986) report to NJDEP
2	Current HBMCL adjusted for 45/70 years	Pooled Ott-Wong-Rinsky cohorts[a]	Crump and Allen (1984)	95% UCL	Yes	0.35	0.10	Based on Crump (1986) report to NJDEP
3	Same as #2 using only Rinsky (1981) cohort	Original Rinsky (1981) follow-up of Pliofilm cohort	Crump and Allen (1984)	95% UCL	Yes	0.25	0.14	Based on Crump (1986) report to NJDEP
4	USEPA IRIS (2000) Lower end of range	Rinsky (1987) update of Pliofilm cohort	Paustenbach et al. (1992)	MLE	Yes	0.015	2.2	Based on Crump (1994) analysis
5	USEPA IRIS (2000) Upper end of range	Rinsky (1987) update of Pliofilm cohort	Crump and Allen (1984)	MLE	Yes	0.055	0.6	Based on Crump (1994) analysis
6	**USEPA (1998) (IRIS Support Document)**	**Rinsky (1987) update of Pliofilm cohort**	**Crump and Allen (1984)**	**95% UCL**	**Yes**	**0.28**	**0.12**	**Based on Crump (1994) analysis**
7	Rinsky (1981) exposure assessment (estimated as 2x slope factor from #5)	Rinsky (1987) update of Pliofilm cohort	Rinsky et al. (1981)	MLE	Yes	0.11	0.3	Estimate based on extrapolation from Crump (1994) analysis
8	Same as #7, using estimated 95% UCL (based on Rinsky et al., 2002)	Rinsky (1987) update of Pliofilm cohort	Rinsky et al. (1981)	95% UCL	Yes	0.16-0.22	0.15-0.2	Estimate based on extrapolation from Crump (1994) and Rinky et al. (2002)
9	Rinsky et al. (2002)	Rinsky et al. (2002)	Rinsky et al. (1981)	MLE	No	0.17	0.2	Update through 1996
10	Rinsky et al. (2002)	Rinsky et al. (2002)	Rinsky et al. (1981)	95% UCL	No	0.33	0.12	Update through 1996
11	Rinsky et al. (2002) adjusted for 45/70 years & 8/24 hours	Rinsky et al. (2002)	Rinsky et al. (1981)	95% UCL	Yes	1.7	0.025	Update through 1996

Row 6 (in bold) represents the recommended approach.

[a] Ott (1978) and Wong (1983) are chemical worker cohorts; Rinsky (1981) is the original follow-up of Pliofilm cohort

[b] 95% upper confidence level (95% UCL), maximum likelihood estimate (MLE) of the slope factor (i.e., the central estimate)

[c] Drinking water concentration at 10^{-6} risk level

NOTE: All assessments based on linear multiplicative model.

Ingestion Cancer Risk

No relevant data exist in the published literature for the oral absorption of benzene in humans. However, route-to-route extrapolation from the inhalation route to the oral route is justified because similar toxic effects are observed in animals through the oral and inhalation route of exposure to benzene (ATSDR, 1998), and because experimental animal data demonstrate that benzene is metabolized to the same products whether it is inhaled or ingested. Nevertheless, the nature of the distribution of benzene metabolites to the bone marrow is not well understood. More than one metabolite may be involved in the induction of leukemia in animals and humans (Smith, 1996).

USEPA (1999) wrote:
A scientifically rigorous method for route-to-route extrapolation involves the development of a pharmacokinetic model to predict the concentration of the ultimate carcinogen in bone marrow (the target tissue for benzene's carcinogenic effects) under a variety of different human exposure scenarios. There are currently several inadequacies in the scientific database required for this approach. No pharmacokinetic models that include metabolism and distribution to the bone marrow are available that have been adequately validated for humans (Smith and Fanning, 1997). A major difficulty is that the particular chemical species responsible for the induction of leukemia in benzene-exposed people and animals is not known with certainty; leukemogenesis may well involve more than one metabolite or combination of metabolites (Smith, 1996).

Most experts agree that benzene metabolites, or by-products of their formation, are responsible for benzene leukemogenesis. This suggests that extrapolation between routes of exposure could be based on a dose defined as the total quantity of benzene metabolized in the body after uptake of equivalent amounts, a somewhat simpler metric than delivered dose of the unknown ultimate carcinogenic compound(s). However, the kinetics of metabolite formation and clearance after inhalation, ingestion, or dermal exposure of benzene are not known for humans. The many uncertainties involved in using animal-based models to predict dosimetry for humans may preclude a risk assessment application for PBPK models dependent on animal-derived data. Using a PBPK model developed primarily with high-dose animal data is not likely to improve the accuracy of risk estimates based on human data.

*Therefore, a **simple approach to route-to-route extrapolation** is perhaps the most scientifically defensible approach at this time. This report summarizes published literature addressing the absorption of benzene after inhalation exposure in humans and laboratory animals, and after oral exposure to animals. No relevant data were located for absorption of benzene after ingestion in humans.*

Inhalation absorption of benzene, like most VOCs, is approximately 50%, while oral absorption is close to 100% (U.S. EPA, 1999), and these assumptions were used in developing the current New Jersey slope factor for benzene (NJDWQI, 1987). While the human data demonstrate good agreement regarding inhalation, indicating that approximately one-half of inhaled benzene is absorbed into the bloodstream at exposure concentrations between 1 and 100 ppm, considerable inter-individual variability was observed in all studies that reported on multiple subjects. Many factors, including activity level, pulmonary health, and metabolic clearance, are likely to influence the amount of benzene actually taken up in a diverse population exposed by the inhalation route. Characterization of the extent of variability is limited. Complete

gastrointestinal absorption occurs in the rat and mouse study as reported by Sabourin et al (1987). However, the simple absorption ratio approach taken for route-to-route extrapolation here may not account for differences in disposition of benzene after it crosses the pulmonary or gastrointestinal barrier. First-pass metabolism of ingested benzene may have significant effects on the dose of benzene metabolites that reaches the target bone marrow cells (Sabourin et al., 1989). Leukemogenic metabolites may be produced more efficiently after ingestion, but, on the other hand, rapid clearance of benzene and metabolites after ingestion may be a mitigating factor. The data are inadequate to address these questions for humans at this time. Thus, the assumption of 50% inhalation absorption relative to oral absorption, discussed above, is used as the basis for the route-to-route extrapolation.

The conversion of inhalation dose to oral dose is presented in the Appendix.

Conclusions and Recommendation

Based on several lines of evidence, it is recommended that the New Jersey cancer slope factor for benzene be based on the upper bound of the 95 percent confidence interval (USEPA, 1998) of the linear-multiplicative model developed by Crump (1994) using the Crump and Allen (1984) exposure assessment of the Pliofilm cohort. The central estimate of the slope factor is 0.055 per mg/kg/day and the upper 95 percent confidence limit is 0.28 per mg/kg/day (Table 3, row 6).

The daily dose of benzene resulting in a one-in-one-million lifetime cancer risk is:

10^{-6} / 0.28 (mg/kg/day)$^{-1}$ = 3.5 x 10^{-6} mg/kg/day

The Health-based MCL for benzene using this factor is:

$$\frac{3.5 \times 10^{-6} \text{ mg/kg/day} \times 70 \text{ kg}}{2 \text{ L/day}} = 1.2 \times 10^{-4} \text{ mg/L, or } 0.12 \text{ ug/L.}$$

Where: 70 kg is the assumed body weight of an adult and 2 L day is the assumed daily water consumption of an adult.

It should be noted that the recommended cancer slope factor and Health-based MCL are derived from data on leukemia mortality, rather than leukemia incidence. Analysis based on incidence would result in an approximately 60% higher estimate of risk, providing supporting evidence for the recommendation of a Health-based MCL which is below the existing one developed by NJDWQI (1987).

Thus, a Health-based Maximum Contaminant Level of 0.12 ug/L is recommended. This represents a slight decrease from the current New Jersey HBMCL of 0.15 ug/L.

Appendix: Route-to-route extrapolation

To derive an oral equivalent, the inhalation unit (10^{-6}) risk range (per mg/m^3) is first converted to the oral slope factor by assuming a standard air intake of 20 m^3/day, a standard body weight of 70 kg for an adult human, and 50% absorption via inhalation. The drinking water unit risk is then calculated from the oral slope factor assuming a drinking water intake of 2 L/day.

The daily dose from 1 mg/m^3 is:

1 mg/m^3 x 20 m^3/day x 0.5 x (1/70) kg = 0.143 mg/kg/day

The risk estimate per mg/m^3 is then divided by this dose, to generate an oral slope factor in units of inverse dose. For example, for the highest USEPA cancer slope factor this is:

$$7.8 \times 10^{-3} \text{ per mg/m}^3 \ / \ 0.143 \text{ mg/kg/day per mg/m}^3$$
$$= 5.5 \times 10^{-2} \text{ (mg/kg/day)}^{-1} \text{ or } 0.055 \text{ (mg/kg/day)}^{-1}$$

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Addendum to Health-Based MCL Support Document:
1,3-Dichlorobenzene

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August 7, 2006

Summary

The basis for the New Jersey Health-based MCL for 1,3-dichlorobenzene, which was developed in 1987, was reevaluated. The current Health-based MCL of 600 ug/L is based on toxicity studies of 1,2-dichlorobenzene, since no appropriate information for 1,3-dichlorobenzene was available when the Health-based MCL was developed.

A subchronic study of 1,3-dichlorobenzene given to rats by gavage is now available (McCauley, 1995). Effects occurred at the lowest dose used in this study, 9 mg/kg/day. A Reference Dose based on this dose is 0.0009 mg/kg/day. This Reference Dose includes an uncertainty factor of 10,000 appropriate for use with a Lowest Observed Adverse Effect Level in a subchronic study.

The Health-based MCL derived from this Reference Dose is 6.3 ug/L. This represents a 100-fold decrease from the current Health-based MCL for 1,3-dichlorobenzene.

Current New Jersey and USEPA Assessments

Currently, both the New Jersey Health-based MCL (NJDWQI, 1987) and the USEPA Lifetime Health Advisory (USEPA, 1987) for 1,3-dichlorobenzene are based upon toxicity studies on 1,2-dichlorobenzene, as no appropriate toxicity data on 1,2-dichlorobenzene were available until after these values were developed. Both USEPA and New Jersey based their assessments on the chronic NTP (1985) study of 1,2-dichlorobenzene in rats, and the New Jersey Health-based MCL and the USEPA Lifetime Health Advisory are identical, 600 ug/L. The Reference Dose upon which the New Jersey MCL and the USEPA Health Advisory are based is 0.085 mg/kg/day, rounded to 0.09 mg/kg/day by USEPA. USEPA has not developed an MCL for 1,3-dichlorobenzene.

Currently the USEPA IRIS data base does not provide a Reference Dose for 1,3-dichlorobenzene, and classifies it as Group D, not classifiable as to human carcinogenicity.

Results of Literature Review

Ten-day and 90-day studies of 1,3-dichlorobenzene given to rats by corn oil gavage were conducted by McCauley et al. (1995). The results of the 90 day studies are reported in detail below, as they are most relevant for chronic drinking water risk assessment.

Groups of 10 male and female Sprague-Dawley rats were dosed with 0, 9, 37, 147, or 588 mg/kg/day 1,3-dichlorobenzene in corn oil, with a dosing volume of 0.1 mg/100 g body weight for 90 consecutive days.

Water consumption (normalized for body weight) was significantly increased in males at 147 mg/kg/day and in both sexes at 588 mg/kg/day. Food consumption was increased in both sexes at 588 mg/kg/day, while body weight was significantly decreased in both sexes in this dose group.

Increased liver to body weight ratios were seen in males and females at 147 and 588 mg/kg/day. Increased kidney weight ratios were seen in males at 147 mg/kg/day and males and females at 588 mg/kg/day. Males at 588 mg/kg/day also had increased brain and testes weight ratios, while females at 147 mg/kg/day had decreased brain weight ratios. No changes in organ weight ratios were seen in the two lower dose groups.

Hematology studies revealed that the white blood cell count of females and the red blood cell count of males were increased in the highest dose group, while the white blood cell count of males was increased at 147 mg/kg/day.

Clinical chemistry studies showed that cholesterol levels were increased in males at 9, 37, and 147 mg/kg/day and in females at 37, 147, and 588 mg/kg/day. Calcium levels were increased in males and females at 37, 147, and 588 mg/kg/day. Lactate dehydrogenase (LDH) was decreased in males in all dose groups. Aspartate aminotransferase (AST) was increased in males in the low and high dose groups. Alkaline phosphatase was increased in females at 37 mg/kg/day, while AST was increased in males at 147 mg/kg/day, and blood urea nitrogen (BUN) levels were decreased in both sexes at 588 mg/kg/day.

1,3-Dichlorobenzene caused histopathological changes in the thyroid and liver of both sexes and in the pars distalis of the pituitary in males. The colloid density of the thyroid follicles was decreased beyond the normal range in 8/10 males and 5/10 females at 9 mg/kg/day, in all males in the 37, 147, and 588 mg/kg/day groups, in 8/10 females at 37 and 157 mg/kg/day, and in 8/9 females at 588 mg/kg/day. These changes were seen in only 2/10 control males and 1/10 control females. The severity of the thyroid effect appeared to increase with dose.

In the liver, cytoplasmic alterations of the hepatocytes increased with dose as follows: controls – 1/10 males and 0/10 females; 9 mg/kg/day- 2/10 males and 0/10 females; 37 mg/kg/day- 1/10 males and 1/10 females; 147 mg/kg/day – 6/10 males and 1/10 females; and 588 mg/kg/day – 7/9 males and 7/9 females. The severity of this effect appeared greater in males in the higher dose groups. Necrotic foci of the hepatocytes were seen in 1/10 control males and no control females, in 2/10 males at 9 mg/kg/day, in 1/10 males at 37 mg/kg/day, in 2/10 males and 3/10 females at 147 mg/kg/day, and in 5/9 males and 5/9 females at 588 mg/kg/day. According to the authors, similar liver pathology, as well as increased liver and kidney weight, have also been reported from 1,2- and 1,4-dichlorobenzene.

Vacuolization of the pars distalis of the pituitary was seen only in males. This effect was seen in 2/10 controls, 6/10 at 9 mg/kg/day and 37 mg/kg/day, 10/10 at 147 mg/kg/day, and 7/7 at 588 mg/kg/day. The severity of this effect increased with dose. According to the authors, the pituitary changes were similar to castration cells seen in gonadectomized rats or aged rats with testicular atrophy, and were said to be a sensitive indicator of gonadal deficiency. Along with the increased cholesterol, it was said that these changes may indicate disruption of endocrine function, or toxicity to pituitary, hypothalamus, or other endocrine organs.

A No Observed Adverse Effect Level (NOAEL) was not established by this study, since effects including increased cholesterol, decreased LDH, and increased AST in males, as well as histopathological changes in the thyroid of males and females and in the pituitary of males were seen at the lowest dose level, 9 mg/kg/day. Therefore, the Lowest Observed Adverse Effect Level (LOAEL) in this study was 9 mg/kg/day.

Although studies in which dosing is via drinking water are preferable to gavage studies for drinking water risk assessment, no such study is available for 1,3-dichlorobenzene. Aside from the subchronic study of McCauley et al. (1995), toxicity data on 1,3-dichlorobenzene is very limited and is summarized by ATSDR (2004). A developmental toxicity study in Sprague-Dawley rats given 1,3-dichlorobenzene by gavage was reported only as an abstract by Ruddick et al. (1983). According to the abstract, rats were dosed with 50, 100, or 200 mg/kg/day on days 6-15 of gestation (controls not specified). No maternal or fetal toxicity or teratological effects were seen. The abstract did not include all relevant information on the study design and results.

Reference Dose Development

The subchronic rat study of McCauley et al. (1995) was judged appropriate as the basis for the Reference Dose for 1,3-dichlorobenzene. In this study, no LOAEL was identified and the NOAEL was 9 mg/kg/day. Statistically significant effects observed at this dose included histopathological changes in the thyroid in males and females, vacuolization of the pars distalis of the pituitary in males, and increased cholesterol and decreased LDH in males. (It should be noted that the toxicological significance of increased cholesterol in the absence of liver toxicity, or of decreased LDH, is not clear, and that these effects might not necessarily be considered adverse.)

To derive a Reference Dose from a LOAEL in a subchronic study, an uncertainty factor of 10,000 is used. This includes a factor of 10 for extrapolation from animals to humans, 10 for intraindividual variation, 10 for subchronic to chronic extrapolation, and 10 for extrapolation from a LOAEL to a NOAEL. Although this is the largest uncertainty factor used in Reference Dose development, an uncertainty factor of this magnitude appropriate in this case, because, in addition to the factors mentioned above, there are significant data gaps in the available toxicity information for 1,3-dichlorobenzene.

$$\frac{9 \text{ mg/kg/day}}{10{,}000} = 0.0009 \text{ mg/kg/day}$$

Health-based MCL Recommendation

The Health-based MCL for 1,3-dichlorobenzene is derived as follows, using default exposure assumptions:

$$\frac{0.0009 \text{ mg/kg/day} \times 70 \text{ kg} \times 0.2}{2 \text{ L/day}} = 0.0063 \text{ mg/L or } 6.3 \text{ ug/L}$$

Where:
0.0009 mg/kg/day = Reference Dose
70 kg = assumed body weight of an adult
0.2 = Relative Source Contribution from drinking water
2 L/day = assumed daily drinking water intake for an adult

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Addendum to Health-Based MCL Support Document:
1,4-Dichlorobenzene

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September 13, 2006

Summary

The basis for the New Jersey Health-based MCL for 1,4-dichlorobenzene was reevaluated. The current MCL in effect in New Jersey is the MCL promulgated by USEPA, 75 ug/L. The Health-based MCL previously developed by New Jersey in 1994 is 150 ug/L, which is higher than the federal MCL. States may not use MCLs less stringent than federal MCLs.

A chronic oral dog study (Naylor and Stout, 1996) has been conducted since the current New Jersey and USEPA Reference Doses were developed, and this study provides a more sensitive endpoint than the previously available studies. The No Observed Effect Level (NOAEL) in this study is 7 mg/kg/day. The Reference Dose based on this NOAEL is 0.0023 mg/kg/day, which includes an uncertainty factor of 100 appropriate for a NOAEL from a chronic study, an uncertainty factor of 3 for small number of animals and minimal duration of study, and an uncertainty factor of 10 for possible carcinogenic effects.

The Health-based MCL derived from this Reference Dose is 14 ug/L. This represents a 5-fold decrease from the MCL of 75 ug/L which is currently in effect in New Jersey.

Risk Assessment developed by New Jersey

The Reference Dose developed by New Jersey for 1,4-dichlorobenzene (NJDWQI, 1994) is based on the Lowest Observed Adverse Effect Level (LOAEL) of 300 mg/kg/day in a chronic oral study in B6C3F1 mice (NTP, 1987). At this dose, liver effects including increased hepatocellular degeneration, necrosis, and cell size alteration were observed in male and female mice. In the Reference Dose calculation, the dose was adjusted to account for exposure on 5 of 7 days per week.

New Jersey classifies 1,4-dichlorobenzene as a possible human carcinogen (NJDWQI, 1994), based on increased liver tumors seen in mice in the NTP (1987) bioassay, but a slope factor has not been derived.

The total uncertainty factor used in developing the Reference Dose was 10,000. This uncertainty factor includes an uncertainty factor of 1000 appropriate for use with a LOAEL in a chronic study, and an additional uncertainty factor of 10 to protect for possible carcinogenic effects for chemicals classified as possible human carcinogens for which no slope factor is available.

The Reference Dose developed by New Jersey, 0.021 mg/kg/day, results in a Health-based MCL of 150 ug/L, using standard assumptions of 2 L/day water consumption, 70 kg body weight, and 20% Relative Source Contribution factor. This Health-based MCL was not used as the basis for the New Jersey MCL for 1,4-dichlorobenzene, since the MCL developed by USEPA is more stringent than the one developed by New Jersey (see below).

USEPA Assessment

USEPA IRIS does not provide an oral Reference Dose or a carcinogenicity assessment for 1,4-

dichlorobenzene. However, the USEPA Office of Water has developed a Reference Dose which forms the health basis for its Maximum Contaminant Level Goal (equivalent to NJ Health-based MCL) and its Lifetime Health Advisory (USEPA, 1987a, b) of 75 ug/L.

USEPA classifies 1,4-dichlorobenzene as a possible human carcinogen, as does New Jersey. The USEPA Reference Dose is based on a No Observed Adverse Effect Level (NOAEL) of 150 mg/kg/day in a subchronic study in mice (NTP, 1987, 1986). An adjustment was made for exposure on 5 of 7 days. The uncertainty factor used was 1000, appropriate for use with a NOAEL in a subchronic study, with an additional uncertainty factor of 10 incorporated to account for possible carcinogenic effects, for a total uncertainty factor of 10,000. The Reference Dose (including the additional factor for possible carcinogenicity) is given by USEPA as 0.01 mg/kg/day. Without rounding, the actual value is calculated as 0.0107 mg/kg/day. Using this latter value with standard assumptions of 2 L/day water consumption, 70 kg body weight, and 20% Relative Source Contribution factor, a health-based drinking water value of 75 ug/L is derived.

The final MCL promulgated by USEPA is 75 ug/L, which is lower than the Health-based MCL of 150 ug/L developed by New Jersey. Since MCLs adopted by New Jersey or other states cannot be less stringent than federal MCLs, the MCL of 75 ug/L was adopted by New Jersey.

Results of Literature Review

A literature review was conducted to determine whether any relevant data had become available since the development of the New Jersey and USEPA Reference Doses. Two studies were located.

A two generation gavage study in which 1,4-DCB in olive oil was given to Sprague-Dawley rats at doses of 0, 30, 90, or 270 mg/kg/day was conducted by Bornatowicz et al. (1994). Groups of 24 rats were dosed prior to mating for 77 days in males and 14 days in females. Exposure was continued for 21 days during mating and during gestation for females. Groups of 24 pups of each sex were treated for 84 days prior to mating, for 30 days during mating, and during gestation and lactation for females, and their offspring were sacrificed at weaning at 21 days of age. Endpoints evaluated included maternal and pup body weight and food consumption, reproductive indices, gestation length, litter size, number of live and dead pups, postnatal survival, postnatal developmental milestones, and neurobehavioral effects. Necropsies were done on all adult animals and on pups culled from the study or dying during the first 4 days. Liver, kidney, and spleens of adult animals were weighed, and histopathology was done on some animals and on all lesions observed at necropsy. Effects on body weight of pups at birth and on mortality of pups during the first four days of life were seen at 90 mg/kg/day and above, as well as dry skin, tail constriction, and reduced percentage of pups with a positive draw-up reflex (in F2 generation). Other effects in pups were seen only at 270 mg/kg/day.

In adults, the relative liver weight was increased in F1 males at 90 mg/kg/day and above, while average body weight was reduced in males and females and other organ weight changes in males were seen at 270 mg/kg/day. No effects were observed at 30 mg/kg/day, and therefore this dose is considered to be the NOAEL.

A chronic oral dog study was completed in 1996 (Naylor and Stout, 1996). This study was conducted by Monsanto Company's Environmental Health Laboratories and was submitted to USEPA's Office of Prevention, Pesticides, and Toxic Substances. Although the study was not

published in a peer reviewed scientific journal, it was conducted under the USEPA Good Laboratory Practices principles, and was certified for Quality Assurance.

Groups of 5 male and 5 female beagle dogs were dosed five days per week for one year with 1,4-dichlorobenzene administered in gelatin capsules. The initial doses were 0, 10, 50, or 150 mg/kg/day. Due to toxic effects at the highest dose, the dose was adjusted to 100 mg/kg/day in the third week in males and to 75 mg/kg/day in both sexes during the sixth week. The dose levels after adjustment for dosing on five of seven days per week were 7 mg/kg/day, 36 mg/kg/day, and 54 mg/kg/day.

In this study, three dogs in the high dose group died before the dose level was reduced, and one control dog died during the third month of the study. No effects on body weight gain occurred except in the highest dose group before the dose was reduced.

Increased organ weight or organ/body weight ratios were seen in mid and high dose groups for adrenal gland in males and females, kidney in females, liver in males and females and thyroid gland in females.

Histopathological examination showed mild to moderately severe hepatocellular hypertrophy in all mid and high dose males and females, and in one low dose female (mild). Other liver lesions, including pigment deposition, bile duct hyperplasia, nodular hyperplasia, bile stasis, and hepatic portal inflammation were seen in one or more animals in the mid or high dose groups. Increased blood levels of several liver enzymes occurred in mid dose and high dose males and females, and other blood chemistry changes which may have been a result of liver toxicity were seen in high dose females and mid and high dose males.

In lungs, chronic active interstitial inflammation, pleural fibrosis, and/or pleural mesothelial proliferation was seen in some males in each dose group and some females in the mid and high dose groups. These lesions were not considered to be treatment related because they did not differ in severity with dose and because of the characteristics of the lesions.

Vacuolization of the kidney collecting duct epithelium was seen to some degree in most animals, both treated and control. A more severe vacuolization was seen in one high dose male, one low dose female, one mid dose female, and two high dose females. In the mid dose female and one high dose female, the kidneys were grossly discolored, and the kidney effects in these two animals were considered to be treatment-related.

Some hematological effects were seen in treated groups during the study. These were characterized as relatively mild and non-persistent. At 6 months, basophils were decreased in high dose females and platelets were increased in mid and high dose females. A mild anemia was seen in high dose males and females, but this was resolved by the end of the study. At the end of the study, numbers of large unstained cells were reduced in males and females, platelets were increased in high dose females, and mean cell volume was increased in mid dose males. Erythroid hyperplasia was seen in the bone marrow of females and increased hematopoiesis in both sexes. These effects may have been a compensatory response to the anemia which occurred earlier.

The NOAEL in this study was 7 mg/kg/day (the low dose), and the LOAEL was 36 mg/kg/day (the middle dose). The multifocal hepatocellular hypertrophy seen in one low dose female was

considered to be an adaptive response, rather than an adverse effect, and no statistically significant effects occurred in low dose males or females.

Reference Dose Development

The LOAEL of 36 mg/kg/day in the Naylor and Stout (1996) chronic dog study was lower than both the LOAEL of 300 mg/kg/day in the NTP (1986) chronic mouse study which forms the basis for the current New Jersey Reference Dose and the LOAEL of 90 mg/kg/day in the two-generation rat study (Bornatowicz et al., 1995). Therefore, the Naylor and Stout (1996) chronic dog study was chosen as the basis for the Reference Dose.

In the Naylor and Stout (1996) chronic dog study, the NOAEL was 7 mg/kg/day. In this study, effects on the liver, kidney, and blood were seen at the higher dose levels. For a NOAEL for a chronic study, an uncertainty factor of 100 is used, which includes a factor of 10 for extrapolation from animals to humans and a factor of 10 for intraindividual variation. An additional uncertainty factor of 3 is included in this case because of the small number of animals in the study (5 per group) and because one year is a minimal time period of exposure for a chronic dog study. Additionally, an uncertainty factor of 10 is included because 1,4-DCB is considered to be a suggestive carcinogen, as discussed above. Therefore, the total uncertainty factor is 3000. The Reference Dose is derived as follows:

$$\frac{7 \text{ mg/kg/day}}{3000} = 0.0023 \text{ mg/kg/day}$$

Health-based MCL Recommendation

The Health-based MCL for 1,4-DCB is derived as follows, using default exposure assumptions:

$$\frac{0.0023 \text{ mg/kg/day} \times 70 \text{ kg} \times 0.2}{2 \text{ L/day}} = 0.014 \text{ mg/L or } 14 \text{ ug/L}$$

Where:
0.0023 mg/kg/day = Reference Dose
70 kg = assumed body weight of an adult
0.2 = Relative Source Contribution from drinking water
2 L/day = assumed adult daily drinking water intake

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Addendum to Health-Based MCL Support Document:
1,1-Dichloroethane

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Summary

The New Jersey carcinogenicity classification, Reference Dose, and Health-based MCL for 1,1-dichloroethane, which were developed in 1994, were reevaluated. Based on reevaluation of the data relevant to carcinogenic effects and the current cancer risk assessment guidelines, it is recommended to classify 1,1-dichloroethane in New Jersey Carcinogenicity Category II, equivalent to possible human carcinogen (Group C) under the previous (1986) USEPA guidance, and analogous to Suggestive Evidence of Carcinogenic Potential under the current (2005) guidance. USEPA IRIS does not provide a slope factor for 1,1-dichloroethane. It is recommended that an additional uncertainty factor of 10 for potential carcinogenicity be incorporated into the Reference Dose.

The current basis of the Reference Dose, kidney effects in cats exposed by inhalation, is a more sensitive endpoint than a newer rat oral subchronic study. Therefore, it is recommended to continue to use the current endpoint as the basis for the Health-based MCL.

It is recommended that the uncertainty factor of 5 currently used for small number of animals in the cat study be removed. The basis for the Reference Dose is already very conservative and health protective and the total uncertainty factor would exceed the maximum uncertainty factor of 10,000 used in Reference Dose development.

Based on the above, the recommended Reference Dose is 0.0032 mg/kg/day, which is a two-fold decrease from current Reference Dose of 0.0065 mg/kg/day. The recommended Health-based MCL is 23 ug/L, also a two-fold decrease from the current value of 46 ug/L.

Current New Jersey Risk Assessment

The current New Jersey Reference Dose, 0.0065 mg/kg/day, for 1,1-dichloroethane (NJDWQI, 1994) is based on kidney effects seen in cats in a subchronic inhalation study (Hofman et al., 1971). In this study, rat, rabbits, and guinea pigs were also tested, but kidney effects were seen only in cats. The No Observed Adverse Effect Level (NOAEL) of 500 ppm (2025 mg/m^3) is equivalent to an oral dose of 32.5 mg/kg/day. As reviewed in NJDWQI (1994), this dose is much lower than the doses used in the oral subchronic and chronic studies conducted by NCI (1978).

This Reference Dose was previously derived by applying an uncertainty factor of 5000 to the NOAEL. This factor of 5000 includes an uncertainty factor of 10 for extrapolation from animals to humans, a factor of 10 for intraindividual variability, a factor of 10 for extrapolation from a subchronic to chronic study, and an additional uncertainty factor of 5 because the number of animals in the study was small.

1,1-Dichloroethane is currently classified as a non-carcinogen for risk assessment purposes, so no additional uncertainty factor to account for possible carcinogenic effects was included. The resulting Health-based MCL, derived by using the standard assumptions of 70 kg body weight, 2

L/day water consumption, and 20% Relative Source Contribution Factor, is 46 ug/L.

Reevaluation of Carcinogenicity Classification.
The data relevant to potential carcinogenicity of 1,1-dichloroethane was reevaluated using current guidance for carcinogen risk assessment to determine whether a revision of the carcinogenicity classification is warranted.

Summary of Data Relevant to Carcinogenicity Classification:
The results of genotoxicity studies on 1,1-dichloroethane are summarized in NJDWQI (1994) and OEHHA (2003), and the results overall can best be described as conflicting or inconclusive. Studies include tests in several strains of *Salmonella typhimurium* (Ames assays) with and without metabolic activation, yeast mutation assays (S. cerevisiae), effects on chromosomes of fungi (*Aspergillus nidulans*), cell transformation and DNA repair assays in mammalian cells *in vitro*, and *in vivo* covalent binding and DNA breakage assays in rodents. Overall, the results of the genotoxicity studies were variable. For example, several investigators reported negative result of Ames tests, while one report (Riccio et al., 1983) showed positive results in the same strains. Mutation tests in yeast were negative, while chromosomal effects were seen in fungi. In mammalian cells, it was positives for viral transformation in Syrian hamster embryo cells and unscheduled DNA synthesis in rats and mice, but negative for viral transformation in mouse BALB/C-3T3 cells. *In vivo* studies involving intraperitoneal injection were negative for induction of DNA strand breaks in mouse liver DNA, but did detect covalent binding to DNA, RNA, and protein.

As reviewed in NJDWQI (1994), conflicting results were also seen in *in vivo* tests of 1,1-dichloroethane as a tumor promoter. It was negative as a tumor promoter when given in drinking water to mice following initiation with diethylnitrosamine (Klaunig et al., 1986). It was also negative as an initiator when given to partially hepatectomized rats followed by the promoter phenobarbital (Herren-Freund and Pereira, 1986). In a third study by Story et al. (1986), it increased the number of liver foci with markers indicating a preneoplastic state when given by gavage to partially hepatectomized rats initiated with diethylnitrosamine.

The National Cancer Institute conducted a carcinogenicity bioassay of 1,1-dichloroethane in Osborne-Mendel rata and B6C3F1 mice (NCI, 1978). 1,1-Dichloroethane was given by gavage in corn oil 5 days per week for 78 weeks. Each dosage group included 50 animals per sex, and untreated control and vehicle control groups included 20 animals of each sex. Vehicle control groups for other studies being tested at the same time in the laboratory were combined with the vehicle control groups for 1,1-dichloroethane, providing larger numbers of animals for statistical analysis. The dosages were adjusted during the course of the study, and the time weighted average doses were calculated to be 382 mg/kg/day and 764 mg/kg/day in male rats, 475 mg/kg/day and 950 mg/kg/day in female rats, 1442 mg/kg/day and 2885 mg/kg/day in male mice, and 1665 mg/kg/day and 3331 mg/kg/day in female mice.

In this study, survival was poor in both treated and untreated groups, and rats had high rates of pneumonia (80%). In male rats, the survival until the end of the study was especially low: 5% in vehicle control, 4% in low dose, and 8% in the high dose, while in female rats, the survivals were 20%, 16%, and 18%, respectively. Survial for male mice was 55% for vehicle control, 62% for low dose, and 32% for high dose, and female mice survival rates were 80%, 80%, and 50%.

The results of the bioassay are summarized in USEPA IRIS (1996). In female rats, there was a statistically significant dose-related positive trend in hemangiosarcomas (0/19 vehicle controls, 0/50 low dose, and 4/50 high dose) and in mammary gland adenocarcinomas in rats surviving at least 52 weeks (0/16 vehicle control, 1/28 low dose, and 5/31 high dose). In male mice, an increase in the incidence of hepatocellular carcinoma which was not statistically significant was seen. However, when the incidence in male mice surviving at least 52 weeks was compared with the pooled vehicle control groups, a statistically significant positive trend was seen. Benign endometrial stromal polyps occurred in 4/46 high dose females, which was statistically significant, and this tumor was not seen in the other groups in this study and had not been seen in 180 female vehicle control mice of this strain used in previous studies in NCI bioassays.

NCI (1978) concluded that the results of the bioassay were "indicative of the possible carcinogenic potential" of 1,1-dichloroethane, but that "under the conditions of this bioassay, there was no conclusive evidence for the carcinogenicity of 1,1-dichloroethane" in the test animals.

USEPA IRIS does not provide a Reference Dose or slope factor for 1,1-dichloroethane. In 1989, USEPA IRIS classified 1,1-dichloroethane as Group C, Possible Human Carcinogen, based upon the results of the NCI (1978) bioassay.

In 2003, the California Office of Environmental Health and Hazard Assessment (OEHHA, 2003) published a Public Health Goal (similar to a New Jersey Health-based MCL) for 1,1-dichloroethane. Both carcinogenic and non-carcinogenic effects were evaluated. California considers 1,1-dichloroethane to be a substance which causes cancer under its Proposition 65, and, as the basis for its Public Health Goal, developed a slope factor for 1,1-dichloroethane based on mammary gland tumors seen in female rats in the NCI (1978) bioassay.

Recommendation for Carcinogenicity Classification

Based upon the data summarized above and the criteria for classification of a chemical as a Possible Human Carcinogen (Group C) under the previous Cancer Risk Assessment Guidelines (USEPA, 1986) and a Suggestive Carcinogen under the current Guidelines for Carcinogen Risk Assessment (USEPA, 2005), it is recommended to place 1,1-dichloroethane in New Jersey's Carcinogenicity Category II (NJDWQI, 1987). Category II applies to chemicals with equivocal evidence of carcinogenicity and was originally defined as equivalent to USEPA Group C. For such chemicals, the risk assessment is based on a slope factor if available from USEPA and judged to be scientifically valid, or a Reference Dose with an additional uncertainty factor of 10 for possible carcinogenicity if a valid slope factor is not available. This classification represents a change from New Jersey's current classification of 1,1-dichloroethane as a non-carcinogen (New Jersey Category III, equivalent to USEPA Group D).

Reevaluation of Reference Dose

Summary of Data Relevant to Reference Dose

A literature review was conducted to determine whether any relevant data had become available since the development of the current New Jersey Reference Dose. In 2001, the results of a subchronic oral study in rats were published (Muralidhara et al., 2001). In this study, groups of 15 male Sprague-Dawley rats were dosed with 0.5, 1, 2, or 4 g/day in corn oil 5 times per week for up to 13 weeks. All rats in the two lowest dose groups survived until the end of the study, and their body weight gain was not affected by treatment. In the 2 g/day group, one death

occurred during the study, moderate CNS depression was seen after dosing, and body weight gain was significantly reduced. In the 4 g/day group, only 7 rats survived until week 11, when the remaining animals were sacrificed. In this group, prolonged narcosis occurred after dosing, and weight gain was lower than in any other group.

1,1-Dichloroethane was not toxic to the liver, as blood levels of sorbitol dehydrogenase and ornithine-carbamyl transferase were not elevated at 4, 8, or 12 weeks. The only histological effects seen in livers from any dose group were slight changes in hepatocyte histopathology consistent with glycogen mobilization in the 4 g/kg animals sacrificed at 11 weeks. Relative liver weights in treated groups did not differ from controls.

Effects on the kidney were also evaluated. There were no elevations of blood urea nitrogen, urinary protein, or urinary glucose at any dose at any time point evaluated. Urinary excretion of the enzymes acid phosphatase and N-acetylglucosaminidase were measured at 2, 4, 6, 8, 10, and 12 weeks. N-Acetylglucosaminidase in urine was increased in the 2 and 4 g/day groups at 6 weeks, and both enzymes were increased compared to controls in the 1, 2, and 4 g/kg groups at 8 weeks. No histopathological changes associated with exposure were seen in the kidneys, lungs, brains, adrenals, spleens, testes, epididymis, or stomach.

The authors state that the subchronic Lowest Observed Adverse Effect Level (LOAEL) in this study is 1 g/kg/day and the NOAEL is 0.5 g/kg/day based on increased enzymes in urine at some time points. As discussed above, these effects were not seen consistently, and kidney pathology was not seen. The Reference Dose based on this NOAEL would be 0.5 mg/kg/day, using an uncertainty factor of 1000 for a NOAEL from subchronic study. The Health-based MCL if this Reference Dose were used as a basis would be 3500 ug/L if 1,1-dichloroethane were treated as a non-carcinogen, using standard assumptions of 2 L/day water consumption, 70 kg body weight, and 20% Relative Source Contribution Factor. With an additional uncertainty factor of 10 for possible carcinogenicity, the Reference Dose would be 0.05 mg/kg/day and the Health-based Maximum Contaminant Level would be 350 ug/L.

As stated above, USEPA IRIS does not provide a Reference Dose or slope factor for 1,1-dichloroethane.

The study and endpoint chosen for the non-carcinogenic assessment in the Public Health Goal developed by California (OEHHA, 2003) were the kidney effects in cats in the study of Hofman et al. (1971), which was the same study and endpoint used for the current New Jersey RfD.

<u>Recommendation for Reference Dose</u>
As stated above, the incorporation into the Reference Dose of an additional uncertainty factor of 10 to protect for possible carcinogenic effects is recommended, based on the classification of 1,1-dichloroethane as New Jersey Category II. No slope factor is available from the USEPA IRIS database for this chemical.

The current Reference Dose is based on a more sensitive endpoint, kidney effects in cats seen in the subchronic inhalation study (Hofman et al., 1971), than would be a Reference Dose based on the newer subchronic oral rat study (Murildhara et al., 2001). In the inhalation study, cats were found to be more sensitive than other species tested, including rats. Although oral studies are generally considered to be preferable to inhalation studies for drinking water risk assessment, it is recommended that data from the most sensitive species be used as a public health-protective

policy. It is therefore recommended to continue to use the kidney effects in cats seen by Hofman et al. (1971) as the basis for the Reference Dose. This is considered a conservative and health protective endpoint, as these kidney effects were not seen in other species tested at higher doses in subchronic and chronic studies.

The current New Jersey Reference Dose for 1,1-dichlorethane includes a total uncertainty factor of 5000 (uncertainty factors of 10 for intraindividual variability, 10 for interspecies variability, 10 for extrapolating from a subchronic study, and 5 for the small number of cats in the Hofman et al. (1971) study). With the incorporation of the additional factor of 10 for possible carcinogenicity, the total uncertainty factor would be 50,000 which exceeds the maximum uncertainty factor of 10,000 permitted by USEPA (2002) for its Reference Dose calculations (a maximum of 3,000 is recommended).

Because of the conservative nature of the endpoint used and the incorporation of an additional protective uncertainty factor of 10 (for possible carcinogenicity), it is recommended that the uncertainty factor of 5 for small number of animals in the current risk assessment be removed. The total uncertainty factor would be 10,000, the maximum uncertainty factor used in Reference Dose development. The recommended Reference Dose would therefore be 0.00325 mg/kg/day.

Health-based MCL Recommendation

The recommended Health-based MCL is derived as follows:

$$\frac{0.00325 \text{ mg/kg/day} \times 70 \text{ kg} \times 0.2}{2 \text{ L/day}} = 0.023 \text{ mg/L} = 23 \text{ ug/L}$$

Where:
0.00325 mg/kg/day = Reference Dose
70 kg = assumed body weight of an adult
0.2 = Relative Source Contribution from drinking water
2 L = assumed adult daily drinking water intake

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Addendum to Health-Based MCL Support Document
1,1-Dichloroethylene

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Summary

The basis for the current New Jersey Reference Dose and Health-based Maximum Contaminant Level (MCL) for 1,1-dichloroethylene which were developed in 1987, was reevaluated. The current Reference Dose is 0.00014 mg/kg/day, based on a Lowest Observed Adverse Effect (LOAEL) level of 2 mg/kg/day for liver necrosis in mice in the National Toxicology Program (NTP, 1982) chronic gavage study. 1,1-Dichlorethylene was classified in New Jersey Carcinogenicity Category II, equivalent to USEPA Group C (Possible human carcinogen) under the previous (USEPA, 1986) guidance. This classification is analogous to Suggestive Evidence of Carcinogenic Potential under the current (USEPA, 2005) guidance. It was based on an increased incidence of renal adenocarcinoma in one strain of mice exposed by inhalation in one study, while many other oral and inhalation carcinogenicity studies were negative. The LOAEL of 2 mg/kg/day from NTP (1982) was adjusted by a factor of 5/7 to adjust for 5 days of dosing per week. Uncertainty factors totaled 10,000 and included an uncertainty factor of 10 to account for potential carcinogenic effects. The current Health-based MCL, using default values of 70 kg for body weight, 2 L/day for drinking water consumption, and 0.2 for Relative Source Contribution, is 1 ug/L.

Subsequent to the development of the current New Jersey assessment, USEPA guidance has been developed that concludes that the gavage route of exposure (bolus dosing, using a vegetable oil vehicle in the case of VOCs) may affect the pharmacokinetics and the exposure-response relationship of the chlorinated solvents. For this reason, studies utilizing drinking water exposure are preferable to gavage studies for these chemicals. A chronic drinking water study in rats (Quast et al., 1983) is now recommended as the appropriate primary basis for New Jersey Reference Dose development, supported by similar findings in a contemporaneous three-generation reproductive and developmental study of rats exposed in drinking water by the same laboratory (Nitschke et al., 1983). The only treatment-related adverse effect observed in rats was minimal hepatocellular midzonal fatty change. This was considered a *minimal* adverse effect in this study, since there was no evidence of a functional change in the liver and glutathione levels were not reduced. The NOAEL for these liver effects was 10 mg/kg-day in male rats and 9 mg/kg/day in female rats.

A Reference Dose of 0.009 mg/kg/day, based on the NOAEL of 9 mg/kg/day and incorporating uncertainty factors for intraspecies (10), interspecies variability (10), and possible carcinogenicity (10), is recommended. No cancer slope factor is available from USEPA and the data and weight of evidence do not support slope factor development. The recommended Health-based MCL based on this Reference Dose and the default exposure assumptions given above is 63 ug/L.

The USEPA MCLG and MCL for 1,1-dichlorethylene are 7 ug/L, based on a 1984 USEPA Office of Water assessment of the Quast et al. (1983) study. Although the Reference Dose

developed by USEPA in its more recent IRIS analysis (USEPA, 2002a) would result in a much higher MCLG, the USEPA MCLG and MCL have not been revised and remain in effect. States may not promulgate an MCL which is less stringent than the federal MCL. The Health-based MCL of 63 ug/L developed in this document is above the federal MCL of 7 ug/L. Therefore, it is recommended that the current New Jersey MCL for 1,1-dichloroethylene be changed from 1 ug/L to 7 ug/L.

Basis for Current New Jersey Risk Assessment

The basis of the current New Jersey Reference Dose and Health-based MCL (NJDWQI, 1987) is the National Toxicology Program (NTP, 1982) gavage study of mice and rats. The NTP conducted 104-week chronic toxicity and carcinogenicity studies of 1,1-DCE in $B6C3F_1$ mice and F344 rats by gavage in corn oil at 0, 2, or 10 mg/kg/day and 0, 1, or 5 mg/kg-day, respectively (NTP, 1982). There were no significant differences in survival, clinical signs, or body weight as compared with controls for any group, suggesting that the maximum tolerated dose was not achieved. Chronic renal inflammation in was seen in male (26/50, 24/48, 43/48) and female rats (3/49, 6/49, 9/44), but the increase was statistically significant only in males. As this lesion commonly occurs in older male rats (Kluwe, 1984, Kluwe et al., 1990), it is not considered biologically significant in this study. In mice, the only noncancer effect observed by histopathological examination was necrosis of the liver (male: 1/46; 3/46; 7/49; female: 0/47; 4/49; 1/49). USEPA (2002a) notes that the effect was of marginal statistical significance at the high-exposure level in males using a two-tailed test ($p = 0.06$). The current Reference Dose and Health-based MCL are based on a Lowest Observed Adverse Effect level of 2 mg/kg/day for liver necrosis in mice in this NTP (1982) study.

1,1-Dichloroethylene was classified in New Jersey Carcinogenicity Category II, equivalent to USEPA Group C, Possible Human Carcinogen, under the previous USEPA (1986) guidance, which is analogous to Suggestive Evidence of Carcinogenic Potential under the current (2005) USEPA guidance. This classification was based on an increased incidence of renal adenocarcinoma in one strain of mice exposed by inhalation (Maltoni et al., 1985), and many negative oral and inhalation carcinogenicity studies. Additional data relevant to carcinogenicity classification are summarized below.

The Reference Dose was set at 0.00014 mg/kg/day, based on a LOAEL of 2 mg/kg/day, and uncertainty factors appropriate for a LOAEL in a chronic study totaling 10,000, including an uncertainty factor of 10 to account for potential carcinogenic effects, and a factor of 5/7 to adjust for 5 days of dosing per week. The resulting Health-based MCL, using default values of 70 kg for body weight, 2 L/day for drinking water consumption, and 0.2 for Relative Source Contribution was 1 ug/L.

Review of Literature Relevant to Reevaluation of New Jersey Risk Assessment

The current New Jersey Health-based MCL was reevaluated based on review of the scientific literature and the Toxicological Review conducted by USEPA (2002a) in support of the current USEPA IRIS Reference Dose. Under current risk assessment guidance, studies of chlorinated solvents using drinking water exposure are preferred over studies where the chemical is administered by gavage, since the bolus dosing which occurs by gavage affects the pharmacokinetics of the chlorinated solvents and the exposure-response relationship. Therefore, the NTP (1982) study that is the basis for the current New Jersey Reference Dose was not used by USEPA.

Quast et al. (1983) conducted a 2-year chronic toxicity and carcinogenicity study of 1,1-DCE in Sprague-Dawley rats (6–7 weeks old). The control group comprised 80 rats of each sex, and each exposed group comprised 48 rats of each sex. The 1,1-DCE was incorporated in the drinking water of the rats at nominal concentrations of 0, 50, 100, or 200 ppm. The time-weighted average exposure over the 2-year period was 7, 10, or 20 mg/kg-day for males and 9, 14, or 30 mg/kg-day for females. Humiston et al. (1978, as cited in USEPA, 2005) reported more detailed data. No significant differences were observed among the groups in appearance and demeanor, mortality, body weight, food consumption, water consumption, hematology, urinalysis, clinical chemistry determinations, organ weights, or organ to body weight ratios.

The only treatment-related effects observed in rats were minimal hepatocellular midzonal fatty change and hepatocellular swelling. At the termination of the study, male rats showed increased incidence of minimal hepatocellular fatty change (control, 14/80; 50 ppm, 5/48; 100 ppm, 13/48; 200 ppm, 19/47). The changes were statistically significant [$p<0.05$] only in the 200 ppm group. Female rats showed an increased incidence of minimal hepatocellular fatty change (control, 10/80; 50 ppm, 12/48; 100 ppm, 14/48; 200 ppm, 22/48; statistically significant [$p<0.05$] at 100 and 200 ppm). No exposure-related neoplastic changes or hepatocellular necrosis were evident at any exposure level. Based on the minimal nature of the hepatocellular swelling reported by the authors and the absence of changes in liver weight, clinical chemistry measurements diagnostic for liver damage, or other indication of abnormal liver function, the hepatocellular swelling is not considered an adverse effect in this study. The statistically significant hepatocellular midzonal fatty change, however, is considered a *minimal* adverse effect in this study. It is considered minimal because there was no evidence of a functional change in the liver and glutathione levels were not decreased. Accordingly, the NOAEL in male rats is 10 mg/kg-day, while the NOAEL in female rats is 9 mg/kg-day.

Quast et al. (1983) also conducted a study in beagle dogs (four per group, 8 months old), 1,1-DCE was administered by gavage in peanut oil at 0, 6.25, 12.5, or 25 mg/kg-day for 97 days. No significant differences were observed among groups in appearance and demeanor, mortality, body weight, food consumption, hematology, urinalysis, clinical chemistry determinations, organ weights, and organ-to-body-weight ratios. Additionally, no exposure-related gross or histopathological changes were present in tissues, and there was no depletion of the nonprotein sulfhydryl levels in the liver or kidneys. The NOAEL in this study is 25 mg/kg-day (the highest exposure tested).

A three-generation companion study (Nitschke et al., 1983) in Sprague-Dawley rats given the same dosage levels used in Quast et al. (1983) corroborates the results of Quast et al. (1983). After 100 days of exposure, the rats were mated. There were no biologically significant changes in fertility index, in average number of pups per litter, in average body weight of pups, or in pup survival at any exposure. Histopathological examination of tissues of rats exposed to 1,1-DCE in the drinking water *in utero*, during lactation, and postweaning revealed slight hepatocellular fatty change. These effects were observed in the 100 and 200 ppm groups in the F_1 generation and in all groups of the F_2 generation. The authors did not present incidence data or statistical analysis. Exposure to 1,1-DCE in drinking water at concentrations causing mild, dose-related changes in the liver did not affect the reproductive capacity of rats through three generations that produced six sets of litters. Exposure levels were not fully characterized since data on drinking water ingestion were not given. However, it can be assumed that the actual ingestion levels in adult animals were similar to those observed by Quast et al. (1983).

There are no focused studies on neurotoxicity or immunotoxicity, but there is no indication from chronic, reproductive, and developmental bioassays in rats and mice by oral or inhalation exposure that either of these is an important toxic endpoint.

One additional recent pathology study was found in the scientific literature. Dawson et al. (1993, and citation in USEPA, 2002a) evaluated the ability of 1,1-DCE administered in drinking water at 110 ppm (18 mg/kg/day) or 0.15 ppm (0.02 mg/kg/day) to induce fetal cardiac changes in female Sprague-Dawley rats. Rats were exposed before mating or during gestation, and the gravid uterus was examined on the last day of gestation. There was no effect on maternal weight gain, average resorption sites, or average implantation sites. There was, however, a statistically significant increase ($p<0.01$) in the percent of fetuses with cardiac changes (atrial septal, mitral valve, and aortic valve changes) when the dams were exposed before mating and during gestation. The incidence was 3% in the control rats (7/232); 12%; at 0.15 ppm (14/121) and 13% at 110 ppm (24/184). The number of affected litters was 5/21 (24%), 8/11 (73%), and 13/17 (76%). The mean number of affected fetuses per litter for affected litters only was 1.40 (13% of the fetuses in the litter), 1.75 (16% of the fetuses in the litter), and 1.85 (17% of the fetuses in the litter).

However, these cardiac changes are of questionable biological significance, as there were no biologically significant effects reported on growth and survival in the three-generation study (Nitschke et al., 1983), and no cardiac effects were reported in the other prenatal developmental study (Murray et al., 1979), in which an oral dose of 40 mg/kg-d was given to pregnant rats via drinking water on days 6 through 15 of gestation. Furthermore, a 900-fold increase in exposure did not produce a significant increase in response in any measure of effect. There is no other experience with the background rates or the functional significance of such alterations from other studies or laboratories.

USEPA (2002a) based its Reference Dose on minimal fatty changes in liver, which is considered a minimal adverse effect, seen in rats in the chronic drinking water study of Quast et al. (1983). The NOAEL and LOAEL in female rats for this effect were determined to be 9 mg/kg/day and 14 mg/kg/day, and 10 mg/kg/day and 20 mg/kg/day for male rats, respectively. Since these values were lower for females than for males, females were used as the basis of the Reference Dose. The data were evaluated by USEPA using benchmark dose (BMD) modeling. The BMD_{10} (dose expected to give a 10% response) was calculated as 6.6 mg/kg/day and the $BMDL_{10}$ (lower 95% confidence limit of the BMD_{10}) was calculated to be 4.6 mg/kg/day. An uncertainty factor of 100 for interspecies and intraspecies variability was applied to the $BMDL_{10}$ to arrive at the Reference Dose of 0.05 mg/kg/day.

Regarding carcinogenicity, recent evidence indicates that the xenobiotic metabolizing enzyme CYP2E1 is responsible for production of metabolites believed to cause the kidney tumors observed in the Swiss-Webster mice in the inhalation study of Maltoni et al. (1985). As stated above, many other studies of the carcinogenic potential of 1,1-dichloroethylene administered orally and by inhalation gave negative results. The CYP2E1 enzyme is present at high levels in the kidney of the susceptible mouse strain, but not in other mice, rats, primates or humans (Speerschneider and Dekant, 1995). There is limited evidence of genotoxicity, as positive results were seen in bacteria with metabolic activation, while most results of in vivo assays in mammalian cells were negative. These data are summarized in NJDWQI, 1987; USEPA, 2002a. The human epidemiological results on the carcinogenicity of 1,1-DCE are too limited to draw useful conclusions.

Based on the above data, EPA (2002a) concluded that 1,1-DCE exhibits suggestive evidence of carcinogenicity following **inhalation** exposure in studies in rodents, but that the data for 1,1-DCE are inadequate for an assessment of human carcinogenic potential by the **oral** route. USEPA reached these conclusions using the 1999 draft revised guidelines for carcinogen risk assessment (USEPA, 1999), which are similar to the final USEPA Guidelines for Carcinogen Risk Assessment (2005). No inhalation or oral slope factor was developed by USEPA for 1,1-DCE, as the available data and the weight of evidence for carcinogenicity does not justify doing so.

Basis for Current USEPA MCLG and MCL

The current USEPA MCL and MCLG (Maximum Contaminant Level Goal, analogous to New Jersey Health-based MCL) of 7 ug/L was finalized in 1987. The RMCL (Recommended MCL, earlier termed used by USEPA for MCLG) for this MCL is summarized in a proposed rule (USEPA, 1984), and the toxicological basis is given in the USEPA Health Advisory (USEPA, 1987), since the basis for the Lifetime Health Advisory and the MCLG are identical.

The Reference Dose used to develop the USEPA MCLG is based on the chronic rat drinking water study of Quast et al. (1983), discussed in detail above. It is stated in USEPA (1987) that a LOAEL of 100 ppm (10 mg/kg/day) for fatty changes in the liver was identified. The choice of 100 ppm as a LOAEL appears to be an error on the part of USEPA. (It should be noted that the confusion of LOAEL versus NOAEL by USEPA in its previous 1986 and 2001 IRIS assessments of 1,1-dichloroethylene was mentioned in the summary of peer review comments in USEPA, 2002a.) Since 100 ppm (10 mg/kg/day) is the **middle** dose used in the study and effects were observed at this dose, the lowest dose, 50 ppm, should have been used as a NOAEL if no effects were seen, or as a LOAEL if effects were seen at the **lowest** dose.

Because 10 mg/kg/day was used as a LOAEL, an uncertainty factor of 1000 appropriate for a LOAEL in a chronic study was used by USEPA (1987). USEPA (1987) classified 1,1-dichloroethylene as Group C, possible human carcinogen, and an additional uncertainty factor of 10 for possible carcinogenic effects was included for a total uncertainty factor of 10,000. The Reference Dose used as the basis for the MCLG was therefore 0.01 mg/kg/day without the uncertainty factor for possible carcinogenicity, and 0.001 mg/kg/day with this additional uncertainty factor. Using default assumptions of 70 kg body weight, 2 L/day water consumption, and 20% Relative Source Contribution, the MCLG was calculated as 7 ug/L.

In 2002, USEPA published the results of its review of existing drinking water standards (USEPA, 2002b). At the time that the review was published, the USEPA IRIS reassessment of 1,1-dichloroethylene (USEPA, 2002a) had not been completed. USEPA stated in its review of drinking water standards that it did not believe that a revision of the MCL for 1,1-dichloroethylene was appropriate as the reassessment of the health risks was ongoing at that time.

Recommendation for New Jerrsey Reference Dose and Health-based MCL

It is recommended that the New Jersey Reference Dose be based on the based on the chronic drinking water study of Quast et al. (1983) rather than the chronic mouse gavage study (NTP, 1982) which forms the current basis. The minimally adverse effect of fatty liver deposits found in rats in the chronic study by Quast et al. (1983) was determined to be the critical endpoint, with a **NOAEL** of **9** mg/kg/day. Because of the minimal nature of the endpoint, benchmark dose

modeling was not considered necessary and was therefore not conducted.

It is recommended to continue to classify 1,1-dichloroethylene in New Jersey Carcinogenicity Category II, equivalent to Possible Human Carcinogen (Group C) under the previous 1986 USEPA guidelines and Suggestive Evidence of Carcinogenic Potential under the current 2005 guidelines. Although the CYP2E1 enzyme thought to be responsible for the production of carcinogenic metabolites is present at high levels in the kidney of the susceptible mouse strain, but not in other mice, rats, primates or humans, other isoenzymes capable of producing carcinogenic metabolites may be present in humans, so the potential for possible human carcinogenicity cannot be dismissed.

To derive the Reference Dose, default uncertainty factors of 10 were used for interspecies extrapolation and intraspecies variability. In addition, an uncertainty factor of 10 was added for suggestive human carcinogenicity, giving a **total uncertainty factor of 1000**, and yielding an **RfD of 0.009 mg/kg/day**.

The recommended Health-based MCL is derived as follows

$$\text{MCL} = \frac{0.009 \text{ mg/kg/day} \times 70 \text{ kg} \times 0.2}{2 \text{ L/day}}$$

$$= 0.063 \text{ mg/L} = 63 \text{ ug/L}$$

Where:
0.009 mg/kg/day = Reference Dose
70 kg = assumed body weight of an adult person
0.2 = Relative Source Contribution from drinking water
2 L = assumed adult daily drinking water intake

Conclusion

Based on the above, a Reference Dose of 0.009 mg/kg/day and a Health-based MCL of 63 ug/L are recommended. However, states may not promulgate an MCL which is less stringent than the Federal MCL for the same contaminant. The recommended Health-based MCL of 63 ug/L is above the federal MCL of 7 ug/L. Therefore, it is recommended that the current New Jersey MCL for 1,1-dichloroethylene be changed from 1 ug/L to 7 ug/L. Additional revision of the New Jersey MCL should be considered in the future if a USEPA reevaluation of its risk assessment results in an increase in its MCL.

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Addendum to Health-Based MCL Support Document:
Ethylene Glycol

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Summary

The basis for the New Jersey Health-based MCL for ethylene glycol which was developed in 1987 was reevaluated. Although a Health-based MCL was developed in 1987, there is currently no New Jersey MCL for ethylene glycol because no appropriate analytical method was available at the time when MCLs were developed. The current Health-based MCL of 290 ug/L is based on renal toxicity in male rats in a chronic dietary toxicity study (Blood, 1965) in which food intake was not measured so that the actual dose of ethylene glycol was not precisely known, requiring that it be estimated. This Reference Dose, 0.042 mg/kg/day, incorporated an additional uncertainty factor of 10 for data deficiencies at the time. The additional uncertainty factor for data deficiencies is no longer warranted, based on current data. Reevaluation of the Health-based MCL derived from Blood (1965) using more up-to-date information on expected dietary intake and the appropriate uncertainty factor would result in a 24-fold increase in this value.

Subsequent to development of the Health-based MCL based on Blood (1965), many additional studies were conducted on the systemic and developmental effects of ethylene glycol, and these are reviewed herein. The most sensitive endpoints for ethylene glycol risk assessment are renal toxicity in male rats and developmental toxicity in mice. Reference Doses were derived for both of these endpoints. For renal toxicity, a Reference Dose of 2 mg/kg/day was derived based on a NOAEL of 200 mg/kg/day in a chronic rat dietary study (DePass et al., 1986a),with an uncertainty factor of 100 appropriate for a NOAEL from a chronic study. This study is more appropriate than Blood (1965) because it utilized constant, known doses of ethylene glycol, more animals per group were used, and more parameters were examined. For developmental toxicity, a Reference Dose of 1.5 mg/kg/day was derived based on a NOAEL of 150 mg/kg/day in a mouse developmental gavage study (Neeper-Bradley et al., 1995) with an uncertainty factor of 100 appropriate for a NOAEL from a developmental study. The recommended Health-based MCL derived from these Reference Doses are 14,000 ug/L and 10,050 ug/L, respectively. Thus, rounding of the Health-based MCLs based on developmental effects and renal effects to one significant figure, as is the policy for determination of the final regulatory MCL, gives an identical result, 10,000 ug/L. This represents a 33-fold increase from the current Health-based MCL for ethylene glycol.

Current New Jersey and USEPA Assessments

The current New Jersey Health-based MCL (NJDWQI, 1987) is 290 ug/L, based on a chronic dietary study in rats (Blood, 1965). A Reference Dose of 0.042 mg/kg/day was derived from an estimated ethylene glycol dose of 42 mg/kg/day at the NOAEL of 0.2% in the diet. At higher doses, renal oxalate deposition was seen in male rats. As discussed in detail below, many additional studies of ethylene glycol toxicity have been conducted since this assessment was developed, and, based on currently available information, the current Health-based MCL is overly conservative. The doses of ethylene glycol in the Blood (1965) study were underestimated, and an uncertainty factor of 10 which was used to account for data deficiencies is no longer warranted.

USEPA has not developed a drinking water MCL for ethylene glycol. A drinking water Lifetime Health Advisory of 7000 ug/L was finalized by USEPA in 1987. Lifetime Health Advisories are developed using the same approaches and exposure assumptions as New Jersey Health-based MCLs and USEPA Maximum Contaminant Levels Goals (MCLGs) which form the human health basis for MCLs. The USEPA Lifetime Health Advisory is based on a Reference Dose of 1 mg/kg/day, based on the same study (Blood, 1965) and NOAEL (0.2% in the diet) as the New Jersey Health-based MCL. There are two factors that account for the 24-fold difference between the current New Jersey Reference Dose of 0.042 mg/kg/day and the USEPA Lifetime Health Advisory (1987) Reference Dose of 1 mg/kg/day. The dose to the animals at 0.2% in the diet was assumed to be 100 mg/kg/day by USEPA (based on information from Lehman, 1959) and 42 mg/kg/day by NJDWQI (1987). Additionally, NJDWQI (1987) included an uncertainty factor of 10 to address issues related to data deficiencies while USEPA (1987) did not.

The IRIS database (USEPA, 1989) developed a Reference Dose of 2 mg/kg/day based on chronic dietary study in rats (DePass et al., 1986a) which is more recent than Blood (1965). In the DePass et al. (1986a) study, toxicity was seen at 1000 mg/kg/day, and the NOAEL was 200 mg/kg/day (see below). An uncertainty factor of 100 appropriate for a NOAEL from a chronic study was applied to derive the Reference Dose of 2 mg/kg/day. The chronic drinking water concentration based on this Reference Dose would be 14,000 ug/L.

Results of Literature Review

A number of additional studies of the toxicity of ethylene glycol have been conducted since the development of the New Jersey Health-based MCL (NJDWQI, 1987). These include subchronic and chronic, developmental, and reproductive studies. The recent toxicology literature on ethylene glycol was extensively reviewed by the National Toxicology Program's Center for the Evaluation of Risk to Human Reproduction (NTP-CERHR, 2004). Only the key studies relevant to consideration for Reference Dose and Health-based MCL derivation are summarized below. Key studies considered in the risk assessment are summarized in Table 1.

Subchronic and Chronic Toxicity

Kidney toxicity is the primary systemic effect of ethylene glycol after subchronic or chronic exposure, and liver toxicity has also been observed in some studies (NTP-CERHR, 2004). Oxalic acid and calcium oxalate are produced when ethylene glycol is metabolized in humans and animals, and the renal toxicity of ethylene glycol is associated with deposition of oxalate crystals in the kidney. As discussed in NTP-CERHR (2004), rats are more sensitive to systemic effects of ethylene glycol, such as renal toxicity, than are mice, and male rats are more sensitive than female rats. Sex, species, and strain differences in sensitivity to the renal toxicity of ethylene glycol may be due to differences in the rate or extent of metabolism of ethylene glycol to its toxic metabolites, differences in the rate of renal clearance of oxalate acid, or differences in the inherent sensitivity of the kidney to ethylene glycol toxicity. Since male rats are more sensitive than mice or female rats to ethylene glycol, the data from male rats are most relevant to Reference Dose development, and are the focus of the summary presented below:

As reported by NTP-CERHR (2004) and Cruzan et al. (2004), **Gaunt et al. (1974)** fed weanling Wistar rats (15 per sex per dose group) diets containing 0, 0.05, 0.1, 0.25, or 1% ethylene glycol for 16 weeks. This study was unpublished and is not available from BIBRA, the sponsoring organization. The average doses received were 0, 35, 71, 180, and 715 mg/kg/day in males and 0, 38, 85, 185, and 1128 mg/kg/day in females. As the animals grew throughout the study, their food consumption per body weight decreased, so that the dose received during the first week

(1410 mg/kg/day in males) was about twice the average dose of 715 mg/kg/day. The only adverse effect attributable to ethylene glycol was kidney toxicity. According to Cruzan et al. (2004), Gaunt (1974) reported that one of 15 males in the 0.25% group had occasional oxalate crystals and degenerative changes in the renal nephrons, while all males in the 1% group had renal oxalate crystals and tubule degeneration. In females, a non-significant increase in renal lesions occurred in the highest dose group. In the highest dose group, oxalic acid excretion was significantly increased in both sexes, and absolute kidney weight, urinary oxalic acid excretion, and urinary volume of reduced specific gravity were increased in males.

In this subchronic study, the authors identified the LOAEL in males as 180 mg/kg/day (0.25%) and the NOAEL as 71 mg/kg/day (0.1%), while in females, the LOAEL and NOAEL were identified as 1128 mg/kg/day (1%) and 185 mg/kg/day (0.25%), respectively. This study has several deficiencies that preclude it from use as the basis for risk assessment. First, it is both unpublished and unavailable from the sponsoring agency. Second, the average doses reported by the authors may not be appropriate to use as the NOAEL and LOAEL, since the observed effects may be due to the much higher doses which the animals received at the beginning of the study. Cruzan et al. (2004) conducted a subchronic dietary study in Wistar rats with constant dose (see below), and these results are more appropriate for consideration for risk assessment than the results of Gaunt (1974).

Melnick et al. (1984) administered ethylene glycol in the diet at concentrations of 0, 0.32, 0.63, 1.25, 2.5 or 5% to 7 week old Fischer 344/N rats (9 or 10 per sex per dose group) for 13 weeks. The authors estimated that 1.25% resulted in a dose of 600-1000 mg/kg /day in males and that 2.5% gave a dose of 1000-1500 mg/kg/day in females. Based on these data, doses at other dietary concentrations were estimated by NTP-CERHR (2004). Four of 10 males in the highest dose group died during the study, and body weight gain was significantly reduced in males in the two highest dose groups. Relative kidney weight was increased in the two highest dose groups in both sexes, and relative thymus weight was decreased in high dose males. In males in the two highest dose groups, nephrosis and oxalate crystal deposition was seen in the kidneys. Similar crystals were also seen in the bladder, urethra and brains of high dose males. Renal lesions but no crystals were seen in high dose females. Blood urea nitrogen and creatinine levels were increased in males in the two highest dose groups. It was concluded that the NOAEL and LOAEL in males were 1.25 % (600-1000 mg/kg/day) and 2.5% (1200-2000 mg/kg/day). In females, the NOAEL and LOAEL were 1.25% (1000-1500 mg/kg/day) and 2.5% (2000-3000 mg/kg/day) for increased relative kidney weight, and 2.5% (1000-1500 mg/kg/day) and 5% (2000-3000 mg/kg/day) for renal lesions with no crystal deposition.

Robinson et al. (1990) gave ethylene glycol in drinking water to Sprague-Dawley rats (10 per sex per group) for 90 days. Males were given 0, 0.25, 0.5, 1 or 2% (0. 205, 407, 947, or 3134 mg/kg/day) and females were given 0, 0.5, 1, 2, or 4% (597, 1145, 3087, or 5744 mg/kg/day). Two males in the 2% group and eight females in the 4% group died during the study. Body weight gain was significantly reduced in high dose males. White blood cell numbers were reduced compared to controls in the 0.5, 2, and 4% females, but not in the intermediate dose of 1% in females. This lack of dose-response suggests that this effect is not treatment-related. In males, blood urea nitrogen and phosphorus were increased in 2% males and creatinine in 1% and 2% males. In males, kidney weight was increased in the 1% and 2% groups, and brain and gonad weights were increased and heart, liver, and lung weights decreased in the 2% group. The incidence and severity of kidney lesions and crystal deposition was increased in the 11% and 2% males and in the 2% and 4% females. The lesions in males were more frequent and more severe

than in the females. The NOAEL and LOAEL in males in this study were 0.5 % (407 mg/kg/day) and 1% (947 mg/kg/day), and in females, the NOAEL and LOAEL were 1% (1145 mg/kg/day) and 2% (30787 mg/kg/day), respectively.

The results of the Gaunt (1974) and Melnick (1984) dietary subchronic studies, as well as the chronic dietary study of DePass et al. (1986a, see above and below), suggest that Wister rats are more sensitive to the effects of ethylene glycol than are Fischer 344 rats. **Cruzan et al. (2004)** conducted a study of male Wistar and Fischer 344 rats (10 per strain per dose group) exposed under identical conditions to ethylene glycol at constant dose in the diet for 16 weeks. The dietary concentrations were adjusted weekly to provide constant doses of 0, 50, 150, 500, and 1000 mg/kg/day. Two of 10 high dose Wistar rats died during the study, and body weight gain and food intake was reduced in the two highest dose Wistar groups. Increased water intake, increased urine volume, and decreased urine specific gravity occurred in the two highest dose Wistar groups and in the highest dose Fischer 344 group. Absolute and relative kidney weights were increased significantly in 500 and 1000 mg/kg/day Wistar rats and 1000 mg/kg/day Fischer 344 rats. Increased excretion of urinary oxalate crystals was seen in at doses of 150 mg/kg/day and higher, but was not considered an adverse effect in the 150 mg/kg/day group because the crystals were excreted and were not deposited in the kidney. Nephropathy associated with oxalate crystal deposition was seen in the two highest dose groups of both strains, with increased severity in the Wistar rats. The NOAEL and the LOAEL were judged to be 150 mg/kg/day and 500 mg/kg/day in both strains, but the Wistar rats were observed to be more sensitive than the Fischer 344 rats to the renal effects of ethylene glycol.

DePass et al. (1986a) conducted a two year dietary study of ethylene glycol in Fischer 344 rats and CD-1 mice. In both species, the dietary concentrations were adjusted every two weeks to provide doses of 0, 40, 200, and 1000 mg/kg/day. As discussed above, rats are more sensitive to the effects of ethylene glycol than are mice, and no ethylene glycol related effects were seen at any dose in mice. Therefore, only the rat results are discussed herein.

There were 80 rats per sex in each dosing group, and interim sacrifices of 10 rats/sex/group took place at 6 and 12 months and 20 rats/sex/group at 18 months. Endpoints observed in this study included survival, body and organ weight, clinical signs, gross and microscopic pathology, hematology, blood chemistry, and urinalysis.

All of the male rats in the high dose group died before the 15th month of the study. Mortality was not increased in any other treated group, and food consumption was not affected in any treated group.

The following effects were observed in the high dose males: At 6 months- a statistically significant increase in renal lesions including tubular hyperplasia, tubular dilation, peritubular nephritis, and calcium oxalate crystalluria. At 12 months-decreased weight gain, hematological changes, a four-fold increased in blood urea nitrogen and creatinine, increased urine volume and decreased urine specific gravity, increased urinary calcium oxalate crystals, decreased absolute and relative liver weight, chronic nephritis in all animals, oxalate crystals in the bladder in 50% of animals. The cause of death in most of the high dose males was oxalate nephrosis.

Effects seen in other groups were as follows: Almost all high dose females had urinary oxalate crystals at 18 and 24 months, and an increase in urinary uric acid was also seen at these times. In both males and females in the mid-dose group, urinary oxalate crystals were increased compared

to controls at 24 months. There was no evidence of kidney toxicity from ethylene glycol in the mid-dose or low-dose males or in any dose in females. It should be noted that, in the absence of renal oxalate crystals or renal toxicity, the presence of urinary oxalate crystals is not considered an adverse effect.

At 24 months, high dose females had a significantly increased incidence of hemosiderosis of the mesenteric lymph nodes and of mild fatty metamorphosis of the liver. The incidence of fatty metamorphosis of the liver was also increased in the mid-dose female group, but this was not significant at the $p \leq 0.05$ level.

The incidence of neoplastic lesions was not increased by ethylene glycol treatment, and there was no indication of carcinogenicity in rats, nor in mice, which were also studied, but for which results are not presented in detail herein.

Based on the data discussed above, the NOAEL in this study in rats was judged to be 200 mg/kg/day, and the LOAEL was judged to be 1000 mg/kg/day by USEPA IRIS (1989), ATSDR (1997), and NTP-CERHR (2004). These results are consistent with the NOAEL of 150 mg/kg/day and the LOAEL of 500 mg/kg/day in the subchronic study of male Wistar and Fischer 344 rats (Cruzan et al., 2004). The fact that the dose of 1000 mg/kg/day resulted in deaths of all animals in the chronic study before 15 months, and that no effects were seen at 200 mg/kg/day, suggests a steep dose-response curve for ethylene glycol toxicity.

As stated above, rats are more sensitive to the systemic effects of ethylene glycol than are mice. The **National Toxicology Program (1993)** conducted subchronic (13 week) and chronic (2 year) dietary studies of ethylene glycol in B6C3F1 mice. In summary, the subchronic NOAEL in males was about 3230 mg/kg/day and the LOAEL was about 6450 mg/kg/day, based on mild liver lesions and nephropathy. Similar effects were seen in males given 12,900 mg/kg/day and there were no effects seen in females given the same doses. In the chronic study, the NOAEL was 1500 mg/kg/day in males and the LOAEL in males was 3000 mg/kg/day based on increased hepatocellular hyaline degeneration. In females, an increase incidence of pulmonary arterial medial hyperplasia was seen in all treated groups. The LOAEL was 3000 mg/kg/day and no NOAEL was established. No increase in the incidence or severity of nephropathy was observed in males or females, although a few oxalate crystals were found in the kidney, urethra, or urinary bladder of a few high dose males.

As discussed above, in the chronic (2 year) study of DePass et al. (1986a), no effects were seen in CD-1 mice treated with ethylene glycol in the diet at doses up to 1000 mg/kg/day.

Developmental Toxicity

As reviewed by NTP-CERHR (2004), ethylene glycol has been shown to cause developmental toxicity in mice and rats, but is not a developmental toxicant in rabbits at doses below those that are maternally toxic. In contrast to systemic effects, mice are more sensitive to the developmental effects of ethylene glycol than rats. The key developmental studies are summarized below:

Price et al. (1985) dosed timed pregnant CD rats (27-29/group) with 0, 1250, 2500, or 5000 mg/kg/day ethylene glycol and CD-1 mice (23-25/group) with 0, 750, 1500, or 3000 mg/kg/day ethylene glycol by gavage on days 6-15 of gestation. Rats were sacrificed on gestation day 20 and mice on gestation day 17.

In rats, maternal toxicity was seen at all doses, with decreased body weight gain occurring at all doses. In the mid and high dose groups, relative kidney weight and water intake were increased, and in the high dose group, liver weight was decreased. Fetal effects were reported at all doses. A dose-related increase in the percent of litters with one or more malformed live fetuses was seen in all dose groups. In the two higher dose groups, decreased average body weight per litter, decreased number of live fetuses per litter, increased number of malformed fetuses per litter, and increased number of litters with skeletal malformations occurred. In the high dose group, increased post-implantation losses per litter and increased number of litters with visceral and external malformations occurred. The authors concluded that the lowest dose, 1250 mg/kg/day , was the LOAEL for both the maternal and fetal effects. NTP-CERHR (2004) disagreed as to the significance of the visceral malformations seen at the lowest dose, classifying them as variations, and concluded that the fetal NOAEL was 1250 mg/kg/day and the LOAEL was 2500 mg/kg/day.

In mice, maternal toxicity including decreased body weight gain and decreased liver weight gain occurred in the mid and high dose groups. Fetal toxicity seen at all doses included decreased average fetal body weight per litter, increased number of malformed fetuses per litter, increased number of litters with malformed fetuses, and increased number of litters with skeletal malformations. At the high dose, a decreased number of live fetuses per litter and and increased number of litters with external and visceral malformations was also seen. At the highest dose, 96% of litters had one or more malformed fetus, as compared to 7% of control litters.
No NOAEL for fetal toxicity was established in this study, and the LOAEL was 750 mg/kg/day. The LOAEL for maternal toxicity was 1500 mg/kg/day, and the NOAEL was 750 mg/kg/day.

Because Price et al. (1985) did not establish the NOAEL for developmental toxicity in mice or rats, **Neeper-Bradley et al. (1995)** conducted a similar study with lower doses of ethylene glycol. Timed pregnant CD rats (25/group) were dosed with 0, 150, 500, 1000, or 2500 mg/kg/day ethylene glycol and CD-1 mice (30/group) were dosed with 0, 50, 150, 500, or 1500 mg/kg/day ethylene glycol by gavage on days 6-15 of gestation. Rats were sacrificed on gestation day 21 and mice on gestation day 18.

In rats, no maternal effects were seen at the three lowest doses. At 2500 mg/kg/day, decreased body weight gain, increased water intake, absolute and relative kidney weight, and relative liver weight occurred. No fetal effects were seen in the two lowest dose groups. In the two highest dose groups, increased average body weight per litter and increased litters with skeletal malformations were seen. In the highest dose group, there was an increase in litters with external, visceral, and total malformations. Therefore, the maternal NOAEL and LOAEL were 1000 mg/kg/day and 2500 mg/kg/day, respectively, and the fetal NOAEL and LOAEL were 500 mg/kg/day and 1000 mg/kg/day, respectively.

Mice were more sensitive than rats to developmental effects in this study. There were no maternal effects in mice at any dose tested. No fetal effects were seen at 50 mg/kg/day or 150 mg/kg/day. At the two highest doses, the number of litters with malformations was increased, and the highest dose, decreased average body weight per litter and increase number of litters with skeletal malformations was observed. The maternal NOAEL was 1000 mg/kg/day, the highest dose tested. The fetal NOAEL and LOAEL were 150 mg/kg/day and 500 mg/kg/day, respectively.

Maronpot (1983) administered ethylene glycol in the diet to timed pregnant Fischer 344 rats (20

per group) at target doses of 0, 40, 200, and 1000 mg/kg/day on days 6-15 of gestation, and the animals were sacrificed on gestation day 21. On gestation day 11, 500 mg/kg of hydroxyurea was administered as a positive control for teratogenicity. No maternal toxicity was seen at any dose tested, and the maternal NOAEL was thus 1000 mg/kg/day. There was no increase in incidence of malformations in any ethylene glycol treated groups, although multiple malformations were seen in the positive control group. The only observation related to ethylene glycol treatment was a significant increase of poorly ossified and unossified vertebral centra in the high dose group, which was interpreted by the authors as evidence of delayed fetal maturation and minimal embryotoxicity. The author and NTP-CERHR (2004) concluded that ethylene glycol was not teratogenic in this study.

An additional study by **Price et al. (1988)** investigated the effects of prenatal exposure to ethylene glycol on postnatal development in rats. Timed pregnant CD rats (38-49/group) were administered doses of 0, 250, 1250, or 2250 mg/kg/day ethylene glycol by gavage on gestation days 6-20. Pups were delivered and fostered to untreated control dams on postnatal day 1. Maternal effects were seen in the mid and high dose groups, including prolonged gestational duration and renal lesions. In the high dose group, additional effects included decreased maternal body weight gain, increased absolute and relative kidney weight, and decreased absolute and relative uterine weight.

Pups were intermittently sacrificed and evaluated on postnatal days 1, 4, 22, and 63. No effects on pups were seen in the low dose group. In the mid and high dose groups, absolute and relative kidney weight was increased on postnatal day 63. In the highest dose group, there was also a decrease in litter size and increased mortality at postnatal days 1 and 4, and decreased postnatal weight gain, kidney weight and brain weight on postnatal day 22, and increased skeletal malformations on postnatal day 22. No effects on developmental landmarks or behavioral tests were seen. The authors concluded that the NOAEL for the dams and the pups was 250 mg/kg/day and the was LOAEL 1250 mg/kg/day. NTP-CERHR discounted the minimal effects seen in pups at 1250 mg/kg/day, and judged the pup NOAEL to be 1250 mg/kg/day and the LOAEL 2250 mg/kg/day.

In the oral developmental studies of ethylene glycol of Price et al. (1985) and Neeper-Bradley et al. (1995), dosing was by gavage, while Maronpot (1983) used dietary dosing. In gavage studies, ethylene glycol is given as a bolus dose rather than continuously as when dosing is in drinking water or food. It is believed that ethylene glycol's developmental toxicity is caused by a metabolite, glycolic acid, or one of the metabolites of glycolic acid, and thus occurs only when saturation of metabolism results in a buildup of glycolic acid. Bolus dosing results in metabolic saturation at a much lower daily dose than does the same dose given as continuous (non-bolus) exposure (NTP-CERHR, 2004). Consistent with this expected difference, developmental toxicity was seen in rats at a lower dose in the Neeper-Bradley (1995) bolus gavage study than in the Maronpot (1983) continuous dosing dietary study. Since human exposure to ethylene glycol in drinking water is expected to be continuous, rather than as a bolus, use of a bolus dose study as the basis for risk assessment adds conservatism and protectiveness to the assessment.

Reproductive Studies

The literature on the reproductive toxicity of ethylene glycol was reviewed by NTP-CERHR (2004). Two continuous breeding studies of ethylene glycol in drinking water in mice (Lamb et al., 1985; Gulati et al., 1986) have been conducted. Drinking water concentrations and doses in the first study were 0, 0.25, 0.5, and 1% and 0, 410, 840, and 1640 mg/kg/day, respectively. In

the second study, concentrations and doses were 0, 0.5, 1, and 1.5% and 0, 897, 1798, and 2826 mg/kg/day. In the Lamb et al. (1985) study, a slight but significant decrease was seen in the number of litters per pair and number of live pups per litter in the offspring of the F_0 generation in the 1% group, but was not seen in the offspring of the F_1 group which had similarly been exposed to 1% ethylene glycol. The effects observed by Lamb et al. (1985) in the offspring of the F_0 group were also not confirmed by Gulati et al. (1986), who used a similar protocol and included a higher dose level than Lamb et al. (1985). Observations of testicular lesions by Gulati et al. (1986) were not considered treatment related because of high rates of these lesions in controls and their absence in the subchronic and chronic studies discussed above. Similarly, effects on sperm parameters observed by Gulati et al. (1985) were not confirmed in another reproductive toxicity study in mice with gavage doses of up to 2500 mg/kg/day (Harris et al, 1992). A three-generation rat reproductive/developmental study with ethylene glycol in the diet at doses of 40, 200, and 1000 mg/kg/day (DePass, 1986b) was negative for all parameters evaluated.

In summary, NTP-CERHR (2004) concluded that fertility of male or female mice is not affected at doses up to 2826 mg/kg/day for about 22 weeks, and ethylene glycol does not cause reproductive toxicity in rats at doses up to 1000 mg/kg/day for 7 weeks prior to mating in parents or from conception through mating in offspring. Renal effects in male rats and developmental effects in mice are thus more sensitive endpoints for ethylene glycol toxicity than are reproductive effects.

Reference Dose Derivation

As discussed above, the most sensitive endpoints for ethylene glycol toxicity are renal toxicity in male rats and developmental toxicity in mice. Reference Doses based on both these endpoints are developed below in order to determine which is the most sensitive endpoint. The key studies which were considered in Reference Dose development or which are the basis for current New Jersey or USEPA assessments are summarized in Table 1. Additionally, a reevaluation of the current RfD based on Blood (1965) using up-to-date assumptions is provided for illustrative purposes.

Reference Dose based on renal toxicity

For evaluation of systemic toxicity, chronic studies are preferable to subchronic studies, and studies using a constant dose are preferable to studies with dosing based on dietary or drinking water concentration. As discussed above, drinking water and dietary intake is higher in young animals on a body weight basis, so that in studies based on dietary or drinking water concentration, the dose is much higher in the young animals than at the end of the study.

The chronic rat study of DePass et al. (1986a) is selected as the basis for the Reference Dose for renal toxicity. As discussed above, in this study, the dietary concentrations were adjusted every two weeks to provide doses of 0, 40, 200, and 1000 mg/kg/day. There were 80 rats per sex in each dosing group, and interim sacrifices of 10 rats/sex/group took place at 6 and 12 months and 20 rats/sex/group at 18 months. Endpoints observed in this study included survival, body and organ weight, clinical signs, gross and microscopic pathology, hematology, blood chemistry, and urinalysis.

Mortality was increased in the high dose males, with no animals in this group surviving beyond the 15th month of the study. Renal toxicity was seen in all animals by 12 months. The cause of death in most of the high dose males was oxalate nephrosis. There was no evidence of kidney

toxicity from ethylene glycol in the mid-dose or low-dose males or in any dose in females.

The NOAEL in this chronic study in Fischer 344 rats was judged to be 200 mg/kg/day, and the LOAEL was judged to be 1000 mg/kg/day by USEPA IRIS (1989), ATSDR (1997), and NTP-CERHR (2004). These results are consistent with the subchronic NOAEL of 150 mg/kg/day and LOAEL of 500 mg/kg/day for both Fischer 344 rats and the more sensitive Wistar rats (Cruzan et al., 2004). Cruzan et al. (2004) also adjusted the dietary concentrations of ethylene glycol in order to keep constant dose levels throughout the study.

The Reference Dose based on renal toxicity to male rats in DePass et al. (1986a) is derived as follows:

$$RfD = \frac{(200\ mg/kg/day)}{100} = 2\ mg/kg/day$$

Where:
200 mg/kg/day = NOAEL for renal toxicity
100 = uncertainty factor for NOAEL from chronic study
(10 – intraspecies, 10 – interspecies)

Reference Dose based on developmental toxicity

As discussed above, mice are more sensitive to developmental effect of ethylene glycol than are rats. The most appropriate study to use as the basis for the RfD based on developmental effects is the Neeper-Bradley et al. (1995), in which ethylene glycol was administered by gavage to pregnant mice on days 6-15 of gestation at doses of 0, 50, 150, 500, or 1500 mg/kg/day. In this study, there were no maternal effects in mice at any dose tested. No fetal effects were seen at 50 mg/kg/day or 150 mg/kg/day. At the two highest doses, the number of litters with malformations was increased, and at the highest dose, decreased average body weight per litter and increase number of litters with skeletal malformations were observed. The maternal NOAEL was 1000 mg/kg/day, the highest dose tested. The fetal NOAEL and LOAEL were 150 mg/kg/day and 500 mg/kg/day, respectively.

The Reference Dose based on developmental toxicity to mice in Neeper-Bradley et al.. (1995) is derived as follows:

$$RfD = \frac{(150\ mg/kg/day)}{100} = 1.5\ mg/kg/day$$

Where:
150 mg/kg/day = NOAEL for developmental effects
100 = uncertainty factor for NOAEL from developmental study
(10– intraspecies, 10– interspecies)

It should be noted that ethylene glycol was administered as a bolus dose in this study. As discussed above, it is believed that ethylene glycol's developmental toxicity is caused by a metabolite, glycolic acid, or one of its metabolites, and thus occurs only when saturation of metabolism results in a buildup of glycolic acid. Bolus dosing results in metabolic saturation at a much lower daily dose than does the same dose given as continuous (non-bolus) exposure (NTP-CERHR, 2004). Since human exposure to ethylene glycol in drinking water is expected to be

continuous, rather than as a bolus, use of a bolus dose study as the basis for the Reference Dose adds conservatism and protectiveness to the assessment.

Reconsideration of current Reference Dose based on Blood (1965)

As discussed above, the current New Jersey Health-based MCL (NJDWQI, 1987) is 290 ug/L, based on a chronic dietary study in rats (Blood, 1965). In this study, groups of 16 male and female mice were fed ethylene glycol (0, 0.1%, 0.2%, 0.5%, 1%, or 4%) in their diets. The actual doses of ethylene glycol (in mg/kg/day) were not reported. The authors reported that renal oxalate deposition occurred at 0.5% and above in males and 1% and above in females, and 0.2% was thus considered to be the NOAEL. Non-statistically significant changes in organ weights were seen in males given 0.1%, and it was reported that treated, but not control, rats had degeneration of the renal tubular epithelium, but the doses at which this occurred were not reported.

A Reference Dose of 0.042 mg/kg/day was derived, based on Blood (1965). Daily food consumption at the NOAEL of 0.2% was estimated as 12 g/day, resulting in an estimated dose of ethylene glycol of 42 mg/kg/day. As discussed below, based on data currently available this estimate of daily food intake was overly conservative. An uncertainty factor of 1000 was applied to this dose, which included a factor of 10 because of data quality issues in addition to the standard factor of 100 (10 for intraspecies and 10 for interspecies extrapolation) appropriate for a NOAEL from a chronic study. Based on the currently available information discussed in this document, this additional uncertainty factor for data quality issues is no longer warranted.

As discussed above, the chronic study of DePass et al. (1986a) is more appropriate to use as the basis for the Reference Dose and Health-based MCL than is the Blood (1965) study. Importantly, the doses of ethylene glycol were kept constant throughout the DePass et al. (1986a) study by adjustment of the dietary concentrations. In the Blood (1965) study, the dose per unit body weight was not constant, but was much higher earlier in the study than the average dose used in RfD calculation. Additionally, dietary intake was not measured in Blood (1965), so the actual doses of ethylene glycol cannot be determined. Furthermore, DePass et al. (1986a) used many more animals per dose group than Blood (1965) and evaluated more parameters.

Although Blood (1965) is not the appropriate basis for the Reference Dose and Health-based MCL proposed herein, it is useful to recalculate these based on the data from this study, using a more appropriate daily food intake value and uncertainty factors based on current knowledge.

In developing the Reference Dose based on in Blood (1965) for its Lifetime Health Advisory for drinking water, USEPA (1987) assumed an average ethylene glycol dose of 100 mg/kg/day at a dietary concentration of 0.2%. The dose of 100 mg/kg/day at 0.2% in the diet is supported by several of the more recent studies discussed above: Gaunt (1974) reported 180 mg/kg/day as the average ethylene glycol dose at 0.25% in the diet (equivalent to 144 mg/kg/day at 0.2%) in a 16 week study. From data provided on dose at the 1% concentration, the dose at 0.2% during the first week of the study would be about twice the average dose (about 300 mg/kg/day) and after four months, about 130 mg/kg/day. Similarly, Melnick (1984) reported that a concentration of 1.25% gives a dose of 600-1000 mg/kg/day over 13 weeks, which would be about 100-160 mg/kg/day at a concentration of 0.2%. Finally, DePass et al. (1986a) reports that concentrations of 0.1%, 0.5%, and 2.5% in the diet provided doses of 40, 200, and 1000 mg/kg/day, respectively, during the last 5 months of a 2 year study, the time period when a dose from a given dietary concentration would be lowest. Based on these data, the NOAEL from Blood

(1965) of 0.2% would provide a dose of 80 mg/kg/day during this final phase of the study. Based on the above, 100 mg/kg/day is a conservative estimate for the dose at 0.2% in Blood (1965).

The additional uncertainty factor of 10 for data quality issues used by NJDWQI (1987) in derivation of the Reference Dose from Blood (1965) is not warranted when developing a Reference Dose from more recent studies, such as DePass et al. (1986a). The uncertainty factor was included because of uncertainties regarding the reporting of the data in Blood (1965) and because of lack of information about the NOAEL and LOAEL for developmental effects of ethylene glycol at the time. The threshold for developmental effects has now been determined, as discussed below.

Based on current information, the Reference Dose based on Blood (1965) would be calculated as follows:

$$RfD = \frac{100 \text{ mg/kg/day}}{100} = 1 \text{ mg/kg/day}$$

Where:
100 mg/kg/day = estimated NOAEL for renal toxicity at 0.2% ethylene glycol in diet.
100 = uncertainty factor for NOAEL from chronic study (10– intraspecies, 10– interspecies)

It should be noted that the RfD of 1 mg/kg/day using assumptions based on current information is 24-fold higher than the existing RfD of 0.042 mg/kg/day. It should also be reemphasized that Blood (1965) is not considered to be the appropriate basis for RfD development, because of the variation in the dose during the study and the other factors discussed above.

Health-based MCL Recommendation

The Health-based MCL for ethylene glycol is derived from the Reference Dose for developmental effects of 1.5 mg/kg/day, since it is lower than the Reference Dose for renal effects of 2 mg/kg/day.

$$\frac{1.5 \text{ mg/kg/day} \times 67 \text{ kg} \times 0.2}{2 \text{ L/day}} = 10.05 \text{ mg/L or } 10{,}050 \text{ ug/L}$$

Where:
1.5 mg/kg/day = Reference Dose
67 kg = assumed body weight of pregnant woman (USEPA Office of Water, 2004)
0.2 = Relative Source Contribution from drinking water
2 L/day = assumed adult daily drinking water intake

For comparison, the Health-based MCL based on the Reference Dose of 2 mg/kg/day for renal toxicity is also calculated as follows:

$$\frac{2 \text{ mg/kg/day} \times 70 \text{ kg} \times 0.2}{2 \text{ L/day}} = 14 \text{ mg/L or } 14{,}000 \text{ ug/L}$$

Where:
2 mg/kg/day = Reference Dose

70 kg = assumed body weight of adult
0.2 = Relative Source Contribution from drinking water
2 L/day = assumed adult daily drinking water intake

Thus, rounding of the Health-based MCLs based on developmental effects and renal effects to one significant figure, as is done for determination of the regulatory MCL, gives an identical result, 10,000 ug/L.

(NOTE: Ethylene glycol is reported to be odorless and to have a sweet taste. No information was located as to the taste threshold for ethylene glycol in water.)

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TABLE 1: Key Studies for Ethylene Glycol Reassessment

Study	Species	Route and Duration	Doses	Critical Effects	NOAEL and/or LOAEL	Uncertainty Factor	Reference Dose	Comments	Health-based Drinking Water Concentration
Blood (1965)	Sprague-Dawley Rat	Oral – diet 2 years	0.1, 0.2, 0.5, 1, 4% in diet. Actual doses not known. Doses vary throughout study and are much higher in younger animals.	Renal oxalate crystal deposition	NOAEL 0.2% Estimated in A-280 document to be equivalent to 42 mg/kg/day LOAEL 0.5%	1000 (10-intraspecies, 10 – interspecies, 10- data deficiencies)	0.042 mg/kg/day (1 mg/kg/day based on current information – see text)	Current NJ RfD and HBMCL (1987) Dose actually higher than assumed based on data from later studies. Extra UF no longer warranted (see text).	290 ug/L Rounds to 300 ug/L
DePass et al. (1986)	Fischer 344 Rat	Oral diet 2 years	0, 40, 200, 1000 mg/kg/day Doses constant throughout study.	Renal lesions and oxalate crystals (Males more sensitive) Mild fatty changes in liver in females	NOAEL 200 mg/kg/day (0.07-0.24% in diet) LOAEL 1000 mg/kg/day (0.35-1.27% in diet)	100 (10-intraspecies, 10-interspecies)	2 mg/kg/day	USEPA IRIS RfD (1989) and ATSDR chronic oral MRL (1997) Basis for recommended New Jersey RfD and HBMCL.	14,000 ug/L
Gaunt (1974) Cited in CERHR (2004)	Wistar rat	Oral diet, 16 weeks	0, 0.05, 0.1, 0.25, 1% in diet Doses vary throughout study and are much higher than average in young animals.	Renal oxalate crystals and lesions (M) Non significant increased renal lesions (F)	NOAEL 71 mg/kg/day (average), 0.1% in diet (M) LOAEL 180 mg/kg/day (average), 0.25% in diet (M) NOAEL 185 mg/kg/day (average), 0.25% in diet (F) LOAEL 1128 mg/kg/day (average), 1% in diet (F)			Wistar rats appear more sensitive than Fischer 344. Study is unpublished and unavailable. According to Cruzan et al. (2002), minimal effects seen in 1/15 males at 180 mg/kg/day.	

TABLE 1: Key Studies for Ethylene Glycol Reassessment (continued)

Study	Species	Route and Duration	Doses	Critical Effects	NOAEL and/or LOAEL	Uncertainty Factor	Reference Dose	Comments	Health-based Drinking Water Concentration
Melnick (1984)	Fischer 344 Rat	Oral diet, 13 weeks	0.32, 0.63, 1.25, 2.5, 5% in diet Doses vary throughout study and are higher than average in young animals.	Decreased body wt., renal oxalate crystals, increased kidney weight, nephrosis (M) Increased relative kidney weight (F) (Renal lesions at 5% in females)	NOAEL 600-1000 mg/kg/day, 1.25% (M) LOAEL 1200-3=2000 mg/kg/day, 2.5% (M) NOAEL 500-750 mg/kg/day, 1.25% (F) LOAEL 1000-1500 mg/kg/day, 2.5% (F)			Wistar rats appear more sensitive than Fischer 344	
Robinson (1990)	Sprague-Dawley Rat	Drinking water, 90 days	Males – 0.5, 1, 2, 4% Females – 0.25, 0.5, 1, 2%. Doses vary throughout study. Values given are averages.	Renal lesions, oxalate crystal deposition	NOAEL 407 mg/kg/day (M) LOAEL 947 mg/kg/day (M) NOAEL 1145 mg/kg/day (F) LOAEL 3087 mg/kg/day (F)				
Cruzan (2002)	Male Fischer 344 Rat	Diet, 16 week	0, 50, 150, 500, 1000 mg/kg/day. Doses constant throughout study.	Renal oxalate crystals and toxicity (1/10)	NOAEL 150 mg/kg/day LOAEL 500 mg/kg/day			Effects less severe at LOAEL of 500 mg/kg/day than in Wistar	
Cruzan (2002)	Male Wistar Rat	Diet, 16 week	0, 50, 150, 500, 1000 mg/kg/day Doses constant throughout study.	Renal oxalate crystals and toxicity Decreased bw gain and food intake Other effects (10/10)	NOAEL 150 mg/kg/day LOAEL 500 mg/kg/day			Effects more severe at LOAEL of 500 mg/kg/day than in Fischer 344	
Neeper-Bradley (1995)	CD-1 mouse	Gavage. Days 6-15 of gestation.	50, 150, 500, 1500 mg/kg/day. Doses constant throughout study. Doses are bolus rather than continuous.	No maternal effects at any dose. Fetal – increased litters with malformations	Fetal NOAEL –150 mg/kg/day Fetal LOAEL – 500 mg/kg/day	100 (10-intraspecies, 10-interspecies)	1.5 mg/kg/day	Mouse more sensitive to developmental effects than rats. Basis for recommended New Jersey RfD and HBMCL.	10,500 ug/L

Addendum to Health-Based MCL Support Document:
Methyl Ethyl Ketone

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Summary

The basis for the New Jersey Health-based MCL for methyl ethyl ketone (MEK), which was developed in 1987, was reevaluated. The current Health-based MCL of 270 ug/L is based on an anecdotal report of effects in workers exposed to MEK by inhalation. There is currently no New Jersey or federal MCL for MEK.

A two-generation reproductive and developmental study of MEK's metabolic precursor, 2-butanol, given in drinking water to rats (Cox et al., 1975) is now considered a more appropriate basis for the oral risk assessment of MEK. The Reference Dose based on decreased pup weight in this study is 0.6 mg/kg/day. This Reference Dose was developed by USEPA for its IRIS database using benchmark dose modeling of effects seen in the study, and includes an uncertainty factor of 1000 to account for intraspecies and interspecies variability as well as uncertainties and deficiencies in the database for MEK.

The Health-based MCL derived from this Reference Dose is 4200 ug/L. This represents a 15-fold increase from the current Health-based MCL for MEK.

Current New Jersey Health-based MCL

The current New Jersey Health-based MCL for methyl ethyl ketone (MEK) is 270 ug/L (NJDWQI, 1987) based on a Reference Dose of 0.039 mg/kg/day. This Reference Dose is based on effects reported by workers exposed to MEK occupationally primarily via inhalation, including dermatitis and numbness of hands, fingers, or legs (Smith and Mayers, 1944). The Lowest Observed Adverse Effect Level (LOAEL) was identified as 300 ppm (5 days per week, 7 hours per day). Assumptions included an adult respiratory rate of 20 m^3/day, body weight of 70 kg, and 0.75 pulmonary absorption fraction. The uncertainty factor of 1000 included 10 for intraindividual variation, 10 for converting a LOAEL to a No Observed Adverse Effect Level (NOAEL), and 10 to prevent the augmentation by MEK of the toxicity of others compounds. A drinking water consumption rate of 2 L/day, a body weight of 70 kg, and a 20% Relative Source Contribution factor were used with the Reference Dose to derive the Health-based MCL.

Review of Relevant Toxicology Data

A literature review was conducted in order to determine whether any relevant information has become available since the development of the New Jersey Health-based MCL. The Toxicological Review written by USEPA (2003b) to support development of the current USEPA IRIS Reference Dose provides a detailed summary of the recent literature relevant to risk assessment of MEK.

Human Occupational Exposure to MEK

The current New Jersey Reference Dose of 0.039 mg/kg/day is based on an anecdotal study of effects of workers exposed occupationally via inhalation at exposure concentrations estimated as 300- 600 ppm (Smith and Mayers, 1944). Workers reported dermatitis as well as numbness of hands, finger, or legs. Insufficient detail is given regarding the exposure concentration, duration of exposure, number of workers affected, and other key information. USEPA (2003b) concluded that this study is of limited use in assessing the dose-response relationship between MEK exposure and neurological impairment.

Several more recent studies of symptoms in workers exposed to MEK (Freddi et al., 1982; Oleru and Onyekwere, 1992) are also not useful for risk assessment because of lack of information on exposure concentration and/or duration, or because there was exposure to other solvents in addition to MEK.

In a series of experiments, Dick et al. (1988, 1989, 1992) observed no effects on neurobehavioral parameters during and after 4 hours of exposure to 100 ppm MEK by volunteers. Nerve conduction velocity was not tested, but such effects on peripheral nerves are generally thought to occur only after long-term exposure to solvents.

Mitran et al. (1997, 2000) examined ulnar, median and peroneal motor nerve conduction velocity (NCV) parameters and sensory nerve impairment (extremity numbness), as well as psychological parameters and gastrointestinal, arthritic, respiratory and ocular irritation in 41 workers exposed to 149 – 342 ppm MEK at a cable factory in Romania and compared them to 63 controls at another factory approximately matched by age, physical activity, shift schedule and level of education. (Psychological parameters included mood disorders, memory difficulties, sleep disturbances, headache, and visual and auditory reaction times. Gastrointestinal parameters included nausea, loss of appetite, abdominal problems, "hyperacidity" (which may have meant gastric reflux), and constipation or diarrhea. Arthritic measures included joint and back pain.) They also examined workers in other factories exposed primarily to acetone or cyclohexanone. The study was conducted during the late 1980s.

They found that workers exposed to MEK exhibited decrements in NCV, particularly latency and velocity, as well as an increased frequency of reported disorders in nearly all other categories. However, auditory and visual reaction times were apparently unaffected, in contrast with workers exposed to acetone and cyclohexanone. There was no effect on serum enzymes, an indicator of liver or kidney toxicity. The lead author noted in a reply to a letter (Mitran, 2000) that tobacco and alcohol use did not affect results.

However, there were major limitations in the information gathered by Mitran et al. (1997) about other factors that can affect many of these parameters, including nerve conduction. The Methods section of this study is extremely short and lacks important information. Factor which can affect NCV measurements are not reported, such as the ambient temperature during testing, workplace exposure to vibration or repetitive motions, anthropometric factors (e.g., weight and height), caffeine use, gender (though subjects may have all been male), and the presence of diabetes. The fact that more subjects from the factory using MEK reported arthritic symptoms could easily be due to differences in repetitive tasks or exposure to vibration. Differences in digestive symptoms could

easily be due to differences in sanitary conditions, diet, work patterns immediately after break, or temporal patterns of alcohol use. Differences in psychological parameters could be related to differences in pay, overall working conditions and job stature (rewarding versus dull and boring), marital status, and so on, all of which were not noted or discussed. It is also difficult to interpret neurobehavioral data, since there is no neurobehavioral data prior to employment and because willingness to accept a job can involve a certain amount of self-selection.

While exposed workers with duration of employment of approximately 14 years were selected for the study, it does not appear that the control and exposed workers were matched by duration of employment based on the wording of the report, and there may have been ethnic and cultural differences if the factories were located in different cities or were located in urban versus small town settings. In addition, although the Mitran et al. (1997) study is the only occupational study on MEK to state that its cohort was exposed to only MEK, without exposure to other solvents, it is by no means assured that MEK was the only solvent used over the 14 years of employment. Exposure to lead was not considered, and there may also have been effects from exposure to cyanide salts if heat treating was involved. The internal validity of the findings would have been strengthened if the authors had analyzed the correlation between the NCV results and the various symptoms on an individual basis. The lack of individual-based exposure data impairs the study by limiting the ability to better examine the dose-response curve. Although the air concentration range was used as a starting point for risk assessment, past practice in factory settings around the world included use of available degreasing solvents for hand washing. Thus, it is probable that exposures were higher than indicated by considering only inhalation.

Mitran (2000) noted that this study should not be used for regulatory purposes, but that it is useful for alerting public health practitioners about the importance of looking further at this topic. Certainly, a single study with a number of important gaps cannot easily serve as anything more than support for further research.

USEPA (2003b) also discusses weaknesses in this report and concludes that it does not provide strong evidence that MEK causes persistent neurological impairment. The issues noted by USEPA include lack of information on criteria for matching exposed and control subjects, on exposure levels, and on the protocols used for the nerve conduction tests, including whether controls and exposed subjects were tested at the same location or at the same temperature (a factor which is known to affect nerve conduction velocity). No information is presented as to whether or not there is a correlation between reported neurological symptoms and changes in nerve conduction velocity, or between exposure and nerve conduction velocity. Additionally, the reported pattern of changes in nerve conduction velocity differed from that seen with solvents such as n-hexane and methyl n-butyl ketone which are known to cause peripheral neuropathy. Finally, animal studies using much higher concentrations of MEK designed to detect neurological changes, such as a study in rats exposed to 14,750 mg/m^3, 6 hours per day, 5 days per week, for 90 days (Cavender et al., 1983), did not find evidence of damage to nerve fibers.

In summary, none of the available studies of effects of MEK in exposed workers are suitable as the basis for risk assessment or Health-based MCL derivation. Additionally, the workers' exposure was through the inhalation (and possibly dermal) route, while oral studies are preferable as the basis for drinking water risk assessment.

Chronic, Subchronic, and Subacute Studies of MEK

No oral chronic or subchronic studies in experimental animals are available for MEK. For the inhalation route, no chronic studies are available, but one subchronic and several shorter duration studies have been conducted. Many of these focused on the potential for MEK to cause neurological effects. These are reviewed in NJDWQI (1987) and USEPA (2003b). Since there is no information suggesting that MEK is carcinogenic, MEK is treated as a non-carcinogen for risk assessment.

In summary, the subchronic rat study (Cavender et al., 1983) showed only transient decreased body weight and increased liver weight in both sexes, and slight decreased brain weight of females exposed to 5000 ppm for 6 hours per day, 5 days per week, for 90 days. The study included special examination of nerve tissues, as well as standard gross and microscopic pathology, and no lesions were increased in animals exposed to MEK.

Other shorter duration studies did not find evidence that MEK alone can cause nerve degeneration or other persistent neurological effects. However, MEK can potentiate the nerve degeneration caused by other neurotoxic solvents including n-hexane, methyl n-butyl ketone, and 2,5-hexanedione, which is the neurotoxic metabolite of the first two. MEK itself is not metabolized to a neurotoxic metabolite. It is thought that MEK potentiates the effect of other solvents by induction of enzymes that convert them to neurotoxic metabolites, and that MEK increases the toxicity of the toxic metabolite 2,5-hexanedione by inhibiting its further metabolism or elimination. MEK itself is not metabolized to a neurotoxic gamma-diketone.

Developmental Studies of MEK

No oral studies of reproductive or developmental effects of MEK are available.

Three inhalation studies of developmental effects of MEK have been conducted using a similar range of doses. The two rat studies (Schwetz et al., 1974 and Deacon et al., 1981) were considered during development of the original New Jersey Health-based MCL (NJDWQI, 1987), while the mouse study is more recent (Schwetz et al., 1991).

Schwetz et al. (1974) exposed pregnant Sprague-Dawley rats (21-23 per group) to filtered air or MEK at average concentrations of 1126 or 2618 ppm (3322 or 7723 mg/m^3) for 7 hours per day on days 6-15 of gestation. The experiments with each of the two doses were conducted separately, at different times. No maternal toxicity or effect on number of resorptions was seen. Slight (3-5%) but statistically significant ($p<0.05$) decreases in fetal weight and crown-rump length were seen at the low dose, but not the high dose. At the high dose, 4 fetuses from 4 different litters had rare gross malformations (2 acaudate [lacking a tail] and 2 with brachygnathia [underdeveloped lower jaw]) that had not been observed previously in over 400 historical control litters of this rat strain. The incidence of gross malformations was statistically significant compared to controls. The percentage of litters with any skeletal malformation was 58%, 95%, and 81% in control, low, and high dose groups. This was significant in the low dose group, but not in the high dose group. However, the incidence of sternebral skeletal anomalies was significant in the high dose group. For total soft tissue malformations (subcutaneous edema and dilated ureters), the percentage of litters affected was increased at both doses (51%, 70%, and 76% in control, low, and high dose groups), and this was significant in the high dose, but not the low dose group. The authors concluded that MEK at both

the high and low concentrations was embryotoxic, fetotoxic, and potentially teratogenic, which suggests a LOAEL of 1126 ppm, the lower concentration used in the study. However, USEPA (2003b) discounted the effects seen in the low dose group, and concluded that the low dose (1126 ppm) is the NOAEL while the high dose (2618 ppm) is the LOAEL for developmental effects.

A second inhalation developmental study in Sprague-Dawley rats (Deacon et al., 1981) exposed 18-26 animals per group to average concentrations of 0, 412, 1002, or 3005 ppm (0, 1215, 2955, or 8865 mg/m^3) for 7 hours per day on days 6-15 of gestation. Slight maternal toxicity, indicated by a slight decrease in weight gain and increased water consumption on day 16, was seen in the high dose group. No effects on resorptions, fetal weight or length, or gross or soft-tissue malformations were seen in this study, as compared to Schwetz et al. (1974). The percentage of litters with extra ribs was increased in the high dose group compared to controls. Therefore, the NOAEL for both maternal and fetal effects in this study was 1002 ppm and the LOAEL was 3005 ppm.

In an inhalation developmental study in CD-1 mice, Schwetz et al. (1991) exposed groups of 23-28 pregnant mice to 0, 398, 1010, or 3020 ppm (0, 1174, 2980, or 8909 mg/m^3) MEK for 7 hours per day on gestation days 6-15. In the dams, the liver-to-body-weight ratio increased with dose, and this effect was statistically significant (approximately 7% increase) at the high dose. A significant decrease in mean fetal weight per litter occurred in the high dose group. There was a dose-related trend in the incidence of fetuses with misaligned sternebrae, but there was no trend for this effect on the basis of number of litters rather than number of fetuses affected. Four malformations (cleft palate, fused ribs, missing vertebrae, and syndactyly [fused digits]) occurred which were not seen in contemporary controls in the test laboratory. The NOAEL for maternal and fetal effects was 1010 ppm and the LOAEL was 3020 ppm.

Metabolism of MEK

MEK is metabolized to 3-hydroxy-2-butanone and 2,3-butanediol, and, to a small extent, to 2-butanol (Figure 1) as reviewed by USEPA (2003b). The equilibrium between MEK and 2-butanol favors MEK. The metabolites of MEK are further broken down to CO_2 and water through intermediary metabolism pathways.

2-Butanol is almost totally converted to MEK within a short time after dosing, and similar concentrations of MEK and metabolites are seen in blood after oral dosing of rats with equimolar doses of MEK or 2-butanol, with a four hour time delay for 2-butanol compared to MEK (Dietz et al., 1981).

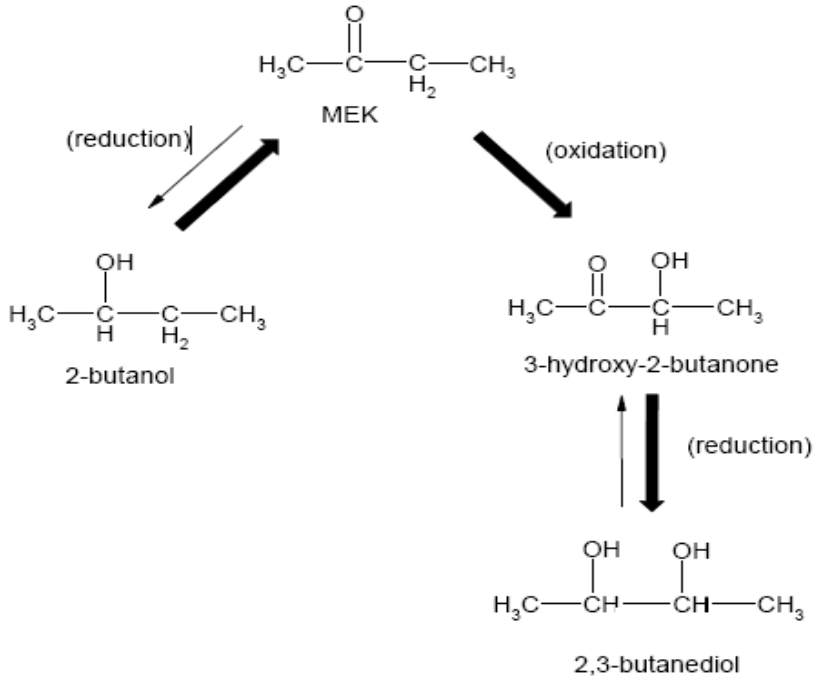

Figure 1. Proposed pathways for methyl ethyl ketone metabolism (USEPA, 2003b)

Studies on Metabolites of MEK

As discussed above, there are no oral chronic, subchronic, or developmental studies of MEK which can be used to develop a Reference Dose. Furthermore, USEPA (2003b) states that extrapolation from inhalation developmental studies in animals to an oral RfD is not possible, due to limitations in the available data on pulmonary absorption. Therefore, MEK's metabolic precursor, 2-butanol, and MEK's metabolite, 3-hydroxy-2-butanone, were considered by USEPA (2003a,b) to be surrogates for MEK, and toxicology data for these two compounds were evaluated as the possible basis for the Reference Dose for MEK. There are no relevant toxicology studies for MEK's other main metabolite, 2,3-butanediol.

Two-generation rat oral study (Cox et al., 1975)

Cox et al. (1975) conducted a two-generation reproductive and developmental toxicology study of 2-butanol in rats. Weanling FDRL-Wistar rats (30/sex/group) were given 2-butanol in drinking water at 0, 0.3, 1, or 3%. These groups of rats are the F0 generation in this study. Water consumption was measured for the first eight weeks, and these data were used to determine the average daily intakes of 2-butanol as 0, 538, 1644, and 5089 mg/kg/day for males and 0, 594, 1771, and 4571 mg/kg/day for females. Because there are no data on water consumption during gestation and lactation, exposure is estimated from the data above.

After 8 weeks of exposure, males and females from each exposure group were mated to produce litters (the F1A generation). Pups were delivered naturally, litters were culled to 8 pups at 4 days of age, and the pups were nursed for 21 days.

In the high dose (3%) group, the body weight of the parental (F0) rats was reduced by about 15%

compared to controls. In the high dose (3%) F1A litters compared to controls, there were reductions in the number of pups per litter born alive, the number of pups per litter alive at 4 days, and the mean body weight per pup at 4 days (22% decrease) and 21 days (39% decrease). In the 1% group, pup weights were reduced by 7% at day 4 and 10% at day 21, and in the 0.3% group, by 5% at day 4 and 4% at day 21. The pup body weight changes in these lower two dose groups were not seen in the litters of the next generation (F2, see below).

Because of the toxicity seen in the 3% group, the F0 and F1A animals were given water without 2-butanol for days 10 to 21 of lactation, and then the dose was reduced to 2% for the remainder of the experiment. Drinking water intake was not measured in the 2% group, and was estimated at 3384 mg/kg/day for males and 3122 mg/kg/day for females by linear regression of the reported intake data for the other concentrations (USEPA, 2003b).

Exposure for some F1A rats (30 per sex per dose group) was continued, and they were mated at age 12 weeks to produce F2 litters which were delivered and nursed through day 21 of lactation, when the F1A rats were sacrificed. No effects were seen on the reproductive performance of the F1A rats. Histopathological examination was done on 35 organs and tissues for 10 male and female rats per group, and on liver and kidneys from all F1A rats. The kidney of males, but not females, was the only organ where changes associated with MEK exposure were seen. In male rats, changes typical of alpha-2-microglobulin toxicity were seen in 0/30, 1/30, 1/30, and 8/30 rats in the 0, 0.3%, 1%, and 2% groups (data summarized by USEPA, 2003b), although the presence of this protein was not determined. Kidney toxicity in male rats due to the alpha-2-microglobulin mechanism is not considered to be relevant to humans (USEPA, 1991).

For the F2 pups, body weight was measured on days 4 and 21. F2 pup body weight was reduced in the high dose (2%) group by 5% at day 4 and 13% at day 21. Unlike what was seen in the earlier generation (F1A) pups, no statistically significant effect on body weight was seen at the two lower dose levels (0.3% and 1%).

In another part of the experiment, two weeks after lactation for the F1A pups ended, the F0 rats were mated again to produce litters of the F1B generation. At gestation day 20, 20 pregnant rats per dose group were sacrificed, and data on number of resorptions, live and dead fetuses, sex and weight of fetuses, and malformations and variations were collected. Maternal weight gain was decreased by 17% in the high dose group but was not changed in the other two groups. Fetal weight was also decreased by 10% in the high dose group. This change was not statistically significant compared to controls at the $p<0.05$ level using a t-test, but was significant with statistical tests using data from all dose levels (USEPA, 2003b). No effects on the incidence of malformations or variations compared to the control group were seen.

In this study, both the fetal and maternal LOAELs were 3,122 mg/kg/day (2% in drinking water) and the NOAELs were 1,771 mg/kg/day (1% in drinking water). Effects at 2% in drinking water included decreased fetal and pup weights, and decreased maternal weight gain. An increased incidence of kidney lesions was seen in male rats exposed to 2% MEK in drinking water from gestation through sacrifice at about 18 weeks of age. These kidney effects may be due to alpha-2-microglobulin toxicity, which is not considered relevant to humans, but this was not confirmed by measurement of this protein. Some reproductive, histopathology, and clinical chemistry parameters

included in more current studies were not included in this study (USEPA, 2003b).

Rat inhalation developmental study (Nelson et al., 1989, 1990)
An inhalation study of developmental toxicity of 2-butanol was reported by Nelson et al. (1989, 1990). In this study, groups of 11-15 pregnant Sprague-Dawley rats were exposed to 0, 3500, 5000, or 7000 ppm (0, 10,605, 15,150, or 21,210 mg/m^3) 2-butanol for 7 hours per day on gestation days 1-19. The two higher doses are higher than the highest doses used in the three inhalation studies of MEK itself which are described above. On day 20, the pregnant rats were sacrificed and fetuses were weighed and examined for malformations.

Maternal toxicity (decreased food consumption and weight gain) occurred at all three doses. A dose-related decrease in fetal weight was seen, but this was not statistically significant in the low dose group. At 7000 ppm, there was a statistically significant increase in the incidence of fetal resorptions. Also, at this dose, the incidence of pooled skeletal variations was 100% compared to 32% in the control group.

USEPA (2003b) graphed the data for fetal weight gain from two inhalation studies of MEK (Schwetz et al., 1974, 1991) along with the same data from the study of 2-butanol (Nelson et al., 1989, 1990). The graph demonstrates that the dose-response curves for changes in fetal body weight are consistent for MEK and its metabolite, 2-butanol, and provides further evidence that 2-butanol is an appropriate surrogate for MEK.

Subchronic Study of 3-Hydroxy-2-Butanone
A 13 week drinking water rat study of the MEK metabolite 3-hydroxy-2-butanone was conducted by Gaunt et al. (1972). Rats (15 per sex per group) were exposed to 0, 750, 3000, or 12,000 ppm in drinking water. Based on measurement of drinking water consumption, average doses were calculated as 0, 80, 318, and 1286 mg/kg/day in males and 0, 91, 348, or 1404 mg/kg/day in females. Other groups (5 per sex per dose) were exposed for 2 or 6 weeks. Urinanalysis, blood chemistry, hematology, and histological examination of organs and tissues were performed.

In this study, 3000 ppm was the NOAEL and 12,000 ppm was the LOAEL. Effects seen at the LOAEL included reduced body weight, which was significant only in males at weeks 8 and 13, increased relative liver weight in both sexes (thought to be an adaptive response to metabolism of the test compound), and slight anemia (decreased hemoglobin and red blood cell count) which was statistically significant in both sexes.

Current USEPA Assessments

Lifetime Drinking Water Health Advisory
There is no USEPA MCL or MCLG for MEK. The Drinking Water Lifetime Health Advisory for MEK (USEPA, 2006) is currently 4000 ug/L, based on the current IRIS Reference Dose discussed below (USEPA, 2003a).

IRIS Assessment

Selection of study

USEPA (2003a) finalized an updated IRIS assessment including an oral Reference Dose, an inhalation Reference Concentration, and a Carcinogenicity Assessment in 2003. The background for this assessment is given in a Toxicological Review (USEPA, 2003b).

The two generation reproductive and developmental study of 2-butanol given to rats in drinking water (Cox et al., 1975) was chosen as the basis for the RfD based on the following rationale: 1) similar effects on developmental toxicity were seen in inhalation studies of MEK and 2-butanol, and the dose response curves for changes in fetal weight are consistent for these two chemicals. 2) Pharmacokinetic studies show that 2-butanol is almost completely metabolized to MEK, and exposure to equimolar doses of MEK and 2-butanol results in a similar quantitative and qualitative profile of MEK and metabolites.

The other study considered for Reference Dose development by USEPA (2003b) was the 13 week subchronic rat study of the MEK metabolite, 3-hydroxy-2-butanone. This study was not chosen as the basis for the Reference Dose because slight anemia (effects on hemoglobin concentration and red blood cell count) which was the major effect observed was not seen in other studies of MEK or 2-butanol.

Benchmark dose modeling

Benchmark dose modeling was performed by USEPA (2003b) on three endpoints from Cox et al. (1975). These were decreased fetal weight in the F1B generation that was sacrificed on gestation day 20, and decreased pup weight on postnatal days 4 and 21 from the F1A and F2 generations. A 5% reduction in fetal or pup weight was selected as the benchmark response to be modeled, and the effective dose (ED_{05}) and 95% lower bound on the effective dose (LED_{05}) were modeled.

Because the high dose exposure (3%) group of the F1A generation exhibited severe toxicity including decreased pup survival, necessitating change of the high dose to 2% for the remainder of the study, only data from the two lower dose groups were modeled for the F1A generation.

The results of the benchmark modeling done by USEPA (2003b) are shown in Table 1. For each endpoint, the benchmark doses are based on the model giving the best fit to the data. The data for decreased pup weight at day 21 for the F1A pups gave the lowest LED_{05}, 657 mg/kg/day, and this was selected as the point of departure for the Reference Dose. Additionally, the F1A pup weight data showed a better dose-response than the data for the other endpoints modeled. The point of departure, 657 mg/kg/day, is below the dose identified as a NOAEL by USEPA, 1644 mg/kg/day (1% in drinking water) and is close to the low dose in the study, 538 mg/kg/day (0.3% in drinking water).

Table 1: Benchmark doses for developmental effects in rats exposed to 2-butanol in drinking water by Cox et al., 1975 (from USEPA, 2003b)

Endpoint	ED_{05} (mg/kg/day)	LED_{05} (mg/kg/day)
F1A pup weight, postnatal day 4[a]	1387	803
F1A pup weight, postnatal day 21[a]	878	657
F1B fetal weight, gestation day 20	2198	1046
F2 pup weight, postnatal day 4	3471	1347
F2 pup weight, postnatal day 21	2056	901

[a] Data modeled did not include high dose group (3%) due to severe toxicity at this dose.

Derivation of USEPA IRIS Reference Dose

The 95% lower bound on the effective dose (LED_{05}) of n-butanol for a 5% decrease in weight on postnatal day 21, 657 mg/kg/day, was used as the point of departure (POD) for the Reference Dose. The point of departure in developing a Reference Dose using benchmark dose modeling is analogous to the NOAEL or LOAEL used in traditional Reference Dose development. It is the dose from the toxicological study to which uncertainty factors are applied to derive the Reference Dose. Based on the molecular weights of n-butanol (74 g/mol) and MEK (72 g/mol), 657 mg/kg/day n-butanol is equivalent to 639 mg/kg/day MEK.

A total uncertainty factor of 1000 was used, including a factor of 10 for extrapolation from animals to humans, a factor of 10 for variation in susceptibility within humans, and a factor of 10 for database deficiencies and uncertainties including the use of 2-butanol as a surrogate for MEK, and the lack of chronic toxicity data for MEK or 2-butanol. The resulting Reference Dose is **0.6 mg/kg/day.**

Although no chronic studies are available, the F1A generation of rats in the Cox et al. (1975) drinking water study was exposed to 2-butanol for about 18 weeks (equivalent to subchronic exposure) and Cavendar et al. (1983) exposed rats to MEK by inhalation for 90 days. No histopathologic changes were seen in these studies, except for the kidney effects in the males in Cox et al. (1975) which are not considered relevant to humans, reducing the uncertainty due to lack of chronic studies. An uncertainty factor for lack of chronic exposure is used when a subchronic study is the basis of the risk assessment, but not when a developmental study is used, since the period of exposure in a developmental study includes the period of exposure of concern for developmental effects. Therefore, the factor of 10 for database deficiencies discussed above is considered sufficiently protective although there is no chronic study for MEK.

It should be noted that USEPA's previous IRIS assessment for MEK which was developed in 1993 derived the same Reference Dose, 0.6 mg/kg/day, from a NOAEL of 1771 mg/kg/day that was based on decreased fetal weight in the F1B generation in Cox et al. (1975), the same study used as the basis for the current IRIS Reference Dose. This Reference Dose was not developed using benchmark dose modeling.

Reevaluation of Current New Jersey Health-based MCL

Choice of Reference Dose

As discussed above, the current New Jersey Health-based MCL for MEK is 270 ug/L (NJDWQI, 1987) based on a Reference Dose of 0.039 mg/kg/day. This Reference Dose is based on effects reported by workers exposed to MEK occupationally via inhalation, including dermatitis and numbness of hands, fingers, or legs (Smith and Mayers, 1944). This study can be considered anecdotal in nature, as insufficient detail is given regarding the exposure concentration, duration of exposure, number of workers affected, and other key. This study is not considered to be appropriate for development of an oral Reference Dose or Health-based MCL according to current risk assessment practices.

The Reference Dose developed by USEPA (2003b) of 0.6 mg/kg/day, discussed in detail above, is recommended as the basis for the New Jersey Health-based MCL for MEK. As discussed above, it is based on the most sensitive endpoint for oral effects of 2-butanol, a metabolic precursor of MEK, and the uncertainty factors used in its development are judged to be sufficiently protective. The Reference Dose is supported by data from other studies of MEK and 2-butanol given by inhalation data on MEK.

Calculation of the Health-based MCL

The recommended Health-based MCL is derived as follows

$$MCL = \frac{0.6 \text{ mg/kg/day} \times 70 \text{ kg} \times 0.2}{2 \text{ L/day}}$$

$$= 4.2 \text{ mg/L} = 4200 \text{ ug/L}$$

Where:
0.6 mg/kg/day = Reference Dose
70 kg = assumed body weight of adult
0.2 = default value for Relative Source Contribution from drinking water
2 L = assumed adult daily drinking water intake

Conclusion

Based on the above, a Reference Dose of 0.6 mg/kg/day and a Health-based MCL of 4200 ug/L are recommended.

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Addendum to Health-Based MCL Support Document:
1,1,2,2-Tetrachloroethane

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Summary

The basis for the New Jersey Health-based MCL for 1,1,2,2-tetrachloroethane which was developed in 1994 was reevaluated. 1,1,2,2-Tetrachloroethane caused a statistically significant increase in the incidence of liver cancer in male and female mice. It is classified in New Jersey Carcinogenicity Category II, analogous to Suggestive Carcinogen, under the 2005 USEPA Guidelines for Cancer Risk Assessment. A cancer slope factor based on liver tumors in female mice has been developed by USEPA and is provided in the IRIS database. The risk assessment approach for Category II chemicals is based on the cancer slope factor at the 10^{-6} risk level, if a slope factor is available from USEPA and not judged to be technically unsound by NJDWQI. A Health-based MCL of 0.18 ug/L, based on the cancer slope factor, is recommended. This represents a five-fold decrease from the current New Jersey Health-based MCL of 1 ug/L.

Current New Jersey Risk Assessment

The current New Jersey Health-based MCL for 1,1,2,2-tetrachloroethane is 1 ug/L (NJDWQI, 1994). This Health-based MCL is based on two toxicity studies which provided very similar Reference Doses.

A Reference Dose of 0.00023 mg/kg/day was based upon a 25 week gavage study in rats (Gohlke et al., 1977). At the Lowest Observed Adverse Effect Level, 3.2 mg/kg/day (given 5 days/week and equivalent to a daily dose of 2.3 mg/kg/day), histological changes were seen in the liver, kidney, testes, thyroid gland, and adrenal gland. An uncertainty factor of 10,000 was applied, including a factor of 1000 for a LOAEL in a chronic study and a factor of 10 to account for possible carcinogenicity (see below). The health-based drinking water concentration derived from this Reference Dose, using standard assumptions of 70 kg body weight, 2 L/day water consumption, and 20% Relative Source Contribution factor, was 1.6 ug/L.

A second Reference Dose of 0.000134 mg/kg/day was derived from the chronic (9 month) rat inhalation study of Schmidt et al. (1972). The Lowest Observed Effect Level was seen at an air concentration of 13.3 mg/mg^3, given 4 hours per day, 7 days per week. At this concentration, the dose was determined to be 1.34 mg/kg/day, based on a body weight of 0.415 kg, a respiratory rate of 0.25 m^3/day, and 100% pulmonary absorption factor. At this dose, effects seen included increased fat content of the liver, increased pituitary hormone (ACTH), increased white blood cell count, and decreased body weights compared to controls. As above, an uncertainty factor of 10,000 was applied, including a factor of 1000 for a LOAEL in a chronic study and a factor of 10 to account for possible carcinogenicity (see below). The health-based drinking water concentration derived from this Reference Dose, using standard assumptions (as above), was 0.94 ug/L.

1,1,2,2-Tetrachloroethane was classified as a possible human carcinogen (New Jersey Group II, USEPA Group C), based on results of the National Cancer Institute (1978) bioassay. In this study,

1,1, 2,2- tetrachloroethane was given by gavage for 78 weeks to male and female Osborne-Mendel rats and B6C3F1 mice. No statistically significant increase in tumors was seen in rats, while in mice, a highly significant dose-related increase in the incidence of liver tumors occurred in both sexes.

USEPA Assessment

USEPA has not developed an MCL or an MCLG for 1,1,2,2-tetrachloroethane. The USEPA Office of Water (1989) developed a Reference Dose of 0.0000456 mg/kg/day which forms the basis for its Lifetime Health Advisory of 0.3 ug/L.

The basis for the Reference Dose is the 9 month inhalation rat study of Schmidt et al. (1972). The assumptions used to develop the Reference Dose differ slightly from those used by New Jersey (above). The rat body weight was assumed to be 0.35 kg, the respiratory rate used was 0.24 m^3/day, and the absorption factor was 0.3. An uncertainty factor of 10,000 was used, including a factor of 10 for less than lifetime study duration. An additional uncertainty factor for possible carcinogenicity was not applied because the drinking water concentration based on the Reference Dose is almost identical to the drinking water concentration based on a 10^{-6} cancer risk level (see below). (The inclusion of this additional uncertainty factor would result in a total uncertainty factor of 100,000, which exceeds the maximum uncertainty factor recommended by USEPA of 10,000.)

USEPA's IRIS database (2005a) classified 1,1,2,2-tetrachloroethane as a possible human carcinogen (Group C) under the 1986 USEPA cancer risk assessment guidelines. A highly significant dose-related increase in the of liver carcinomas was seen in mice in the NCI (1978) bioassay, while no significant increase in tumor incidence was seen in rats. In this study, groups of 50 each male and female Osborne- Mendel rats and B6C3F1 mice were gavaged with technical grade (90% pure) 1,1,2,2 -tetrachloroethane in corn oil, 5 days/week. Treatment occurred for 78 weeks, followed by observation periods of 32 weeks for the rats and 12 weeks for the mice. The high and low average doses were, respectively, 108 and 62 mg/kg/day for male rats, 76 and 43 mg/kg/day for female rats, and 282 and 142 mg/kg/day for mice of both sexes. Corn oil and untreated control groups consisted of 20 animals/sex and species.

The incidence of liver tumors in female mice was 0/20 in controls, 30/48 at the low dose, and 43/47 at the high dose. Based on these data, USEPA developed an oral slope factor of 0.2 $(mg/kg/day)^{-1}$. The drinking water concentration at the 10^{-6} cancer risk level based on this slope factor is 0.2 ug/L.

Results of Literature Review

A literature review was conducted in order to determine whether any relevant studies had become available since the development of the New Jersey Health-based MCL. Two studies completed by the National Toxicology program were located.

NTP (1996) conducted a short term (21 day) renal toxicity assessment in male rats on a series of ten halogenated ethanes including 1,1,2,2-tetrachloroethane in order to study the structure-activity relationships in renal toxicity involving hyaline drop nephropathy. This phenomenon in male rats is associated with alpha-2-microglobulin accumulation which leads to renal tumors. Since this does not occur in humans, tumors arising through this mechanism are considered not relevant as indicators of carcinogenic potential in humans. Of the chemicals tested, only hexachloroethane,

pentachloroethane, and 1,1,1,2-tetrachloroethane caused hyaline drop nephropathy, while 1,1,2,2-tetrachloroethane did not. This study does not impact the risk assessment of 1,1,2,2-tetrachloroethane, as it did not cause kidney tumors in male rats.

NTP (2004) also completed a 14 week study of 1,1,2,2-tetrachloroethane administered in microcapsules in feed. The rationale for the study was that a drinking water study would not be feasible due to the limited solubility of 1,1,2,2-tetrachloroethane in water, and that microencapsulation in feed simulates exposure via drinking water. Doses were chosen based on an earlier 15-day range finding study. Groups of 10 male and female F344/N rats and B6C3F1 mice were fed diets containing 268, 589, 1180, 2300 or 4600 ppm (rats) or 589, 1120, 2300, 4550, or 9100 (mice). Two separate control groups were fed normal feed or microcapsules with no 1,1,2,2-tetrachloroethane. The average daily doses for rats were 20, 40, 80, 170, and 320 mg/kg/day for both sexes. For mice, the average daily doses were 100, 200, 370, 700, and 1360 mg/kg/day for males and 80, 160, 300, 600, and 1400 mg/kg/day for females.

In rats, body weight gains were significantly reduced at 80 mg/kg/day or higher. Relative liver weights were increased significantly at 40 mg/kg/day and above. Treatment related changes in enzyme levels and biochemical parameters indicative of liver toxicity were seen, and at the two highest doses, hypertrophy and necrosis of the liver occurred. Additionally, atrophy of the bone, bone marrow, and reproductive systems was seen in the highest dose group in males and the two highest dose groups in females. The No Observed Adverse Effect Level for male and female rats was 268 ppm (20 mg/kg/day).

In mice, body weight gain at 2300 ppm (370 mg/kg/day in males and 300 mg/kg/day in females) was decreased compared to controls. Liver weights were significantly increased in all but the lowest dose group in males and in all groups of females. Hypertrophy of the hepatocytes, as well as necrosis, focal pigmentation, and bile duct hyperplasia were seen in all but the lowest dose group in males and females. The authors of the study do not provide a No Observed Adverse Effect Level (NOAEL) or Lowest Observed Adverse Effect Level (LOAEL) for mice because 1,1,2,2-tetrachloroethane has been shown to be carcinogenic in mice, but, based on the above data, no NOAEL was seen and the LOAEL was 80 mg/kg/day (589 ppm) in females based on increased liver weight.

Additionally, the authors point out that body weight gain was not affected in mice given 1120 ppm while body weight gains were decreased in rats given a similar dose, 1180 ppm. However, the incidence of hepatic hypertrophy was greater in mice than in rats at this dose. This suggested that mice could tolerate 1,1,2,2-tetrachloroethane better than rats, but that their livers may be more sensitive to its effects.

Reevaluation of Current Health-based MCL

Reevaluation of Reference Dose

The subchronic microencapsulation study (NTP, 2004) is relevant to Health-based MCL development because the dosing regimen is designed to simulate drinking water exposure. In this study, the most sensitive endpoint was increased liver weight in rats. The NOAEL for this endpoint was 20 mg/kg/day.

A Reference Dose based upon this endpoint is derived as follows:

$$\frac{20 \text{ mg/kg/day}}{1000 \times 10} = 0.0002 \text{ mg/kg/day}$$

Where:
1000 is the uncertainty factor appropriate for use with a NOAEL for a subchronic study (10 for intraspecies variability, 10 for interspecies extrapolation, 10 for subchronic to chronic)

10 is the additional uncertainty factor for chemicals classified as Suggestive Carcinogens or Possible Human Carcinogens.

Calculation of Health-based MCL
The health-based drinking water concentration based on the above Reference Dose is:

$$\frac{0.0002 \text{ mg/kg/day} \times 70 \text{ kg} \times 0.2}{2 \text{ L}} = 1.4 \text{ ug/L}$$

Where:
70 kg = assumed body weight of adult
0.2 = default value for Relative Source Contribution from drinking water
2 L = assumed adult daily drinking water intake

This concentration is very close to the current Health-based Maximum Contaminant Level of 1 ug/L. It should be noted that this Reference Dose derivation is presented for illustrative purposes only, as the recommended Health-based MCL is based on carcinogenic effects, as discussed below.

Risk Assessment based on Carcinogenic Endpoint

1,1,2,2-Tetrachloroethane was classified as a Possible Human Carcinogen (Group C) by New Jersey (NJDWQI, 1994) and USEPA (2005a) under the 1986 USEPA risk assessment guideline, based on carcinogenic effects in mice in the NCI (1978) bioassay. Based on these results, it is similarly appropriate to classify 1,1,2,2-tetrachloroethane as a Suggestive Carcinogen under the 2005 USEPA Guidelines for Carcinogen Risk Assessment (USEPA, 2005b).

New Jersey policy for chemicals classified as Suggestive Carcinogens or Possible Human Carcinogens is to base the risk assessment upon the carcinogenic slope factor at the 10-6 risk level, if such a slope factor is available from USEPA and is judged technically sound by the Department.

As discussed above, for 1,1,2,2-tetrachloroethane, a slope factor has been derived by USEPA and is presented in the IRIS database (USEPA, 2005a). The slope factor of 0.2 $(\text{mg/kg/day})^{-1}$ is based upon the incidence of hepatocellular carcinomas in female mice in the NCI (1978) bioassay.

The health-based drinking water concentration using this slope factor, at the 10^{-6} risk level, is derived as follows:

Daily dose at 10^{-6} risk level: $\frac{10\text{-}6}{0.2\ (\text{mg/kg/day})^{-1}} = 0.000005$ mg/kg/day

Health-based drinking water concentration:

$$\frac{0.000005\ \text{mg/kg/day} \times 70\ \text{kg}}{2\ \text{L}} = 0.000175\ \text{mg/L or } 0.175\ \text{ug/L}$$

Where:
70 kg = assumed body weight of adult
0.2 = default value for Relative Source Contribution from drinking water
2 L = assumed adult daily drinking water intake

Health-based MCL Recommendation

In accordance with the New Jersey policy for risk assessment of chemicals classified as Suggestive Carcinogens, it is recommended that the Health-based MCL for 1,1,2,2-tetrachloroethane be based on the carcinogenic endpoint derived above.

The recommended Health-based MCL is 0.18 ug/L, which is rounded from the value of 0.175 ug/L derived above. This represents a five-fold decrease from the current New Jersey Health-based MCL of 1 ug/L.

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Addendum to Health-Based MCL Support Document:
1,2,4-Trichlorobenzene

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Summary

The current New Jersey Reference Dose, carcinogenicity classification, and Health-based MCL for 1,2,4-trichlorobenzene, which were developed in 1987, were reevaluated. Chronic oral studies in rats and mice have been conducted which were not available when the current Health-based MCL was developed.

In the chronic mouse study, 1,2,4-trichlorobenzene caused liver tumors in male and female mice. Based on these data and the current USEPA cancer risk assessment guidelines, it is recommended that 1,2,4-trichlorobenzene be placed in New Jersey Carcinogenicity Category II, analogous to Suggestive Evidence of Carcinogenic Potential under the current USEPA (2005) guidance. USEPA IRIS does not provide a slope factor for 1,2,4-trichlorobenzene, and it is recommended that an additional uncertainty factor of 10 for potential carcinogenicity be incorporated into the Reference Dose.

A Reference Dose of 0.0026 mg/kg/day, based on a LOAEL of 26.3 mg/kg/day for increased liver weight in the chronic oral mouse study and a total uncertainty factor of 10,000 is recommended to replace the current Reference Dose. The current Reference Dose of 0.0012 mg/kg/day is based on a NOAEL of 1.235 mg/kg/day (converted from inhalation concentration) for increased excretion of porphyrins in urine in a subchronic inhalation study in rats, with a total uncertainty factor of 1000.

The recommended Reference Dose of 0.0026 mg/kg/day is about a two-fold higher than the current Reference Dose of 0.0012 mg/kg/day. The recommended Health-based MCL is 18 ug/L, also a two-fold increase from the current value of 8.6 ug/L.

Risk Assessment developed by New Jersey

The Reference Dose developed by New Jersey for 1,2,4-trichlorobenzene (NJDWQI, 1987) is based on the No Observed Adverse Effect Level (NOAEL) of 3 ppm in a 3 month subchronic inhalation study in rats (Watanabe et al., 1978). At a higher dose (10 ppm), a slight increase in urinary excretion of porphyrins occurred, which returned to control levels within several months after exposure ended. This dose is equivalent to 1.235 mg/kg/day, assuming exposure 6 hours per day, 5 days per week, pulmonary absorption factor of 50%, 0.011 m^3/hr breathing rate, and 0.423 kg body weight. An uncertainty factor of 1000, appropriate for a NOAEL from a subchronic study was applied to derive the Reference Dose of 0.001235 mg/kg/day.

1,2,4-trichlorobenzene was classified as New Jersey Carcinogenicity Category III (not classifiable as to human carcinogenicity, equivalent to USEPA Group D) as there was no evidence for carcinogenicity in experimental animals.

The Reference Dose developed by New Jersey, 0.0012 mg/kg/day, resulted in a Health-based MCL of 8.6 ug/L, using standard assumptions of 2 L/day water consumption, 70 kg body weight, and 20% Relative Source Contribution factor.

USEPA Assessment

USEPA (1989) developed a lifetime Health Advisory of 9 ug/L based on the same study (Watanabe et al., 1987), endpoint, uncertainty factors, and almost identical assumptions as those used by NJDWQI (1987), discussed above. USEPA (1990) proposed a Maximum Contaminant Level Goal (MCLG) of 9 ug/L based on this approach.

In response to comments received regarding its proposed MCLG, USEPA (1992) developed a Reference Dose of 0.01 mg/kg/day and adopted a final MCLG of 70 ug/L based on a different study than Watanabe et al. (1987) which is discussed below. In addition to being used as the basis for the MCLG, this Reference Dose was also incorporated into the USEPA IRIS (2002) database in 1996.

The USEPA Reference Dose is based on a multigeneration reproductive study in rats (Robinson et al., 1981). (This study was cited by NJDWQI, 1987, but was not used as the basis for the Reference Dose.) At birth of the F0 generation, litters (17-23 litters/dose group) were randomly reduced to 4 males and 4 females. Male and female progeny were dosed with 0, 25, 100 or 400 ppm of 1,2,4-trichlorobenzene in the drinking water. During the study, maternal weights, litter size, neonate sex and weight, and 24-hour food and water intake were recorded. Blood samples and organs were collected on days 27 and 95 of age from selected rats from each group for chemistry determinations (i.e., glucose, BUN, creatinine, Na, K, Cl, uric acid, Ca, P, cholesterol, triglyceride, bilirubin, alkaline phosphatase, SGOT, SGPT, LDH, CPK, protein, globulin and albumin) and organ weights (i.e., liver, kidney, uterus, adrenals, lungs, heart and gonads). Similar procedures were performed with the F1 generation. The study ended when the F2 generation was 32 days old. Fertility (as indexed by conception rate of dams) of the F0 and F1 generation rats was not affected by treatment. A significant increase (11% in males, 13% in females) in adrenal gland weights was observed in the 400 ppm groups of males and females of the F0 and F1 generations.

The authors duplicated the increase in adrenal weights in an acute experiment in which preweanling females were given three daily intraperitoneal injections of 1,2,4-trichlorobenzene. The acute experiment was performed to show that the adrenal enlargement was not due to either estrogenic properties of 1,2,4-trichlorobenzene or to long-term stress. The NOAEL was determined to be 100 ppm from the mid-dose group. The LOAEL was determined to be 400 ppm on the basis of increased adrenal gland weight.

A 1-month study, which repeated part of the Robinson et al. (1981) study, was performed by the USEPA (described in USEPA, 2002). Five rats/group were dosed with 53 mg/kg/day 1,2,4-trichlorobenzene (the LOAEL from the Robinson study) in corn oil by gavage. Microscopic examination of the 1,2,4-trichlorobenzene treated rats showed moderate vacuolization of the adrenal zona fasciculata; the control group showed only slight vacuolization. Twenty-four hour urine and serum specimens were collected prior to post mortem examination. A 14% increase in absolute adrenal gland weight was observed and a 13% adrenal gland/body weight ratio was observed. This study indicated that the increase in adrenal gland weight observed by Robinson et al. (1981) could be

associated with vacuolization of the zona fasciculata (Cicmanec, 1991). In addition, the treated rats had decreased serum corticosterone levels when compared with controls.

The USEPA Reference Dose is based upon a dose of 14.8 mg/kg/day, which is the dose received by the female rats in the 100 ppm group. An uncertainty factor of 1000, appropriate for a NOAEL from a subchronic study, was applied to derive a Reference dose of 0.01 mg/kg/day. Standard assumptions of 70 kg body weight, 2 L/day water consumption, and 20% Relative Source Contribution factor were applied to develop the MCLG of 70 ug/L.

Results of Literature Review

Results of chronic dietary studies in rats and mice were submitted to USEPA's TSCA in 1994 by the Chemical Manufacturers Association.

In the mouse study (Hazleton Washington, 1994a), B6C3F1 mice (50 per sex per dose group) were exposed to dietary concentrations of 0, 150, 700 or 3200 ppm for at least 104 weeks. The mean daily consumed doses were 21.0, 100.6, and 519.9 mg/kg/day in males and 26.3, 127.0, and 572.6 mg/kg/day in females. Parameters evaluated were mortality, clinical observations, body weight, food consumption, hematology parameters, organ weights, and gross and microscopic pathology.

Results of the study indicate that the liver was the target organ for 1,2,4-trichlorobenzene toxicity, and various observations regarding other organs were not considered to be related directly to exposure to 1,2,4-trichlorobenzene.

In the low dose group (150 ppm), an increased incidence of distended abdomen (22% of males and 26% of females) was observed compared to 12% of control animals. A significant increase was seen in the mean liver weight in both sexes, with a significant increase in the liver-to-body weight and liver-to-brain weight ratios in females. An increased incidence in benign or malignant liver tumors was not seen in this dose group.

In the mid-dose group (700 ppm), 34% of males and 38% of females had distended abdomens, and liver masses were observed in 74% of each sex. Mean absolute liver weights and live-to-body weight ratios were increased in males and females, and liver-to-brain weight ratios were increased in females. The incidence of both liver adenomas and carcinomas was increased compared to controls, as shown in Table 1 below. Centrilobular hepatocytomegaly was seen in 54% of males and 2% of females, as compared to none of the control or low dose animals.

In the high-dose group (3200 ppm), survival was significantly reduced compared to controls. Among high-dose mice, only 5/50 males and 0/50 females survived to termination compared with 74-90% survival in all other groups. The increase in mortality of high-dose animals began at approximately week 65-70, and progressed rapidly for the remainder of the study. Mean body weights were significantly lower in high-dose males and females throughout the study relative to control animals. In other treatment groups, body weights were inconsistent compared with controls, but were frequently higher over the course of the study.

Most deaths in high-dose mice occurred as a result of hepatocellular neoplasms, primarily

carcinomas. Hepatocellular carcinomas were present in 100% of high-dose males, 92% of high-dose females, and approximately 55% of mid-dose males and females (Table 1). The tumors were reported to be mostly large and often multiple, frequently with pulmonary metastases. Hepatocellular adenomas were also increased in incidence (except for in high-dose males, in which it was noted that they were likely overwhelmed by the extent of carcinoma development). Incidences of combined adenomas and carcinomas were not provided. In addition to hepatic neoplastic lesions, 1,2,4-trichlorobenzene resulted in enlargement of hepatocytes from many mid- and high-dose males, including animals with and without concurrent hepatic neoplasia. Other hepatic alterations included focal necrosis, portal inflammation and fibrosis, regenerative changes. Mean terminal liver weights were significantly increased in males of all treatment groups compared to controls, and in low- and mid-dose females compared to controls (all high-dose females died prior to termination).

Table 1. Tumor incidence data from mice exposed to 1,2,4-trichlorobenzene (Hazleton Washington, 1994a)

	Male Mice		Female Mice	
Dose group (mg/kg-day)	Hepatocellular adenoma	Hepatocellular carcinoma	Hepatocellular adenoma	Hepatocellular carcinoma
0	4/49 [1]	8/49	3/50	1/50
150	7/50	5/50	4/50	1/50
700	16/50	27/50	16/50	28/50
3200	2/50	50/50	8/50	46/50

[1] Number of animals with the tumor / number of animals examined.

Based on the results summarized above, a NOAEL for non-carcinogenic effects of 1,2,4-trichlorobenzene in mice was not observed in this study. The LOAEL was 21 mg/kg/day in males and 26.3 mg/kg/day in females, based upon the effects on liver weight in the low-dose group. These effects are considered especially significant because the liver was the target organ for the toxicity of 1,2,4-trichlorobenzene in this study. For carcinogenic effects, a dose related increase in the incidence of liver tumors was seen.

In the rat study (Hazleton Washington, 1994b), F-344 mice (50 per sex per dose group) were exposed to dietary concentrations of 0, 100, 350 or 1200 ppm for at least 104 weeks. The mean daily consumed doses were 5.6, 19.4, and 66.5 mg/kg/day in males, and 6.9, 23.5, and 81.4 mg/kg/day in females. Parameters evaluated were mortality, clinical observations, bodyweight, food consumption, hematology parameters, organ weights, and gross and microscopic pathology.

No treatment-related effects were observed in the low-dose or mid-dose groups. In the high-dose group, a significant decrease in survival of males was seen at week 104 and mean body weight gain was decreased in both sexes in weeks 1 through 24. Heptocellular hypertrophy was seen in 60% of males and 74% of females, compared to 4% of control males and 12% of control females. The incidence of fatty liver in males and females and hepatic focal cystic degeneration was also increased. Liver weight and liver-to-body weight ratios were significantly increased in both sexes and liver-to-brain weight ratio was significantly increased in males. Additionally, renal pelvis

mineralization, transitional cell hyperplasia of the renal pelvic urothelium in males, and chronic progressive nephropathy were increased compared to controls.

No evidence of carcinogenicity was seen in rats in this study.

The results summarized above indicate that the NOAEL for 1,2,4-trichlorobenzene in rats in this study was 19.4 mg/kg/day in males and 23.5 mg/kg/day in females.

Reevaluation of Carcinogenicity Classification and Risk Assessment Approach

1,2,4-trichlorobenzene caused a dose-related increase in the incidence of liver cancers in male and female mice (Hazleton Washington, 1994a), but did not cause tumors in rats (Hazleton Washington, 1994b).

As reviewed by California EPA (1999), genotoxicity tests have given mixed results. 1,2,4-Trichlorobenzene was negative for mutagenicity in multiple strains of *Salmonella typhimurium* and in *E. coli* with and without metabolic activation, and was also negative for DNA repair rat hepatocytes in culture. It was positive for cellular transformation in adult rat liver epithelial cells, and caused a dose-related increase in the number of micronucleated bone marrow cells in eight week old mice injected intraperitoneally.

Based on the above information, 1,2,4-trichlorobenzene meets the criteria for the descriptor "suggestive evidence of carcinogenic potential" under the USEPA Guidelines for Carcinogen Risk Assessment (2005).

For chemicals classified as having suggestive evidence of carcinogenic potential, the risk assessment approach used by NJDWQI preferentially utilizes a carcinogenic slope factor at the 10^{-6} risk level, if such a slope factor is available from USEPA and is judged technically sound by the Department. If such a slope factor is not available, a Reference Dose based upon non-carcinogenic toxicity with an additional uncertainty factor of 10 to protect for possible carcinogenic effects is used.

For 1,2,4-trichlorobenzene, a slope factor is not available. Therefore, the risk assessment is based upon a Reference Dose approach.

Reference Dose Development

Four studies were considered in selecting the study most appropriate as the basis for the oral Reference Dose.

The subchronic rat inhalation study of Watanabe et al. (1978) forms the basis for the current New Jersey Health-based MCL. The NOAEL in this study, 3 ppm, was calculated to be 1.2 mg/kg/day, based on extrapolation from inhalation exposure. At a higher dose of 10 ppm, equivalent to 4 mg/kg/day, a slight increase in excretion of urinary porphyrins occurred, which was reversible after exposure ended. This study is not judged to be the most appropriate for Reference Dose development, as oral studies are preferable to inhalation studies, and suitable chronic oral studies are now available.

The multigeneration rat drinking water study (Robinson et al., 1981) which forms the basis for the

USEPA IRIS Reference Dose and MCLG was also considered. The duration of exposure in this study was subchronic, and the NOAEL was 14.8 mg/kg/day in females and 8.9 mg/kg/day in males. At higher doses, adrenal gland weight was increased. This study was not was not judged most appropriate because chronic oral studies in mice and rats are now available, and chronic studies are preferable to subchronic studies.

In the chronic dietary rat study discussed above (Hazleton Washington, 1994b), the NOAEL was 19.4 mg/kg/day in males and 23.5 mg/kg/day in females. At a higher dose, effects on survival and body weight occurred, and pathological changes in the liver and kidney were seen.

In the chronic dietary mouse study discussed above (Hazleton Washington, 1994a), a NOAEL was not observed. In the lowest dose group, 21.0 mg/kg/day in males and 26.3 mg/kg/day in females, an increased incidence of distended abdomens and effects on liver weight were seen. In males, the absolute liver weight was significantly increased, while in females, the absolute liver weight as well as the liver-to-body weight and the liver-to-brain ratios were significantly increased. At higher doses, additional liver toxicity occurred.

Increased urinary porphyrins, the basis for the current New Jersey Reference Dose, were not measured in the chronic rat and mouse studies (Hazleton Washington, 1994 a, b) as these studies were designed to evaluate carcinogenic potential. However, the NOAEL for increased urinary porphyrins in rats was 50 mg/kg/day in an oral 120 day study (Carlson, 1977), while increased urinary porphyrins occurred at 100 mg/kg/day and above. Thus, the oral NOAEL for increased urinary porphyrins is greater than the LOAEL in the chronic mouse study (Hazleton Washington, 1994a) study.

Based on the above, the mouse appears to be more sensitive than the rat to the effects of 1,2,4-trichlorobenzene, and the chronic mouse study (Hazleton Washington, 1994a) is judged most appropriate as the basis of the Reference Dose. Since the ratio of the liver weight to both body weight and brain weight were significantly increased in females but not in males, the female dose of 26.3 mg/kg/day is used as the LOAEL.

For a LOAEL from a chronic study, an uncertainty factor of 1000 is used, which includes a factor of 10 for extrapolation from a LOAEL to a NOAEL, a factor of 10 for extrapolation from animals to humans and a factor of 10 for intraindividual variation. Additionally, an uncertainty factor of 10 is included because 1,2,4-trichlorobenzene is considered to be a suggestive carcinogen, as discussed above. Therefore, the total uncertainty factor is 10,000. The Reference Dose is derived as follows:

$$\frac{26.3 \text{ mg/kg/day}}{10{,}000} = 0.0026 \text{ mg/kg/day}$$

Health-based MCL Recommendation

The Health-based MCL for 1,2,4-trichlorobenzene is derived as follows, using default exposure assumptions:

$$\frac{0.0026 \text{ mg/kg/day} \times 70 \text{ kg} \times 0.2}{2 \text{ L/day}} = 0.018 \text{ mg/L or } 18 \text{ ug/L}$$

Where:
0.0026 mg/kg/day = Reference Dose
70 kg = assumed body weight of adult
0.2 = Relative Source Contribution from drinking water
2 L/day = assumed adult daily drinking water intake

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Addendum to Health-Based MCL Support Document:
1,1,1-Trichloroethane

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Summary

The basis for the New Jersey Health-based MCL for 1,1,1-trichloroethane, which was developed in 1987, was reevaluated. At that time, no oral study suitable for risk assessment was available, and the current Health-based MCL of 26 ug/L was based on liver toxicity in mice in a subchronic inhalation study (McNutt et al., 1975).

A subchronic study in which 1,1,1-trichloroethane was administered in microcapsules in the feed (NTP, 2000) is now the most appropriate study for the basis for the Health-based MCL. The most sensitive endpoint in this study was decreased body weight gain in male mice. The Lowest Observed Adverse Effect Level (LOAEL) for body weight gain in male mice was 850 mg/kg/day (5000 ppm in the diet). An uncertainty factor of 3000 appropriate for a LOAEL for a minimally adverse effect from a subchronic study was used to derive a Reference Dose of 0.28 mg/kg/day. The Health-based MCL derived from this Reference Doses is 2000 ug/L. This represents a 70-fold increase from the current Health-based MCL for 1,1,1-trichloroethane.

The USEPA MCLG and MCL are 200 ug/L, based on a 1984 Office of Water assessment of the McNutt et al. (1975) study. States may not promulgate an MCL which is less stringent than the federal MCL, and the Health-based MCL of 2000 ug/L developed in this document is above the federal MCL of 200 ug/L. Therefore, it is recommended that the current New Jersey MCL for 1,1,1-trichloroethane be increased from 30 ug/L to 200 ug/L, the current federal MCL. This represents a 7-fold increase in the New Jersey MCL for 1,1,2-trichloroethane.

Current New Jersey Health-based MCL

The current New Jersey Health-based MCL for 1,1,1-trichloroethane is 26 ug/L (NJDWQI, 1987). When the Health-based MCL was developed, no oral studies appropriate for risk assessment were available. In a chronic bioassay conducted by the National Cancer Institute (1977), survival was very poor in both treated and control rats and mice, and only 3% of animals survived until the end of the study. Several inhalation studies were considered, and the Health-based MCL was based on a subchronic inhalation study in which mice were exposed continuously to 0, 250, or 1000 ppm 1,1,1-trichloroethane for 14 weeks (McNutt et al., 1975). In this study, the Lowest Observed Adverse Effect Level (LOAEL) was 250 ppm. At this concentration, minimal to mild cytoplasmic alterations in the liver occurred, while at 1000 ppm, increased liver weight, triglyceride accumulation, necrosis, and cytoplasmic alterations were seen. Pharmacokinetic modeling (Reitz et al., 1985, 1986) was used to predict the drinking water concentration which would result in the same body burden in humans as continuous inhalation of 250 ppm in mice, 22.8 mg/kg. An uncertainty factor of 10,000 appropriate for a LOAEL from a subchronic study, an assumed drinking water consumption of 2 L/day, and a Relative Source Contribution factor of 20% were used to derive a Health-based MCL of 26 ug/L.

Current USEPA MCLG and MCL

The current USEPA MCL and MCLG (Maximum Contaminant Level Goal, equivalent to New Jersey Health-based MCL) of 200 ug/L were finalized in 1987. The RMCL (Recommended MCL, an earlier term used by USEPA instead of MCLG) for this MCL is summarized in a proposed rule (USEPA, 1984), and the toxicological basis is given in the USEPA Health Advisory (USEPA, 1987), as the basis for Lifetime Health Advisory is identical to that of the MCLG.

The USEPA MCLG is based on the LOAEL of 250 ppm for liver effects in mice exposed by inhalation for 14 weeks (McNutt et al., 1975), the same study and endpoint used as the basis for the New Jersey Health-based MCL. Unlike New Jersey's approach, pharmacokinetic modeling was not used. The equivalent human absorbed dose was estimated as 35 mg/kg/day by assuming a 1 m^3/hour ventilation volume and 0.3 as the fraction of the administered dose which is absorbed. The Reference Dose of 0.035 mg/kg/day was derived by applying an uncertainty factor of 1000, which was stated to be "chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study". Drinking water ingestion of 2 L/day, body weight of 70 kg, and a Relative Source Contribution factor of 20% were assumed to derive the MCLG of 200 ug/L.

The approximately 10-fold difference between the New Jersey Health-based MCL and the USEPA MCLG results from the use of an uncertainty factor of 10,000 by New Jersey and 1000 by USEPA. USEPA did not include an uncertainty factor of 10 to account for the shorter duration of exposure of the subchronic study used. Thus, although New Jersey used pharmacokinetic modeling, and USEPA instead used assumptions for volume of air inhaled and fraction of applied dose absorbed to estimate the equivalent human oral dose, the two approaches gave very similar results.

In 2002, USEPA published the results of its review of existing drinking water standards (USEPA, 2002a). At the time that the review was published, the USEPA IRIS reassessment of 1,1,1-trichloroethane (USEPA, 2007) had not been completed. USEPA stated in its review of drinking water standards that it did not believe that a revision of the MCL for 1,1,1-trichloroethane was appropriate, as the reassessment of the health risks was ongoing at that time.

Results of Literature Review

A literature review was conducted in order to determine whether any relevant information has become available since the development of the New Jersey Health-based MCL. Additionally, the Toxicological Review written by USEPA (2007) to support development of the current USEPA IRIS Reference Dose was evaluated.

Changes in Production and Uses of 1,1,1-Trichloroethane (reviewed in ATSDR, 2006)

1,1,1-Trichloroethane is less toxic than many other chlorinated solvents, and therefore was previously commonly used in many household products and industrial applications. However, 1,1,1-trichloroethane is an ozone depleting substance, and its production is currently being phased out under the Clean Air Act and the Montreal Protocol. It is no longer used in household products, and exposure of the general population is expected to be much lower currently than it was in the past.

Toxicology Information Not Previously Considered

Developmental Studies

Several oral developmental studies were not considered in the development of the current Health-based MCL for 1,1,1-trichloroethane. Dapson et al. (1984) reported an increased incidence of cardiac anomalies in rat pups on postnatal day 21 after maternal and paternal exposure to 10 ppm 1,1,1-trichloroethane in drinking water prior to mating, and maternal exposure throughout pregnancy and lactation. The dose was estimated to be 1.4 mg/kg/day. This study was considered preliminary in nature.

NTP conducted a postnatal developmental study of 1,1,1-trichloroethane in drinking water in rats to determine the reproducibility of the results of Dapson et al. (1984). The NTP study was reported by George et al. (1989). Experimental groups were water-only control, water containing 0.05% Tween 80 emulsifying agent and 0.9 ppm 1,4-dioxane (a stabilizer found in 1,1,1-trichloroethane being tested), and 3, 10, 30 ppm 1,1,1-trichloroethane (97% pure, 3% 1,4-dioxane) with 0.05% Tween 80. Males and females were exposed for 14 days prior to cohabitation for up to 13 days. Sperm-positive females (24-30 per group) were exposed during pregnancy and through lactation (postnatal day 21). Average maternal doses were reported as 0.3, 1.2, and 3.5 mg/kg/day during pregnancy and 0.6, 2.0, and 5.9 mg/kg/day through lactation. Litters containing more than 10 pups were culled to a litter size of 10 on postnatal day 4, and the remaining pups were sacrificed on postnatal day 21. No increased incidence of malformations of the heart or of other organs was seen in treated pups on either postnatal day 4 or 21, although the doses were higher than the dose used in Dapson et al. (1984).

A teratology study was also conducted by NTP (1987) in conjunction with the postnatal developmental study of George et al. (1989). Control and treatment groups were the same as those used in George et al. (1987). Males and females were exposed for 14 days prior to cohabitation and for up to 6 days during cohabitation, and sperm-positive females were exposed throughout pregnancy. Pregnant females were sacrificed on gestation day 20 and the pups were examined. No evidence of maternal toxicity, developmental toxicity, or increased incidence of malformations was seen in the treated animals.

Maurissen et al. (1994) reported no effects on milestones of physical maturation nor cognitive or neurobehavioral effects in offspring of dams dosed with up to 750 mg/kg/day 1,1,1-trichloroethane on gestation day 6 through lactation day 10. The pups were studied up to 2-3 months of age.

Several inhalation developmental studies in rats, rabbits, and mice are reviewed by ATSDR (2006) and USEPA (2007). In summary, minor effects associated with developmental delay were reported only at high doses, and, in most studies, occurred only at maternally toxic doses.

Subchronic and Chronic Studies

Inhalation

As with most VOCs, exposure to high levels of 1,1,1-trichloroethane orally or by inhalation causes central nervous system toxicity such as behavioral effects, unconsciousness, and death due to respiratory depression (NJDWQI, 1987; ATSDR, 2006; USEPA, 2007).

Rosengren et al. (1985) studied the effects of long term inhalation exposure of 1,1,1-trichloroethane on proteins in the brain. Mongolian gerbils (four of each sex) were exposed to 70, 210, or 1000 ppm 1,1,1-trichloroethane containing 5% dioxane-free stabilizers continuously for three months, followed by a four month period without exposure. The animals were sacrificed and two proteins, S-100 and glial fibrillary acid protein (GFA), were measured in three different regions of the cerebral cortex. These proteins are indicators of the formation of astroglial fibers which form following injury to the brain. GFA protein was significantly increased in one of the three regions studied, the sensorimotor cerebral cortex at 210 ppm and 1000 ppm. The magnitude of the increase was not reported but was estimated from the figures provided to be approximately 33% at 210 ppm and 40% at 1000 ppm by USEPA (2007). The authors suggested that these results indicate lasting or irreversible brain damage from 1,1,1-trichloroethane. However, the significance of these results is uncertain due to the small number of animal used, the fact that S-100 protein did not increase similarly to GFA, and questions about details of the conduct and reporting of this study.

In another study by the same research group (Karlsson et al., 1987), Mongolian gerbils (four of each sex) were exposed to 70 ppm 1,1,1-trichloroethane continuously for three months, followed by a four month period without exposure. Small but statistically significant decreases in DNA concentration per wet weight were seen in three of nine brain regions studied, while no changes in total protein concentration occurred. The area of the brain with increased GFA protein in Rosengren et al. (19850, the sensorimotor cortex, was not one of the areas of the brain affected in this study.

In a neurotoxicity study, Mattson et al. (1993) exposed groups of 16 week old F344 rats (14 of each sex) to 0, 200, 630, or 2000 ppm 1,1,1-trichloroethane (99.9% pure) for 6 hours per day, 5 days per week, for 13 weeks. Body weight measurements, physical examinations, behavioral tests, and hindlimb and forelimb grip testing were conducted at intervals throughout the study. Following the exposure period, electrophysiological testing was performed on all animals. Brains of 5 animals per groups were weighed and histological examination was performed on brains of 5 animals per group. The remaining animals were held for retesting of grip performance 7 weeks after exposure ended, and forelimb muscles and nerves were examined by histopathology. The only notable finding was a slight decrease in forelimb grip performance at the highest exposure concentration. Histopathology and electrophysiological measurements were not affected, and the significance of the effect seen is unclear.

Oral

Maltoni et al. (1986) dosed 7 week old Sprague-Dawley rats (40 per sex) with 500 mg/kg/day 1,1,1-trichloroethane (containing 3.8 % 1,4-dioxane and lower concentrations of other impurities) by gavage in olive oil for 4 or 5 days per week for 104 weeks. The average daily dose adjusted for partial weekly exposure was estimated as 321 mg/kg-day (USEPA, 2007). The control group consisted of 50 rats of each sex dosed with olive oil alone. After treatment, the animals were allowed to live until their spontaneous death, and the experiment lasted for 141 weeks. Survival of the treated and control animals appear to be similar from the figure presented by Maltoni et al. (1986), although no statistical analysis is provided. Body weight of females, but not males, was reduced compared to controls beginning at about 80 weeks of age. As for survival, body weight data is shown only in a figure and no numerical data are provided. USEPA (2007) estimated that body weight in exposed females was ~12% and ~25% lower than in controls at the end of the treatment

and observation periods, respectively. Maltoni et al. (1986) state that 1,1,1-trichloroethane increased the onset of leukemia in this experiment, but that the design of the experiment does not allow definite conclusions to be made.

The National Toxicology Program (2000) conducted a subchronic study of 1,1,1-trichloreothane (>99% pure) administered in microcapsules in feed to F344/N rats and B6C3F_1 mice. Microcapsules were used to prevent the loss of the chemical through volatilization which would occur if it was administered in drinking water (as in the NTP developmental studies described above) or mixed with the feed. Groups of animals per sex were given feed containing 5,000, 10,000, 20,000, 40,000 or 80,000 ppm 1,1,1-trichlorethane for 13 weeks. Two control groups, one receiving feed without microcapsules and the other receiving feed with empty microcapsules, were included. Because the microcapsules were composed of 80% food grade modified corn starch and 20% sucrose and therefore contribute to the caloric content of the diet, the vehicle control group was considered the most appropriate comparison group for body weight.

Average doses for male rats were 290, 600, 1200, 2400, and 4800 mg/kg/day, and for female rats, 310, 650, 1250, 2500, and 5000 mg/kg/day for the 5,000, 10,000, 20,000, 40,000 or 80,000 ppm groups, respectively. All rats survived until the end of the study and did not show clinical signs of toxicity. Food consumption was similar in the control groups and the exposed groups. The body weight of males was decreased at the end of the study in the 40,000 ppm and 80,000 ppm dose groups by 5% and 10%, respectively, and the body weights of females in the 80,000 ppm dose group was decreased by 4%. These body weight changes were statistically significant, but NTP does not consider a body weight change of 10% or less to be an adverse effect.

Absolute and relative liver weights were significantly reduced in female rats treated with 80,000 ppm by about 15% and 11%, respectively, in comparison with untreated and vehicle controls. In male rats treated with 80,000 ppm, absolute liver weight was significantly reduced by about 13% compared with vehicle controls but did not differ from untreated controls, and relative liver weight was unaffected.

Renal lesions considered by NTP (2000) to be consistent with alpha-2-microglobulin nephropathy were seen in male rats treated with 20,000 ppm and above. Significant, dose-related increases in incidence and/or severity of renal tubule hyaline degeneration, cast formation, and regeneration and chronic interstitial inflammation of the kidney were observed, but assays for the presence of alpha-2-microglobulin were not conducted. Alpha-2-microglobulin is a protein specific to the kidneys of male rats, and these effects are not considered to be relevant to humans (USEPA, 1991).

Vaginal cytology (over 12 days prior to sacrifice) and sperm motility (at necropsy) evaluations were performed on rats in the vehicle control, 20,000, 40,000, and 80,000 ppm groups. No effects on vaginal cytology parameters in female rats were seen, but epididymal spermatozoal concentration was significantly reduced by about 10% in males in the 80,000 ppm group compared with vehicle control.

In mice, average doses were 850, 1770, 3500, 7370, and 15,000 mg/kg/day in males and 1340, 2820, 5600, 11,125, and 23,000 mg/kg/day in females day for the 5,000, 10,000, 20,000, 40,000 or 80,000 ppm groups, respectively. As for the rats, all mice survived until the end of the study, and no signs

of clinical toxicity were seen. Although food consumption was greater in treated mice than in untreated or vehicle controls, statistically significant dose-related reductions in body weight gain and terminal body weight were observed in male mice in all dosed groups, and in female mice treated with 10,000 ppm or above (Table 1).

Statistically significant changes in the weights of the heart, liver, and kidney in male mice and in the kidney in female mice were considered by NTP (2000) to be secondary to the changes in body weight and not biologically significant. No gross or microscopic lesions due to 1,1,1-trichloroethane were seen in male or female mice. As in the rats, vaginal cytology parameters in treated female mice were similar to those in controls, and male mice in the 80,000 ppm group had a significant 20% reduction in epididymal spermatozoal concentration compared with vehicle controls

Effects on body weight were the most sensitive indicators of 1,1,1-trichloroethane toxicity, and NTP (2000) estimated the NOAEL to be 10,000 ppm, based on decreases in terminal body weight of greater than 10% in male and female mice at doses of 20,000 ppm and above.

Table 1
Average Doses, Body Weights, and Feed Consumption in Mice in 13-Week Study (NTP, 2000)

Group	Male					Female				
	Average Dose (mg/kg/day)	Final body weight[a] (g)	Mean weight change[a] (g)	Relative Body Weight[b] (%)	Average Feed Consumption (g/kg/day)	Average Dose (mg/kg/day)	Final body weight[a] (g)	Mean weight change[a] (g)	Relative Body Weight[b] (%)	Average Feed Consumption (g/kg/day)
Untreated control	------	35.4 ± 0.8	12.8 ± 0.5	-----	160	------	28.8 ± 0.9	10.1 ± 0.8	-----	250
Vehicle control	------	36.9 ± 0.7	13.7 ± 0.5	-----	156	------	29.3 ± 0.8	11.2 + 0.8	------	261
5,000 ppm	850	33.6 ± 0.7[c]	11.2 ± 0.5[c,d]	91	170	1340	28.4 ± 0.6	9.6 ± 0.7	97	268
10,000 ppm	1770	33.7 ± 0.6[c]	10.8 ± 0.5[c,e]	91	177	2820	27.2 ± 0.8	8.7 ± 0.6c	93	282
20,000 ppm	3500	32.7 ± 0.5[c,e]	9.9 ± 0.4[c,e]	88	177	5600	26.0 ± 0.8[c,e]	7.5 ± 0.7[c,e]	89	280
40,000 ppm	7370	33.1 ± 0.5[c,e]	10.0 ± 0.3[c,e]	90	184	11,125	25.8 ± 0.7[c,e]	7.2 ± 0.6[c,e]	88	278
80,000 ppm	15,000	31.3 ± 0.4[c,e]	8.7 ± 0.3[c,e]	85	187	22,900	24.5 ± 0.5[c,e]	6.2 ± 0.5[c,e]	84	287

[a]Values are mean ± SE. [b] Body weight relative to vehicle control. [c]Significantly different ($p \leq 0.01$) from the vehicle control group.
[d]Significantly different ($p \leq 0.05$) from the untreated control group. [e]Significantly different ($p \leq 0.01$) from the untreated control group.

Reevaluation of Current Health-based MCL

Choice of study and endpoint for Reference Dose development

The current Health-based MCL (NJDWQI, 1987) is based on hepatic toxicity in a subchronic inhalation study (McNutt et al., 1975), as no appropriate oral study was available at the time when it was developed. 1,1,1-Trichloroethane is not highly toxic to the liver, and other inhalation studies of 1,1,1-trichloroethane have generally shown only mild effects on the liver, such as minor histopathologic changes or fat accumulation (reviewed by ATSDR, 2006 and USEPA, 2007). Hepatic toxicity was not seen in the few subchronic or chronic oral studies previously available (NCI, 1977; Bruckner et al., 1985, which was later reported as Bruckner et al., 2001) which were considered in developing the current Health-based MCL.

The subchronic study in which 1,1,1-trichloroethane was administered in microcapsules in the feed (NTP, 2000) is considered to be the most appropriate study for Health-based MCL development. It is an oral study, and the dosing regimen is designed to simulate drinking water exposure. The other subchronic and chronic oral studies are not appropriate as the basis for the risk assessment. All of these studies used gavage, so that the dose was received as a bolus rather than continuously. In the subchronic study (Bruckner et al., 1985, 2001), only one dose, 0.5 mg/kg/day, was administered for 13 weeks, as the higher dose groups were accidentally given a different chemical on day 50, causing the death of all animals in these groups. In the chronic study conducted by NCI (1977), excessive mortality occurred in all groups and only 3% of animals lived until the end of the study. Maltoni et al. (1986) used only one dose group and did not evaluate non-neoplastic lesions.

In the NTP (2000) study, the most sensitive endpoint was decreased body weight compared to vehicle controls in mice. The lowest dose at which statistically significant decreases in final body weight compared to vehicle controls occurred was 850 mg/kg/day in males (5000 ppm in the diet). At this dose, the final body weight was 91% of the vehicle control. In females, final body weight was significantly decreased at 2820 mg/kg/day (10,000 ppm), to 93% of the vehicle control. Reduced body weight gain also occurred in rats in the NTP (2000) study, but at higher doses than in the mice. The body weight of treated mice was lower than the vehicle controls despite the fact that food consumption in the treated animals was increased compared to the controls. Therefore, the LOAEL for 1,1,1-trichloroethane is 850 mg/kg/day.

NTP (2000) estimated the NOAEL to be 10,000 ppm, based on decreases in terminal body weight of greater than 10% in male and female mice at doses of 20,000 ppm and above. At 20,000 ppm, the final body weights of males and females were 88% and 89% of vehicle controls. Apparently NTP (2000) did not consider the statistically significant changes in body weight of males to 91% of the vehicle control value to be adverse, although this is not stated in the NTP (2000) report.

The use of body weight changes only if they are greater than 10% as the basis for a LOAEL appears to be a subjective decision by NTP (2000). For 1,1,1-trichloroethane, it is felt that the use of the lower dose (5000 ppm) at which a body weight change of 9% occurred is appropriate, since body weight changes were seen consistently at all doses above 5000 ppm, and since treated animals ate more than controls, indicating that the change in body weight is not due to decreased food consumption. The USEPA Technical Guidance for Benchmark Dose Modeling (2000) states that for continuous parameters such as body weight, “the amount of change to be considered adverse has not

been defined by toxicologists or health scientists. Consequently, the endpoint is often decided in the context of the endpoint itself, the study, and the relationship of changes in that endpoint to other effects of the agent." The choice of the dose resulting in 9% decrease of body weight is also supported by a recent textbook on risk assessment by Nielsen et al. (2008), when, in a discussion of adverse versus non-adverse effects, they mention "decreased body weight…which can be related to the palatability of the feed" as an example of a non-adverse effect. They also mention that "deviations exceeding 5%-10% of the control value, e.g. in body weight, are often considered biologically significant."

Decreased body weight gain was seen also in two chronic gavage studies of 1,1,1-trichloroethane (NCI, 1977; Maltoni et al., 1986). Although these studies are not appropriate as the basis for the risk assessment, the effects on body weight in these additional studies support its use as the endpoint for risk assessment. In Maltoni et al. (1986), the adjusted dose of 321 mg/kg/day is lower than the lowest dose tested in NTP (2000), and body weight effects were not seen until 80 weeks. This suggests that chronic exposure may affect body weight at doses having no effect with subchronic exposure.

Derivation of Reference Dose

Body weight gains were significantly reduced compared to vehicle controls in male mice at the lowest dose given, 850 mg/kg/day. At higher doses, reductions in body weight gain of a similar magnitude occurred, and the final body weight at the highest dose, 15,000 mg/kg/day, was 85% of the vehicle control. Therefore, 850 mg/kg/day is the LOAEL and no NOAEL can be identified in this study.

A Reference Dose based upon this endpoint is derived by applying an uncertainty factor of 3000 as follows:

$$\frac{850 \text{ mg/kg/day}}{3000} = 0.28 \text{ mg/kg/day}$$

The total uncertainty factor of 3000 includes factors of 10 for intraspecies variability, interspecies variability, and subchronic to chronic exposure durations, and a factor of 3 for extrapolation from a LOAEL to a NOAEL. A factor of 3 for extrapolation from NOAEL to LOAEL is used because the change in body weight was minimal at the LOAEL (USEPA, 2002b).

Comparison to USEPA IRIS Reference Dose

USEPA (2007) derived a chronic Reference Doses for 1,1,1-trichloroethane of 2 mg/kg/day based on the changes in body weight in mice seen in NTP (2000). They performed benchmark dose analysis of the body weight data from the male and female mice, and selected a 10% change in body weight as the benchmark response level. For female mice, all four models tested gave an adequate fit of the data, with the Hill model giving the best fit, while for male mice, only one model, the Hill model, gave an adequate fit. The $BMDL1_0$ (95% lower confidence limit on the Benchmark Dose for a 10% response) was 2155 mg/kg/day for females and 594 mg/kg/day for males.

USEPA (2007) chose to base its Reference Dose on the higher benchmark dose from the females, 2155 mg/kg/day, rather than the males which were more sensitive to 1,1,1-trichloroethane. Their

rationale was that the data from the females showed a better dose-response relationship than the male data, which gives a flatter dose-response curve.

However, body weight in all groups of males was decreased significantly, and the fact that the male data does not fit the Benchmark Dose models as well as the female data does not appear to be a valid reason to discount using the data from the males. The Benchmark Dose for males of 594 mg/kg/day is very close to the LOAEL for males of 850 mg/kg/day identified above.

USEPA (2007) used a total uncertainty factor of 1000 to derive its Reference Dose. This included factors of 10 for intraspecies variability and10 for interspecies variability, 3 for subchronic to chronic exposure durations, and 3 for database deficiencies. No uncertainty factor for extrapolation from a LOAEL to a NOAEL was needed because a benchmark dose approach is used. USEPA (2007) felt that a factor of 3, rather than 10, for subchronic to chronic was warranted because in some chronic studies, body weight changes did not become more pronounced with duration of exposure. However, in Maltoni et al. (1986), body weight effects were not seen in the rats until week 80. The factor of 3 for database deficiencies was included because subtle neurotoxic effects were not evaluated by NTP (2000) or in other subchronic or chronic oral studies.

Choice of Relative Source Contribution Factor

The default value of 20% for the Relative Source Contribution (RSC) factor is recommended. Although production of 1,1,1-trichloroethane is being phased out, and its use in household products and industrially is expected to decrease, there is no quantitative data on human exposure, such as is available for pesticides or for metals which are essential nutrients, which can be used to develop a specific RSC. Additionally, exposure through inhalation, such as through showering, is not taken into account in the exposure assumption of 2 L water ingested per day in Health-based MCL development.

Derivation of Health-based MCL

$$MCL = \frac{0.28 \text{ mg/kg/day} \times 70 \text{ kg} \times 0.2}{2 \text{ L}}$$

= 1.96 mg/L or 1960 ug/L, or 2000 ug/L using two significant figures.

Where:
0.28 mg/kg/day = Reference Dose
70 kg = assumed body weight of adult
0.2 = Relative Source Contribution from drinking water
2 L = assumed adult daily drinking water intake

Conclusion

Based on the above, a Reference Dose of 0.28 mg/kg/day and a Health-based MCL of 2000 ug/L are recommended.

States may not promulgate an MCL which is less stringent than the federal MCL for the same

contaminant, and the recommended Health-based MCL of 2000 ug/L is above the federal MCL of 200 ug/L. Therefore, it is recommended that the current New Jersey MCL for 1,1-dichloroethylene be changed from 30 ug/L to 200 ug/L, the current federal MCL.

Additional revision of the New Jersey MCL should be considered in the future if USEPA's reevaluation of its risk assessment results in an increase in its MCL. If USEPA revises its MCL to a value greater or equal to 2000 ug/L in the future, it is recommended that New Jersey revise its MCL to 2000 ug/L.

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Addendum to Health-Based MCL Support Document:
1,1,2-Trichloroethane

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July 24, 2006

Summary

The basis for the New Jersey Health-based MCL for 1,1,2-trichloroethane, which was developed in 1994, was reevaluated. 1,1,2-Trichloroethane is classified in New Jersey Carcinogenicity Category II, analogous to Suggestive Carcinogen under the 2005 USEPA Guidelines for Cancer Risk Assessment. 1,1,2-Trichloroethane caused an increased incidence of liver carcinomas and adrenal pheochromocytomas in male and female mice. A cancer slope factor based on liver tumors in male mice has been developed by USEPA and is provided in the IRIS database. The risk assessment approach for Category II chemicals is based on the cancer slope factor at the 10^{-6} risk level, if available from USEPA and not judged to be technically unsound by NJDWQI. A Health-based MCL of 0.61 ug/L, based on the cancer slope factor, is recommended. This represents a five-fold decrease from the current Health-based MCL of 3 ug/L.

Current New Jersey Risk Assessment

The current New Jersey Health-based MCL (and MCL) for 1,1,2-trichloroethane is 3 ug/L (NJDWQI, 1994). This Health-based MCL is based upon a Reference Dose of 0.00039 mg/kg/day. In a subchronic (90 day) drinking water study in CD-1 mice (White et al., 1985; Sanders et al., 1985), the No Observed Adverse Effect Level (NOAEL) was 3.9 mg/kg/day. At higher doses, changes in liver enzymes and clinical chemistry parameters, as well as alterations in immune response, were seen. A Reference Dose of 0.00039 mg/kg/day was derived by applying an uncertainty factor of 1000 appropriate for a NOAEL from a subchronic study and an additional uncertainty factor of 10 for possible carcinogenic effects (see below)

1,1,2-Trichloroethane was classified as a possible human carcinogen (New Jersey Group II, USEPA Group C), based on results of the National Cancer Institute (1978) bioassay. In this study, 1,1,2-trichloroethane was given by gavage for 78 weeks to male and female Osborne-Mendel rats and B6C3F1 mice. No statistically significant increase in tumors was seen in rats, while in mice, an increase in the incidence of liver tumors and adrenal gland pheochromocytomas occurred in both sexes. The National Cancer Institute concluded that 1,1,2-trichloroethane was positive for carcinogenicity in male and female mice and negative in male and female rats.

USEPA Assessment

The USEPA Maximum Contaminant Level Goal (MCLG) for 1,1,2-trichloroethane is 3 ug/L. The basis for this MCLG is identical to the basis for the New Jersey Health-based MCL described above in regard to the carcinogenicity classification and the Reference Dose. The USEPA MCL for 1,1,2-trichloroethane is 5 ug/L based on the analytical Practical Quantitation Limit (PQL). USEPA determined that the PQL for 1,1,2-trichloroethane, as well as other volatile organic chemicals, is 5 ug/L (USEPA, 1990), while New Jersey determined the PQL to be 2 ug/L (NJDWQI, 1994).

The USEPA IRIS database (USEPA, 2005a) contains a Reference Dose and a carcinogenicity

assessment for 1,1,2-trichloroethane. The basis for the Reference Dose, 0.004 mg/kg/day, is the same as the basis for the Reference Dose developed by New Jersey, as well as the Reference Dose used by USEPA to develop its MCLG. However, the IRIS Reference Dose is 10-fold higher since it does not include an additional uncertainty factor of 10 for possible carcinogenic effects, which was incorporated by both New Jersey and USEPA in the development of the health-based drinking water concentration.

1,1,2-Trichloroethane is classified as a possible human carcinogen (Group C) in the IRIS database, based upon the occurrence of liver cancers and adrenal pheochromocytomas in male and female mice in the NCI (1978) bioassay. A slope factor of 5.7×10^{-2} $(mg/kg/day)^{-1}$ was developed by USEPA based upon the incidence of liver carcinomas in male mice; the incidence of these tumors in female mice was similar to that in the males.

Results of Literature Review

A literature search did not reveal any studies published since the New Jersey (NJDWQI, 1994) assessment was completed which should be considered in the development of the Health-based MCL.

Reevaluation of Current Health-based MCL

Reevaluation of Reference Dose

As discussed above, no new information is available which warrants reevaluation of the Reference Dose for 1,1,2-tetrachloroethane.

Risk Assessment based on Carcinogenic Endpoint

1,1,2-Trichloroethane was classified as a Possible Human Carcinogen (Group C) by New Jersey (NJDWQI, 1994) and USEPA's Office of Water (USEPA, 1990) and IRIS database (USEPA, 1995) under the 1986 USEPA risk assessment guideline, based on carcinogenic effects in mice in the NCI (1978) bioassay. Based on these results, it is similarly appropriate to classify 1,1,2-trichloroethane as a Suggestive Carcinogen under the 2005 USEPA Guidelines for Carcinogen Risk Assessment (USEPA, 2005b).

New Jersey DEP and DWQI policy for chemicals classified as Suggestive Carcinogens or Possible Human Carcinogens is to base the risk assessment upon the carcinogenic slope factor at the 10^{-6} risk level, if such a slope factor is available from USEPA and is not judged technically unsound.

As discussed above, for 1,1,2-trichloroethane, a slope factor has been derived by USEPA and is presented in the IRIS database (USEPA, 1995a). The slope factor of 0.057 $(mg/kg/day)^{-1}$ is based upon the incidence of hepatocellular carcinomas in male mice in the NCI (1978) bioassay.

The health-based drinking water concentration using this slope factor, at the 10^{-6} risk level, is derived as follows:

Daily dose at 10^{-6} risk level: $$\frac{10^{-6}}{0.057\ (mg/kg/day)^{-1}} = 0.0000175\ mg/kg/day$$

Health-based drinking water concentration:

$$\frac{0.0000175 \text{ mg/kg/day} \times 70 \text{ kg}}{2 \text{ L}} = 0.00061 \text{ mg/L or } 0.61 \text{ ug/L}$$

Where:
0.28 mg/kg/day = Reference Dose
70 kg = assumed body weight of adult
0.2 = Relative Source Contribution from drinking water
2 L = assumed adult daily drinking water intake

Health-based MCL Recommendation

In accordance with the New Jersey policy for risk assessment of chemicals classified as Suggestive Carcinogens, it is recommended that the Health-based MCL for 1,1,2-trichloroethane be based on the carcinogenic endpoint derived above.

The recommended Health-based MCL is 0.61 ug/L.

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Addendum to Health-Based MCL Support Document:
2,4,6-Trichlorophenol

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Summary

A Health-based MCL of 1 ug/L was adopted for 2,4,6-trichlorophenol in 1994. However, there is currently no New Jersey MCL for this contaminant because no appropriate analytical method was available at the time. 2,4,6-Trichlorophenol is classified as a likely carcinogen (New Jersey Category I), and its risk assessment is based on low dose extrapolation at the 10^{-6} risk level. The current New Jersey slope factor, 2.6×10^{-2} $(mg/kg/day)^{-1}$, is based on liver tumors in a chronic dietary study in mice. This slope factor was reevaluated based on information suggesting that the mouse liver tumors may have resulted from dioxins and furans that were contaminants of the 2,4,6-trichlorophenol administered to the mice. 2,4,6-Trichlorophenol also caused leukemia in rats, and dioxins and furans do not cause leukemia. A revised slope factor of 1.1×10^{-2} $(mg/kg/day)^{-1}$ based on the increased incidence of leukemia in male rats is recommended as the basis for the New Jersey Health-based MCL. The Health-based MCL derived using this slope factor is 3.1 ug/L. This represents a three-fold increase from the current New Jersey Health-based MCL of 1 ug/L.

Current New Jersey and USEPA Assessments

The Health-based Maximum Contaminant Level Support Document for 2,4,6-trichlorophenol was finalized in 1989, and the current New Jersey Health-based MCL (NJDWQI, 1994) is 1 ug/L. 2,4,6-Trichlorophenol was classified in New Jersey Carcinogenicity Category I, analogous to Probable Human Carcinogen (B2) under the 1986 USEPA cancer risk assessment guidelines and Likely Carcinogen under the 2005 USEPA Guidelines for Cancer Risk Assessment. A cancer slope factor of 2.6×10^{-2} $(mg/kg/day)^{-1}$ was derived from the combined incidence of hepatocellular carcinomas and adenomas in male mice in a dietary study (NCI, 1979). The Health-based MCL of 1 ug/L was based on this slope factor at a risk level of 10^{-6}.

USEPA has not developed a drinking water MCL for 2,4,6-trichlorophenol. The current USEPA slope factor for 2,4,6-trichlorophenol of 1.1×10^{-2} $(mg/kg/day)^{-1}$ was posted on the USEPA IRIS database in 1990, after New Jersey had developed its slope factor in 1989. This slope factor is based on the incidence of leukemia in male rats in the NCI (1979) chronic dietary study.

Prior to 1990, the USEPA IRIS slope factor for 2,4,6-trichlorophenol was 2×10^{-2} $(mg/kg/day)^{-1}$, and was based on mouse liver tumors, as is the New Jersey slope factor. The derivation of this slope factor is provided in USEPA (1984). This slope factor was replaced by the slope factor based on leukemia in rats because of concerns that the liver tumors in the mice resulted from contamination of the technical grade trichlorophenol used in NCI (1979) with dioxins and related compounds:

USEPA (1990) states : *While the contaminants in the 2,4,6-TCP used in NCI (1979) were not determined, Firestone et al. (1972) found 49 ppm of 1,3,6,8-TCDD and 93 ppm of 2,3,7-trichlorodibenzo-p-dioxin, as well as unquantified amounts of tetra-, penta- and hexa-chlorinated*

dibenzofurans in commercial grade 2,4,6- trichlorophenol. If the 2,4,6-trichlorophenol used in NCI (1979) was contaminated with 1,3,6,8-TCDD, (less than or equal to 4%), the liver tumor incidence observed in the NCI (1979) study could be obscured since this chemical may induce liver tumors. When the Toxic Equivalency Factor approach (U.S. EPA, 1987) is used, and the same amount of contamination as shown by Firestone et al. (1972) is assumed, the risk determined for the development of hepatocellular carcinomas and adenomas in male mice that is due to this contaminant could theoretically account for the observed tumors. Confidence in use of this data set for quantitation is decreased. Since chlorinated dibenzodioxins do not induce leukemia, the rat data are more appropriate for derivation of the slope factor.

The possible contribution of dioxins and furans to the carcinogenicity of 2,4,6-trichlorophenol in the NCI (1979) study, and its consideration in the risk assessment for 2,4,6-trichlorophenol, are further discussed on page 3.

Reevaluation of the New Jersey Slope Factor

The New Jersey slope factor for 2,4,6-trichlorophenol is based on the chronic dietary bioassay conducted by the National Cancer Institute (1979), and this study is described in NJDWQI (1994). In this study, groups of 50 male and female rats and groups of 50 male mice were administered 5000 or 10,000 ppm 2,4,6-trichlorophenol in the diet for two years. Groups of 50 female mice were initially given 10,000 or 20,000 ppm 2,4,6-trichlorophenol in the diet. Due to excessive depression of body weight in the female mice, the doses were reduced after week 38 to 2500 and 5000 ppm. Control groups consisted of 20 rats or mice of each sex.

Body weights of treated animals were lower than those of controls throughout the study, but increased mortality did not occur. A statistically significant dose related increase in hepatocellular adenomas and carcinomas was seen in male and female mice. These tumors were also significantly increased in high and low dose male mice and high dose female mice in direct comparison with controls.

In male rats, there was a dose-related increase in lymphomas or leukemias (Control 4/20, low-dose 25/50, high-dose 29/50). All but two of these malignancies were leukemias, and the incidence for leukemia alone was: Control – 4/10; low-dose – 23/50; high-dose – 29/50. The incidence of these was significantly higher in both the low and high dose group compared to controls. For the female rats, the incidence of leukemia was 3/20 in controls, 11/50 in the low-dose group, and 11/50 in the high-dose group. The increase in leukemia in females was not statistically significant. Hematopoietic toxicity including leukocytosis and monocytosis of the peripheral blood and hyperplasia of the bone marrow was seen in many treated male and female rats which did not have leukemia. The daily doses to the rats were estimated by NJDWQI (1994) to be 250 mg/kg/day and 500 mg/kg/day, and by USEPA to be 258 mg/kg/day and 544 mg/kg/day in the low and high dose groups.

The current New Jersey slope factor is based on the data on liver tumors in male mice, since the increased incidence of these tumors compared to the controls was higher than in the female mice and was higher than the incidence of leukemia in male or female rats. The previous USEPA IRIS slope factor for 2,4,6-trichlorophenol was also based on liver tumors in male mice.

The basis for the New Jersey slope factor was reevaluated to consider whether the mouse liver tumors seen in the NCI (1979) bioassay may have resulted from contamination of the test chemical with dioxins and related chemicals. It is reasonable to consider this possibility since dioxin contamination has been found to cause hepatic toxicity in studies of other chemicals. For example, technical grade pentachlorophenol contaminated with dioxins and furans caused hepatic effects that were not seen with the pure chemical (Goldstein et al., 1977). The proposed Health-based MCL for dacthal (NJDWQI Health Effects Subcommittee, 2008) also considers the possible contributions to toxicity of hexachlorobenzene and dioxins which contaminated the dacthal used in the chronic study that forms the basis for the risk assessment (ISK Biotech Corp., 1993).

NCI (1979) states that the 2,4,6-trichlorophenol used was 96-97% pure, with up to 17 minor contaminants, and that the chlorinated dibenzo-p-dioxin content was not determined. 2,3,7,8-TCDD causes liver tumors in mice, but not leukemia in rats (reviewed in USEPA, 2000). Like USEPA (1990), the World Health Organization (WHO, 2003) based its drinking water guideline for 2,4,6-trichlorophenol on leukemia in rats, rather than liver tumors in mice, because of the possibility that the liver tumors resulted from dioxin contamination. ATDSR (1999) also discusses the possible dioxin contamination of the 2,4,6-trichlorophenol used in NCI (1979).

Although the dioxin content of the 2,4,6-trichlorophenol used in NCI (1979) is not known, chlorinated dioxins and furans have been detected as contaminants of this chemical. Firestone et al. (1972) found 93 ppm 2,3,7-trichlorodibenzo-p-dioxin and 49 ppm 1,3,6,8-tetrachlorodibenzo-p-dioxin in a sample of 2,4,6-trichlorophenol. Currently, these dioxins are not considered to have toxicity similar to 2,3,7,8-tetrachlorodibenzodioxin, while 2,3,7,8-chlorinated dioxins and furans are considered to have toxicity similar to 2,3,7,8- tetrachlordibenzodioxin (WHO, 2005). Rappe et al. (1978) found tetra- (1.5 ppm), penta- (17.5 ppm), hexa- (36 ppm), and hepta- chlorinated furans in 2,4,6-trichlorophenol, including many which are chlorinated in the 2,3,7,8- positions.

Furans with chlorine atoms in the 2,3,7,8- positions cause the same toxic effects as 2,3,7,8-TCDD, and their potencies are related to that of 2,3,7,8-TCDD by toxic equivalency factors (TEFs; WHO, 2005). The TEFs can be used to estimate the carcinogenic potential of the furans found as contaminants of 2,4,6-trichlorophenol by Rappe et al. (1978). The concentration of 2,3,7,8-tetrachlorodibenzofuran (TCDF) is not given, but the peak for the 2,3,7,8- isomer was the largest peak of the several tetra-CDFs detected. Therefore, it is necessary to estimate the concentration of 2,3,7,8-TCDF in order to estimate the potential contribution of this contaminant to the carcinogenicity observed for technical grade 2,4,6-TCP. Based on the size of the peaks shown for the tetra-CDFs, it can be assumed that 2,3,7,8-TCDF accounts for one-third of the total of tetra-CDF concentration of 1.5 ppm, and the concentration of 2,3,7,8-TCDF can be estimated as 0.5 ppm.

Assuming the 2,4,6-trichlorophenol used in NCI (1979) contained the same concentration of TCDFs as the material tested by Rappe et al. (1978), the possible exposure of the rats in NCI (1979) to 2,3,7,8-TCDF can be estimated as 0.16 ug/kg/day, 0.33 ug/kg/day, and 0.65 ug/kg/day at the 2,4,6-trichlorophenol doses of 325 mg/kg/day, 650 mg/kg.day, and 1300 mg/kg/day used in the study. The TEF for 2,3,7,8-TCDF is 0.1 (WHO, 2005), so these 2,3,7,8-TCDF doses are equivalent to doses of 0.016 ug/kg/day, 0.033 ug/kg/day, and 0.065 ug/kg/day of 2,3,7,8-TCDD. These doses are similar to the range of doses used in the chronic gavage study in which 2,3,7,8-dioxin was found to cause liver tumors in mice (NTP, 1982; USEPA, 2003). In this study, the average daily doses

ranged from 0.0014 to 0.071 ug/kg/day in males and 0.0057 to 0.286 ug/kg/day in females. Similarly, the TEFs for 2,3,7,8-chlorinated CDFs found in technical grade 2,4,6-trichlorophenol range from 0.01 to 0.3, and may also contribute to the formation of liver tumors.

Based on the above discussion, it is recommended that the New Jersey slope factor for 2,4,6-trichlorophenol be based on the incidence of leukemia in male rats (NCI, 1979). Dioxin does not cause leukemia in rats, and the presence of dioxins and furans may account for the liver tumors observed in mice in the NCI (1979) study.

USEPA IRIS (1990) has derived a slope factor of 1.1×10^{-2} $(mg/kg/day)^{-1}$ for leukemia in male rats from the NCI (1979) study using the linearized multistage model. As mentioned above, the daily doses to rats in mg/kg/day estimated by USEPA (1990) are very close to those estimated by NJDWQI (1994). It is recommended that this slope factor be adopted by New Jersey.

Recommended New Jersey Health-based MCL

The health-based drinking water concentration using the recommended slope factor of 1.1×10^{-2} $(mg/kg/day)^{-1}$, at the 10^{-6} risk level, is derived as follows:

Daily dose at 10^{-6} risk level: $\dfrac{10^{-6}}{0.011\ (mg/kg/day)^{-1}} = 0.00009$ mg/kg/day

The resulting health-based drinking water concentration, with assumed body weight of 70 kg and daily water ingestion of 2 L, is:

$$\frac{0.00009\ mg/kg/day \times 70\ kg}{2\ L} = 0.0031\ mg/L \text{ or } 3.1\ ug/L$$

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Addendum to Health-Based MCL Support Document:
Vinyl Chloride

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Summary

The current New Jersey cancer potency slope factor for vinyl chloride, 0.42 $(mg/kg/day)^{-1}$, was developed in 1987 using a linearized multistage model of hepatocellular carcinoma incidence in female rats exposed orally (Feron et al., 1981). Extrapolation, from rats to humans was based on the rat-to-human body weight ratio to the 2/3 power. The Health-based MCL based on this slope factor is 0.08 ug/L, using a 10^{-6} cancer risk level and default exposure assumptions of 70 kg adult body weight and 2 L daily adult tap water consumption.

USEPA IRIS (2000) reevaluated the same data used as the basis for the New Jersey Health-based MCL. They modeled the combined incidence of liver angiosarcomas, hepatocellular carcinomas, and precursor liver nodules in female rats from Feron et al., 1981. USEPA used a physiologically-based pharmacokinetic (PBPK) model for interspecies extrapolation, rather than the previously used approach based on the rat-to-human body weight ratio to the 2/3 power. The PBPK model estimates the human equivalent dose from the rat oral dose by converting the rat oral dose to the human target tissue (liver) concentration of the active metabolite of vinyl chloride.

Studies of vinyl chloride's carcinogenicity in which exposure was started at birth have shown that the cancer slope factor is approximately doubled compared to when exposure is started in adulthood. Since exposure in the Feron et al. (1981) study began in early adulthood, USEPA (2000) increased the slope factor based on Feron et al. (1981) by a factor of two to account for exposure throughout the lifetime, beginning in childhood.

Since drinking water standards are intended to protect for exposure throughout the whole lifetime, the cancer potency slope factor using the USEPA (2000) approach incorporating early life exposure, 1.5 $(mg/kg/day)^{-1}$, is recommended. The Health-based Maximum Contaminant Level based on this slope factor and a one-in-one million (10^{-6}) lifetime cancer risk is 0.023 ug/L. This is a 3.5-fold decrease from the current New Jersey Health-based Maximum Contaminant Level of 0.08 ug/L.

Background

The association between occupational exposure to vinyl chloride (VC) and the development of liver angiosarcomas is one of the best characterized examples of chemical-induced carcinogenicity in humans. Liver angiosarcomas are an extremely rare tumor, with only 20-30 cases per year reported in the United States. Since the introduction of VC manufacturing, nearly all of the reported cases have been associated with VC exposure. VC exposure has also been associated with increased death due to primary liver cancer. Brain cancer and cancer of the lymphopoietic system, connective tissue,

and soft tissue have been associated with VC exposure in some studies, but not others.

The association of VC with angiosarcoma and liver cancer in numerous epidemiologic studies has been supported by findings in rats, mice, and hamsters administered VC via the oral and inhalation routes. Increases in non-liver tumors have also been detected in some of the animal studies. However, they were generally sporadic in nature with little evidence of a positive dose response, and the tumors were of different types than those seen in human epidemiology studies. The genotoxic mode of action of VC is well characterized, involving a reactive metabolite, chloroethylene oxide (CEO), which forms DNA adducts that lead to tumor formation.

On the basis of sufficient evidence for carcinogenicity in epidemiology studies, positive bioassays in oral animal studies, positive results of genotoxicity studies, and the knowledge that it is well absorbed orally, VC is considered to be a known human carcinogen by both the oral and inhalation routes.

The cancer slope factor for VC in humans is based on animal experiments because of uncertainties in the exposure levels (see below) in epidemiology studies (NJDWQI, 1987; USEPA, 2000). Moreover, evidence from bioassays and epidemiologic data suggests that the cancer slope factor for VC based on animal data is sufficiently protective of human cancer risk. USEPA (2000) concluded that uncertainties about the exposure concentrations and duration of exposure at high concentrations in the epidemiology studies precluded recommendation of quantitative risk estimates derived from these studies. Furthermore, the occupational work was generally based on mortality rather than incidence. Most of the workers in the most recent follow-ups of the North American and European studies were still alive, with the likelihood of further deaths or incidence from liver cancer and angiosarcoma. In addition, misclassification of exposure in these studies may result in underestimation of the actual risk at lower doses, and the occupational cohorts for VC did not include females or children.

Bosetti et al. (2003) summarized the most current updates of the overall workplace findings from around the world. Mundt et al. (2000) provided an analysis of the combined data (N = 10,100) from 37 North American facilities. Duration of exposure was correlated with increased mortality from liver cancer and angiosarcomas. The Simonato (1991) study and its follow-up through 1997 (Ward et al., 2001) analyzed a cohort (N = 12,700) from 19 European factories, and also demonstrated dose-response by duration of employment and cumulative exposure (ppm-years). However, exposure uncertainty was high because systematic exposure data were not collected at most factories until the mid-1970s, because the workplace exposure matrix was composed of overly broad job categories and time frames, and because of the considerable uncertainty regarding exposure durations.

The earlier New Jersey cancer slope factor (NJDWQI, 1987) and the more recent USEPA IRIS (2000) cancer slope factors are both based on the Feron et al. (1981) study of rats fed diets with PVC particles containing varying amounts of VC (Table 1). A study in which VC was administered by gavage (Maltoni et al., 1981) was not chosen by USEPA as the basis for the slope factor, because Feron et al. (1981) used a lower range of doses, and because bolus dosing by gavage dosing results in a higher systemic dose than does dietary exposure. The New Jersey (1987) cancer slope factor was based on hepatocellular carcinomas in female rats, while the USEPA IRIS (2000) cancer slope

factor is also based on the results in female rats but considers all liver tumors, including angiosarcomas, hepatocellular carcinomas, and neoplastic nodules, as a more conservative approach. Current USEPA Guidelines for Carcinogen Risk Assessment (2005) recommend basing risk assessment on results from the species and sex with the greatest response (female rats in this case) and recommend combining data from benign and malignant tumors, if the benign tumors have the potential to progress to malignancy.

Additionally, New Jersey (1987) and USEPA (2000) differed in the method used for adjusting for interspecies differences to calculate a human equivalent concentration (HEC). The default approach for interspecies extrapolation is based on the fractional power of the animal-to-human body weight ratio, which is roughly proportional to mammalian metabolic differences. New Jersey (1987) used the rat-to-human body weight ratio to the 2/3 power (which algebraically simplifies to the human-to-rat body weight ratio raised to the 1/3-power), as was recommended at the time. Currently the 3/4-power exponent (or the human-to-rat body ratio raised to the 1/4-power) is recommended as a default assumption. For VC, USEPA (2000) used a validated physiologically-based pharmacokinetic (PBPK) model (see below) which provides an estimate of the target tissue (liver) concentration of the active metabolite, CEO, instead of the default procedure based on the fractional power of animal-to-human body weight ratio. USEPA (2000) noted that the cancer slope calculated with the pharmacokinetic model was very similar to a slope factor derived by using the 3/4-power of the animal-to-human body weight ratio.

The PBPK model used by USEPA (2000) was developed by Clewell et al. (2001). It incorporates two enzymatic steps, including formation of the DNA-reactive metabolite, CEO, and elimination of CEO through reaction with glutathione. Parameters that had a significant impact on the calculated dose metric (and, thus, the risk) were body weight, alveolar ventilation, cardiac output, liver blood flow and volume, blood/air partition coefficient, the capacity and affinity for metabolism and, the oral uptake rate. Sensitivity/uncertainty Monte Carlo analysis of the parameters used in the model showed that none of the parameters displayed sensitivities markedly greater than 1.0, indicating that there is no amplification of error from the inputs to the outputs, a desirable trait in a model. (The 95th percentile of the distribution of risks was within 50% of the mean risk.) Pharmacodynamics were not addressed by the PBPK model. However, the dose metric is the amount of reactive metabolite produced which is believed to interact directly with DNA in both animals and humans. Such direct reaction of the CEO metabolite with DNA suggests similar production of DNA adducts in laboratory animals and humans. Thus, given the use of a dose metric that is normalized for the size of the liver (i.e., amount of metabolite produced per liter of liver), the pharmacodynamics of the vinyl chloride cancer response in animals and humans may be reasonably expected to be quite similar. Even with inherent variability, humans are considered unlikely to be more susceptible to cancer induction by VC than are laboratory species.

The low dose risk modeling conducted by USEPA (2000) is based on the dose to target tissue (liver) in animals. The animal dose metric was then converted to a human dose, and the human cancer risk in units of (mg vinyl chloride ingested/kg body weight/day)$^{-1}$ was calculated by USEPA (2000) as follows:

Slope factor for administered dose of VC $(mg/kg/day)^{-1}$ =

$$\frac{0.1}{\text{Tissue Dose at BMDL}_{10}\ (\text{mg metabolite/kg tissue/day})} \times 1.01 \frac{\text{mg metabolite/kg tissue/day}}{\text{mg/L vinyl chloride in drinking water}} \times \frac{70\ \text{kg}}{2\ \text{L/day}}$$

Where:

Tissue dose at $BMDL_{10}$ is the lower bound on the BMD_{10} (the dose causing an effect in 10% of the animals), in units of (mg metabolite/kg tissue/day) and was derived from the TOXRISK (life table statistical package) output.

0.1 represents the 10% response that is divided by the calculated $BMDL_{10}$ to derive the slope factor at the $BMDL_{10}$.

1.01 is the conversion factor for the dose of metabolites to the human liver from a sample human continuous oral exposure (1 mg/L in drinking water).

The use of a PBPK dose metric reflecting lifetime average daily dose to the target tissue resulted in similar potency estimates for liver angiosarcoma from VC across different species. USEPA (2000) reported that the human inhalation risk estimates based on studies with mice, 1.0×10^{-6} - 2.3×10^{-6} $(\mu g/m^3)^{-1}$ agreed very well with those based on inhalation studies with rats, 1.6×10^{-6} - 3.7×10^{-6} $(\mu g/m^3)^{-1}$. The estimated range of lifetime risk of liver cancer from VC exposure through inhalation in human occupational studies is in good agreement with the estimates based on animal inhalation data (USEPA, 2000).

The equivalent analysis using all liver tumors including angiosarcomas, hepatocellular carcinomas, and neoplastic nodules in the oral study of Feron et al. (1981) yielded an equivalent inhalation risk of 1×10^{-4} $(\mu g/m^3)^{-1}$. Notably, the cancer slope factor based on the Feron et al. (1981) oral rat study is higher than a slope factor (above) based on inhalation studies in animals (USEPA, 2000). The greater potency via the oral route than the inhalation route is biologically plausible, since the production of active metabolites would be expected to be greater with oral than with inhalation exposure due to first pass through the liver. Because both human and animal data indicate that the liver is the most sensitive site for cancer induction by VC, it is concluded that a slope factor based on liver cancer will be protective against cancers at other sites.

USEPA IRIS (2000) estimated the cancer slope factor for continuous adult oral exposure to VC as 0.75 $(mg/kg/day)^{-1}$ using the Clewell PBPK model and the $BMDL_{10}$/linear method recommended in the current USEPA (2005) cancer risk assessment guidelines. The drinking water concentration at the one-in-one-million risk level for VC based on this potency factor is 0.047 µg/L for adult lifetime exposure, assuming a 70 kg adult consuming 2 L/day. The slope factor derived from the same data using the linearized multistage model recommended in earlier (1986) USEPA cancer risk assessment guidance is very similar, 0.72 $(mg/kg/day)^{-1}$ (USEPA, 2000). Since VC metabolism is linear in the human exposure range, and carcinogenic activity is proportional to the formation of etheno-DNA adducts by the highly reactive VC metabolite CEO, there is high confidence in extrapolating to low

doses.

A slope factor of 1.5 $(mg/kg/day)^{-1}$ for VC which accounts for the increased risk of cancer when exposure starts in childhood was derived by applying an adjustment factor of 2 to the VC slope factor of 0.75 $(mg/kg/day)^{-1}$ based on exposure starting in early adulthood (USEPA, 2000). An increased cancer risk with neonatal exposure was observed in several animal inhalation studies (Maltoni et al., 1981; Drew et al., 1983; Laib et al., 1985, 1989). Maltoni et al. (1981) reported markedly increased cancer incidence in rats exposed via inhalation beginning at 1 day of age compared with those exposed beginning at 13 weeks of age. Mice, rats, and hamsters were also shown by Drew et al. (1983) to be more sensitive to cancer induction if exposed at a younger age. Vinyl chloride induction of preneoplastic liver foci in rats occured with VC exposures at approximately 7 to 21 days of age, but not with exposures during adulthood (Laib et al., 1985). Alkylation of liver DNA was also higher in younger animals (Laib et al., 1989). These studies provide a basis for assuming that early-life exposure increases lifetime cancer risk by approximately two-fold.

The lifetime drinking water concentration at the one-in-one-million risk level based on this slope factor of 1.5 per mg/kg-day is 0.023 µg/L. This represents a 3.5 fold decrease from the current New Jersey Health-based MCL of 0.08 µg/L, which is based on a cancer slope factor of 0.42 $(mg/kg/day)^{-1}$, derived by the linearized multistage model.

Conclusions and Recommendation

It is recommended that the New Jersey Drinking Water Quality Institute adopt the slope factor developed by USEPA (2000) for lifetime exposure to vinyl chloride of 1.5 $(mg/kg/day)^{-1}$. This slope factor is based on liver tumors in female rats in the oral cancer study of Feron et al. (1981) and the evidence for a doubling of risk with neonatal and pre-pubertal exposure compared to adult-only exposure from Maltoni et al. (1981), Drew et al. (1983), and Laib et al. (1979). The daily dose resulting in a one-in-one-million risk of vinyl chloride is:

$10^{-6} / 1.5\ (mg/kg/day)^{-1} = 6.7 \times 10^{-7}$ mg/kg/day

The Health-based MCL for vinyl chloride using this slope factor is:

$$\frac{6.7 \times 10^{-7}\ mg/kg/day \times 70\ kg}{2\ L/day} = 2.3 \times 10^{-5}\ mg/L \text{ or } 0.023\ \mu g/L$$

Where: 70 kg is the assumed body weight of an adult and 2 L day is the assumed daily water consumption of an adult.

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Table 1. Tumor incidence in male and female Wistar rats exposed to dietary vinyl chloride (Feron et al., 1981)

	Incidence [1]				
Tumor type/Sex	**Vinyl chloride (mg/kg-day)**	**0**	**1.7**	**5.0**	**14.1**
Liver angiosarcoma					
male		0/55	0/58	6/56* [2]	27/59 *** **
female		0/57	0/58	2/59	9/57 **
Hepatocellular carcinoma					
male		0/55	1/58	2/56 ***	8/59 ***
female		0/57	4/58	19/59	29/57
Neoplastic nodules					
male		0/55	1/58	7/56**	23/59***
female		2/57	26/58***	39/59***	44/57***
Lung angiosarcoma					
male		0/55	0/58	4/56*	19/59***
female		0/57	0/58	1/59	5/57*
Abdominal mesotheliomas					
male		3/55	1/58*	7/56	8/59
female		1/57	6/58	3/59	3/57
Mammary tumors[3]					
female		3/57	2/58	5/59	9/57

[1] Number in denominator = number of animals necropsied.

[2] values marked with asterisks differ significantly from controls as determined using the Chi-square test.
* = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$.

[3] Including mammary adenomas, adenocarcinomas, and anaplastic carcinomas.

Health-Based MCL Support Document for New Contaminants

Health-Based MCL Support Document
Dacthal (DCPA)

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Executive Summary

A Health-based Maximum Contaminant Level (HBMCL) of 0.028 mg/L (28 ug/L) for the total of dacthal and its degradates is recommended. Dacthal is classified in New Jersey Carcinogenicity Category II, equivalent to a designation of suggestive carcinogen under the current USEPA (2005) guidelines for cancer risk assessment. The Health-based MCL is based on a Reference Dose of 0.001 mg/kg/day, based on the No Observed Adverse Effect Level for toxicity to multiple organs in a chronic rat study (ISK Biotech, 1993) with an additional uncertainty factor of 10 for suggestive carcinogenicity. A Relative Source Contribution factor of 0.8, instead of the default value of 0.2, is recommended based on data on dietary exposure. Available data on the degradates of dacthal indicates that they have low toxicity. It is recommended that the Health-based MCL that be applied to the total of the parent compound and degradates. The Health-based MCL for the total of dacthal and its degradates is expected to be protective from potential health effects of the degradates as well as the parent compound.

Overview

Dacthal (dimethyl tetrachloroterephthalate, DCPA) is a pre-emergent herbicide, primarily used on residential lawns and golf courses. Its use in agriculture for certain lettuces and greens, squashes, turnips, soybeans and snap beans was terminated over the late 1990s and early 2000s. The parent compound is not particularly mobile or persistent in the environment, but its primary degradate, the di-acid tetrachloroterephthalic acid (TPA), is both mobile and persistent. Because of groundwater contamination concerns, the manufacturer voluntarily limited registered uses to four vegetable crops starting in 2005.

There are several good studies of the toxicological effects of dacthal, but the information on its degradates/metabolites is limited. The oral reference dose (RfD) for dacthal in the USEPA IRIS database of 0.01 mg/kg/day is based on a 2-year feeding study in rats (ISK Biotech Corp., 1993). Based on toxicity in the lung, liver, kidney and thyroid, the No Observed Adverse Effect Level (NOAEL) in both sexes is 1 mg/kg/day and the Lowest Observed Adverse Effect Level (LOAEL) is 10 mg/kg/day. Thyroxine (T4) was decreased throughout the study in a dose-dependent manner, especially among males, and thyroid stimulating hormone (TSH) from the pituitary increased in a dose-related fashion. The RfD of 0.01 mg/kg/day includes an uncertainty factor of 100, including

factors of 10 each for intraspecies variability and interspecies extrapolation from laboratory animals to humans. There are insufficient data to derive a Reference Dose (RfD) for the degradate/metabolites, TPA or monomethyl tetrachloroterephthalic acid (MTP). Effects of dacthal were seen in mice at doses an order of magnitude higher than the doses at which effects were seen in rats (ISK Biotech Corp., 1993).

The two year rat feeding study which forms the basis for the Reference Dose (ISK Biotech Corp., 1993) also examined tumor incidence. A statistically significant dose-response was observed for the incidence of liver tumors in female rats and mice, and thyroid tumors (adenomas and carcinomas) in male rats (USEPA 1995, 1998b). There was also suggestive evidence of increased thyroid tumors in female rats, but only at the highest dose.

The significance of the liver tumors observed in the ISK Biotech (1993) study is tempered by the presence of the liver carcinogens, hexachlorobenzene (HCB) and dioxins, in the technical grade dacthal used in the study. In contrast, there was no significant increase incidence of tumors in the Paynter and Kuzdin (1963) albino rat study, which used purified dacthal. However the animals in this study suffered from a chronic respiratory infection and had decreased survival. Dacthal and TPA were negative in assays of mutagenicity and genotoxicity.

The Carcinogenicity Peer Review Committee of the USEPA Office of Pesticide Programs classified dacthal as a Group C carcinogen under the 1986 USEPA guidelines for carcinogen risk assessment (USEPA, 1995). They derived a cancer slope factor from the data on liver tumors in female rats of 0.0015 $(mg/kg/day)^{-1}$, using linearized multistage modeling (q_1*) and an interspecies conversion based on animal-to-human body weight to the ¾ power (USEPA, 1998b). However, the carcinogenic potency of HCB and dioxins at the concentrations found in the technical grade dacthal could account for the liver tumors observed, in ISK Biotech Corp. (1993). On the other hand, the increased incidence of renal tumors characteristic of HCB were not seen in the ISK Biotech (1993) study. No carcinogenicity studies have been conducted on TPA or MTP.

Data on thyroid hormone levels in the ISK Biotech (1993) rat study suggest that the thyroid tumors were caused by over-stimulation of the pituitary-thyroid endocrine feedback system due to low thyroxine levels, probably caused by increased metabolic degradation of thyroxine in the liver.

It is New Jersey policy to base the risk assessment for suggestive carcinogens on a slope factor at a risk level of 10^{-6} if there is sufficient data to warrant the development of the slope factor. If development of a slope factor is not warranted, the risk assessment is based on a Reference Dose with an additional uncertainty factor of 10 to protect for suggestive carcinogenic effects. For dacthal, it is recommended that the Health-based MCL be based on an RfD with an additional uncertainty factor, rather than on low dose extrapolation of tumor data, because uncertainties about the carcinogenic effects observed in the chronic study preclude the development of a cancer slope factor.

An RfD of 0.001 mg/kg/day is recommended, based on the NOAEL of 1 mg/kg/day in the ISK Biotech (1993) chronic rat study and an uncertainty factor of 1000, including 10 each for intraspecies and interspecies variability and 10 to account for possible carcinogenicity. The Reference Dose is based on the same study and endpoints chosen by USEPA (1994) as the basis for

the RfD in its IRIS database.

For development of the Health-based MCL, a Relative Source Contribution (RSC) factor of 0.8 is recommended, since dacthal has only minimal uses as an herbicide currently and the most recent data from the FDA Total Dietary Study indicate that exposure from the diet is far below 20% of the Reference Dose.

The Health-based MCL based on the RfD of 0.001 mg/kg/day and an RSC of 0.8 is 0.028 mg/L. Though the data is limited, both TPA and MTP appear to have low toxicity, and this HBMCL is expected to be protective for TPA and MTP, as well as dacthal. It is further recommended that the HBMCL be applied to the total of the parent compound and degradates.

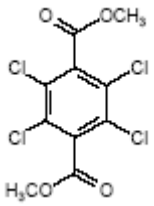
Background Information and Properties

Chemical Properties

Chemical Name: 2,3,5,6-tetrachlorodimethyl-1,4-benzenedicarboxylic acid

Synonyms: DCPA; dimethyl tetrachloroterephthalate; dacthal; chlorothal; chlorothal- dimethyl

CAS #: 1861-32-1
Chemical Formula: $C_{10}H_6O_4Cl_4$
Chemical Structure:



Molecular Weight: 331.99 g/mol
Physical State: crystalline (room temperature)
Melting Point: 156 ° C
Boiling Point: 360-370 ° C
Vapor Pressure: 2.5×10^{-6} mm Hg at 25 ° C
Water Solubility: 0.5 mg/L at 25 ° C
Log octanol/water partition coefficient: 6.8×10^{3}

Production and Use

Dacthal has been used as a selective pre-emergence herbicide to control annual grasses and some broad-leaf weeds in turf, ornamentals, certain fruits, beans and a variety of root, leaf, and seeded

vegetables. USEPA (1998b) noted 62 products containing dacthal. Its use on strawberries, lettuce, beets. squash, cucumber, beans, peas, peppers, potatoes, and yams has been terminated, but some uses remain (USEPA, 1998b, 2005b). Application rates ranged between 9 – 15 pounds per acre.

Guidelines, Regulations and Standards

The original USEPA (1988) Lifetime Health Advisory for dacthal in drinking water was 3.5 mg/L, based on a NOAEL of 50 mg/kg/d in a 2 year dietary study (Paynter and Kundzin, 1963), a total uncertainty factor of 100, 70 kg adult body weight, and a Relative Source Contribution factor of 0.2. However, this study is regarded as inadequate because of a persistent respiratory infection in both treated and untreated animals.

A chronic oral Reference Dose of 0.01 mg/kg/d was entered on the IRIS database in 1994. This RfD is based on a NOAEL of 1 mg/kg/d in a chronic rat feeding study (ISK Biotech Corp., 1993). The LOAEL was 10 mg/kg/d based on toxicity in the lungs, liver, kidney and thyroid in both sexes and in the eyes of females. This LOAEL is lower than the NOAEL of 50 mg/kg/day in the Paynter and Kundzin (1963) study. The calculation of the RfD employed an uncertainty factor of 100, appropriate for a NOAEL from a chronic laboratory animal study. The weight of evidence for carcinogenicity was not determined by IRIS. However, the USEPA Office of Pesticide Programs (1998) classified dacthal as a possible carcinogen (Group C), based on liver tumors in female rats and mice and thyroid tumors in male rats at doses that did not exceed the Maximum Tolerated Dose (ISK Biotech Corp., 1993).

Arizona and Florida have established drinking water guidelines of 3.5 mg/L and Wisconsin has established a guideline of 4.0 mg/L. All of these are based on the original USEPA (1988) Lifetime Health Advisory, which was rounded by Wisconsin to 4 mg/L.

Environmental Exposure

Dacthal has been found in a variety of produce in the FDA Total Dietary Study (2008). In the most recent data available (2003), only kale, romaine and radish had detectable levels. Residues (including mono- and di-acid degradates) were not found in meat, grains and fruit, nor in most vegetables. The data includes the total concentrations of dacthal and its degradates, but degradate data were not available separately. In particular, 42 percent of romaine samples had detectable residue levels, with mean and 90th percentile concentrations of 0.004 ug/g and 0.012 ug/g.

Of these three vegetables, consumption is greatest for romaine, representing an estimated one-quarter of per capita lettuce consumption (ERS, 2005). This is equivalent to mean and 90th percentile consumption of romaine of approximately 50 mg/kg/day and 125 mg/kg/day. Consumption of these amounts of romaine would result in ingestion of 0.0006 - 0.0015 ug/kg/day of dacthal and degradates, based on the 90th percentile of the residue data. The total daily ingestion of dacthal in the diet during the early 1980s was estimated to be 0.0011 - 0.0024 ug/kg (Gunderson et al, 1988). An update of this estimate has not yet been developed, but current exposure to dacthal would be expected to be similar since the restriction on dacthal use (see above, USEPA, 1998) probably compensates for the increase in consumption of vegetables since 1988.

In New Jersey, dacthal is used primarily on cabbage and other cole crops and leafy greens, but a small amount was used at least through 2003 on other crops (NJDEP Pesticide Control Program, personal communication). In 2005, approximately 7500 pounds were applied for agricultural purposes (NJDEP, 2008), primarily in the Vineland area. Approximately 34 pounds were used on golf courses in 2005 (NJDEP, 2008).

There are two available databases which provide information on dacthal in community water systems in New Jersey. Both are part of the Synthetic Organic Compound (SOC) Waiver Sampling Program (NJDEP Bureau of Safe Drinking Water, personal communication). One database (2000-2006) which includes results from one or more points of entry in 210 community water systems. Dacthal (including mono- and di-acid degradates) was found in 28 of the 210 systems at a 90th percentile level of 0.54 ug/L and a maximum level of 166 ug/L. Dacthal was detected at greater than 1.0 ug/L in 16 of these systems, and the 90th percentile level in systems with greater than 1 ug/L is 33.5 ug/L. In the other database (2001-2002), dacthal was detected at > 1 ug/L in one or more points of entry in 14 community water systems, with a maximum level of 39 ug/L.

No information was available separately on environmental exposure to degradates.

Metabolism and Pharmacokinetics

The information on toxicokinetics of dacthal is summarized below. TPA and MTP are metabolites and environmental degradates of dacthal, but there is little information on the toxicokinetics of either chemical.

Absorption

In Sprague-Dawley rats given single oral doses of dacthal, 79% of a dose of 1 mg/kg and 8% of a dose of 1000 mg/kg was absorbed, based on amounts measured in urine, blood, bile, cage rinse and carcass (Magee et al., 1991). These data indicate that that a greater percentage of a dose was absorbed at lower doses compared to higher doses.

In contrast, a small study in humans found that approximately 6% of a 25 mg dose (0.36 mg/kg, assuming a 70 kg adult) and 12% of a 50 mg dose (0.72 mg/kg, assuming a 70 kg adult) was absorbed, based on the presence of metabolites in the urine (Tusing, 1963). However, both of the doses used were below the lower dose of 1 mg/kg used in the rat study.

Dogs excreted 97% of single oral doses of 100 to 1000 mg/kg as unabsorbed and unmetabolized dacthal in the feces (Skinner and Stallard, 1963). An additional 1% was found in feces as MTP. Thus, only 2-3% of the dose appeared to be absorbed. The time course of excretion was not given in available documents.

Distribution

Dacthal metabolites were found in a variety of organs in dogs after oral dosing (Skinner and Stallard, 1963).

Metabolism

MTP (or 4-carbomethoxy-2,3,5,6-tetrachlorobenzoic acid) and TPA were found in the urine of humans who took a single dose of 25 or 50 mg dacthal (Tusing, 1963). After three days, 6% of the 25 mg dose and 12 % of the 50 mg dose were found in urine as MTP, along with a small amount of TPA. The TPA metabolite may be the final metabolic product (Klopmann et al., 1996).

DCPA was not found in the liver, kidneys, or adipose tissues of dogs given 10,000 ppm (250 mg/kg/day) in the diet for 2 years (Skinner and Stallard, 1963). In dogs given a single dose of 100 or 1000 mg/kg of DCPA, TPA was detected in kidney, and MPA was found in kidney, liver, and adipose tissue. Some DCPA was also found in adipose tissue. (The DCPA used in this study contained one percent TPA and MTP.) Most of the absorbed dose in dogs was excreted in the urine as MTP, but a small amount of TPA was also found in the urine.

In Sprague-Dawley rats, MTP, but no unmetabolized dacthal, was found in the urine after a single oral dose of 1 or 1000 mg/kg of radiolabelled dacthal (Medvedeff et al., 1991).

Elimination

Dogs excreted 97% of a single dose of 100-1000 mg/kg unchanged in the feces (Skinner and Stallard, 1963). Approximately 2% was excreted in the urine and 1% in the feces as MTP. A small amount of TPA was also found in the urine.

In Sprague-Dawley rats. 61% of a single oral dose of 1 mg/kg radiolabelled DCPA was excreted in the urine, while 55% of a 1000 mg/kg dose was found in feces or gastrointestinal tract (Magee et al., 1991). Negligible amounts of radiolabel were found in tissues 48 hours after a single dose of 1 or 1000 mg/kg (Ho et al., 1991).

An estimated half-life of 18 hours was calculated in a 2-week study of Crl:CD BR VAF/Plus rats dosed with 1 mg/kg of non-labeled dacthal daily for 13 days, and with 1 mg/kg of radiolabelled dacthal on the 14th day (Liu et al., 1992, 1993a). Although most of the dose was absorbed and excreted in urine, radiolabel was found in all tissues examined. At a dose of 1000 mg/kg/d, most of the dose was not absorbed and was eliminated in feces. Excretion of unmetabolized dacthal was not observed (Liu et al., 1993b)

Human Exposure and Body Burden

There are no studies of human body burden.

Health Effects

Overview

A series of chronic oral studies conducted in the late 1980s and early 1990s provide a better basis for evaluating the toxicity of dacthal than the earlier chronic study conducted in the early 1960s. The

earlier study was marred by a long-term colony wide respiratory infection.

There is little toxicity data on the metabolites, MTP and TPA.

Human Studies

No adverse effects were observed in humans given a single 25 or 50 mg/kg dose of dacthal in the toxicokinetic study conducted by Tusing et al. (1963). There are no studies of human poisonings with the metabolites, MTP and TPA.

Acute and Short-term Laboratory Animal Studies

The 50% lethal single oral dose (LD50) for dacthal was not achieved in rats (Wazeter et al., 1974a) or beagles (Wazeter et al., 1974b), and would be greater than 12,500 mg/kg and greater than 10,000 mg/kg in these species, respectively.

In a reproductive outcome study (Fermenta Plant Protection Co., 1989) in which pregnant rabbits were dosed during gestation days 6-19, dose-related lethality occurred in the dams. Mortality was 4/20, 13/20 and 12/20 in the 500, 1000, and 1500 mg/kg/d groups.

In a 30-day dietary study of Sprague-Dawley rats (ISK Biotech Corp., 1990), increased liver weight and centrilobular hypertrophy were observed at the lowest dose given, 250 mg/kg/d, which was thus judged to be the LOAEL.

A NOEL of 500 mg/kg/d was observed at the highest dose of the dacthal degradate TPA in a 30-day gavage study of Sprague-Dawley rats (Major, 1985). In this study, dacthal was administered in 0.5% methylcellulose. Soft stool (probably due to the colligative properties of TPA causing water to be pulled into the gut) and occult blood in urine were observed at the highest dose, and increased hematocrit and hemoglobin occurred in males at the highest dose (2000 mg/kg/day). There were no changes in organ weights. The USEPA Office of Pesticide Programs (1998b) established a NOEL and LOEL from this study, rather than a NOAEL and a LOAEL, as they did not consider the high dose effects to be adverse.

Chronic and Subchronic Laboratory Animal Studies

In the largest chronic dietary study (ISK Biotech Corp., 1993) which has been conducted for dacthal, Sprague-Dawley rats (70/dose/sex) were given 0, 1, 10, 50, 500 and 1000 mg/kg/d of technical grade dacthal for 2 years (104 weeks). Survival was similar in all dose groups, except for in males at the highest dose, where survival was 73% compared to 52% in controls. The cause of death in the high dose males appeared to be chronic infections. Weight gain was similar across all groups of males in the first year but was decreased at the highest dose in the second year. Weight gain was decreased during both years in the two highest dose groups in females.

The assessment in the USEPA IRIS database (1994) concludes that liver, kidneys, and thyroid were affected in both sexes at doses of $\geq$10 mg/kg/d. However, a more detailed analysis of the data from this study indicates that the results were more complex.

After one year, liver weight was increased in the two highest dose groups of males by 12 and 16% compared to controls, and in females by 29% and 37% compared to controls. At termination, liver weight increases in these dose groups compared to controls were 35% and 40% in males and 18% and 22% in females. This was mirrored by similar increases in the liver-to-body weight ratios. The increases in liver weight were accompanied by hepatocytic hypertrophy and enlargement. At termination, these changes were seen at 50 mg/kg/d in females and at 10 and 50 mg/kg/d in males. Increased eosinophilic foci were observed in both sexes at doses of 10 mg/kg/d and higher, reaching statistical significance at the ≥50 mg/kg/d dosages in males and the ≥500 mg/kg/d dosages in females. These effects were categorized into the two highest severity grades (out of five possible grades of severity) only at the two highest doses.

Kidney weight was significantly elevated in the ≥50 mg/kg/d dose groups in males, but only in the 500 mg/kg/d dose group in females. The severity of chronic nephropathy in males was increased with ≥50 mg/kg/d dosage, while in females severity was increased at doses of ≥10 mg/kg/d. Chronic nephropathy is an aging-related set of lesions seen in Sprague-Dawley rats, which includes regenerative tubular epithelium, dilated tubules, casts, interstitial fibrosis and mononuclear cell infiltrates. Treated males also exhibited renal infarcts, cysts, and papillary necrosis, as well as pelvic hemorrhaging. Tubular cell neoplasms (adenomas and carcinomas) occurred only in treated males, with a maximum incidence of adenomas or carcinomas in the 500 mg/kg/d dosage group. In this dose group, these tumors occurred in four animals.

In the thyroid glands, follicular cell hypertrophy and hyperplasia and basophilic clumped colloid occurred at doses ≥ 10 mg/kg/d in males and ≥ 50 mg/kg/d in females. At 52 weeks, non-neoplastic thyroid lesions were increased in males receiving ≥10 mg/kg/d, while at the terminal sacrifice, males exhibited additional lesions, especially follicular cell hypertrophy and hyperplasia at doses ≥10 mg/kg/d. Females showed similar increases at ≥50 mg/kg/d at the terminal sacrifice. At 52 and 104 weeks, thyroid weight was increased in both sexes at the highest dose, while at termination, thyroid weight was increased in females in the three lowest dose groups as well.

These goitrogenic phenomena were accompanied by a statistically significant dose-related decrease of serum thyroxine (T4) at 52, 83, and 104 weeks at doses ≥10 mg/kg/d in males and at doses ≥50 mg/kg/d in females, while triiodothyronine (T3) was only minimally affected. Additionally, among females, average serum T4 was decreased at 83 and 104 weeks in the 10 mg/kg/d dose group, but this change was not statistically significantly. Elevated thyroid stimulating hormone (TSH) was seen in males at almost all doses and time points, but was statistically elevated only in the 104 week group of the 500 mg/kg/d dose group. A dose related increase of TSH was seen in females at doses ≥50 mg/kg/d, particularly at the 104 week termination. These data suggest that the goitrogenic phenomena described above may be caused by increased hepatic metabolism of T4 and T3, which would result in feedback increase in TSH and resulting thyroid hyperplasia.

In addition, in males receiving ≥10 mg/kg/d and in females receiving ≥500 mg/kg/d, focal accumulations of macrophages with “foamy” inclusions were seen in alveolar spaces of the lung in a dose-related manner. These foci were typically accompanied by a thickening of alveolar walls, fibrosis (appearing like collagen in polarized light microscopy), and focal interstitial pneumonitis. At the two highest doses, focal granulomatous pneumonitis and presumptive hemosiderin and

cholesterol deposits were observed.

Retinal atrophy (bilateral and unilateral) was also observed in a dose-related manner in female rats.

Thus, the NOAEL in this study was 1 mg/kg/day and the LOAEL was 10 mg/kg/day, based on effects in several organs in males and females.

In a 2-year feeding study (Diamond Alkali Co., 1963; Paynter and Kundzen; 1963) of rats (35/sex/dose), there were no differences in growth and a minor increase in food consumption in both sexes at the high dose (500 mg/kd/d). At termination, the kidney weight in high dose males and the adrenal weight in high dose females were significantly increased. Hepatocyte hypertrophy and thyroid follicular cell hypertrophy also occurred. The NOAEL was 50 mg/kg/d. However, the animals in this study suffered from a chronic respiratory infection and had decreased survival. This study was used as the basis for the original USEPA (1988) Health Advisory.

Mild hepatic toxicity was seen in a 2-year feeding study (Fermenta Plant Protection Co., 1988) of CD-1 mice (90/sex/dose). Effects observed included increased liver weight and hepatocyte enlargement and vacuolation in both sexes at the high dose (930 mg/kg/d in males, 1141 mg/kg/d in females), increased (but not dose-related) serum glutamic-pyruvic transaminase and sorbitol dehydrogenase in both sexes at 76 weeks in the three highest dose groups, increased GPT and SDH in females after 2 years, and small dose-related changes in urinary ketones and serum cholesterol. Corneal opacity was noted, though not seen in a follow-up study (USEPA, 1994).

A 13-week dietary study (Fermenta Plant Protection Co., 1986) of dacthal in CD-1 mice (15/sex/dose) did not show adverse effects at any dose, with the exception of the non-adverse effect of minimal centrilobular hepatocyte enlargement in the both sexes at the high dose groups (1235 mg/kg/d in males and 1049 and 2198 mg/kg/d in females). The NOELs are 406 mg/kg/d in males and 517 mg/kg/d in females.

A 13-week dietary study (ISK Biotech Corp., 1991) of dacthal in Sprague-Dawley rats (15/sex/dose) found that liver weight and kidney weights were increased in a dose-related manner, and that hepatocyte enlargement and renal tubular regenerative hyperplasia and thyroid follicular hypertrophy were present at doses $\geq$50 mg/kg/d. The NOAEL was 10 mg/kg/d.

No adverse effects from TPA were seen in a 90-day feeding study (Goldenthal et al., 1977) in Charles River CD rats at or below a dose estimated to be 500 mg/kg/d.

Behavioral and Central Nervous System

Ataxia, decreased motor activity, and poor righting reflex were observed in a dose-related manner in New Zealand white rabbits that received lethal or near lethal doses of 500 mg/kg/d and higher during gestational days 6-19 in a reproductive outcome study discussed below (Fermenta Plant Protection Co., 1989).

Reproductive, Embryonic and Teratogenic

Two related studies of pregnant Sprague-Dawley (Crl:COBS CD and Crl:COBS CD(SD)BR) rats (25/dose) did not find effects on offspring at up to 2500 mg/kg/d during gestational days 6-15 (SDS Biotech Corp., 1986). The high dose dams exhibited decreased weight gain and food consumption, as well as abnormal stools during the first four days of dosing. The NOAEL for maternal toxicity was 1250 mg/kg/d.

Two related studies (Fermenta Plant Protection Co., 1989) of pregnant New Zealand White rabbits (20/dose, gestational days 6-19 and 7-19) showed no embryotoxicity, fetotoxicity or teratogenicity at any dose that was not lethal to dams. The NOAEL for developmental toxicity was 500 mg/kg/d, but that dose was a marginal LOAEL for maternal toxicity, based on lethality.

In a two generation reproductive study (ISK Biotech Corp, 1990) with Sprague-Dawley CD VAF/Plus rats (35/sex/dose), body weight and body weight gain were significantly decreased in both generations of parents in the mid- and high-dose groups (233 and 952 mg/kg/d in males, and 319 and 1273 mg/kg/d in females), but the changes were slight. Offspring showed good viability, but body weight was decreased at the mid- and high-doses. Reproductive performance was not affected. The NOEL for maternal toxicity (body weight and body weight gain) was 63 mg/kg/d for females and 233 mg/kg/d for paternal toxicity. The NOAEL for pup weight gain was 63 mg/kg/d in the F1a, F1b, and F2a litters. The dose was decreased in the F2b litter, so that the NOAEL at the end of the study was 18 mg/kg/d.

Genotoxicity

Dacthal and TPA have not shown positive results in tests of mutagenicity and genotoxicity. Dacthal was examined with and without metabolic activation in Salmonella Ames mutagenicity assays (Auletta et al., 1977), in vivo genotoxicity tests (Kouri et al., 1977a), DNA repair tests (Auletta and Kuzava, 1977) and dominant lethal tests (Kouri et al., 1977b). TPA was negative with and without metabolic activation in both Ames and hypoxanthine guanine phosphoribosyl transferase mutagenicity assays, sister chromatid exchange assay in Chinese hamster ovary cells, unscheduled DNA synthesis, and in vivo mouse micronucleus assay (USEPA, 1998). No data on MTP could be located.

Carcinogenicity

In the 2-year dietary study of Sprague-Dawley rats discussed above (ISK Biotech Corp., 1993), a dose-related increase was seen in the incidence of combined liver adenomas and carcinomas in females (0%, 0%, 3%, 1%, 11%, and 19% at 0, 1, 10, 50, 500, and 1000 mg/kg/d, respectively), and thyroid adenomas and carcinomas in both sexes (3%, 5%, 5%, 13%, 16%, 10% in males, and 2%, 2%, 5%, 7%, 3%, and 12% in females). The USEPA Office of Pesticide Programs (1998b) developed a cancer slope factor (q_1*, the upper 95% confidence interval) of 1.49×10^{-3} $(mg/kg/day)^{-1}$, based on the female liver tumors and a body weight scaling to the ¾ power.

However, this study used technical grade dacthal which was contaminated by 0.13% hexachlorobenzene (HCB). Contamination by trace levels of dioxins equivalent to 0.0000001% (10^{-7} %) 2,3,7,8-TCDD by weight, based on Toxic Equivalency Factors for dioxins (USEPA, 2003),

was also reported by USEPA (1998b) in a Registration Eligibility Decision. Like the rats exposed to dacthal in the ISK Biotech (1993) chronic study, female Sprague-Dawley rats chronically exposed to HCB or dioxin exhibited a significant dose-response for the increased incidence of hepatocellular carcinomas, as well as for bile duct tumors, and HCB and dioxins are classified as probable human carcinogens by USEPA. The 0.13% (by weight) contamination of the dacthal by HCB would result in exposure to 0.65 and 1.3 mg/kg/d HCB in the two highest dose groups in which an increased incidence of liver tumors was observed in the ISK Biotech (1993) chronic dacthal study.

In comparison, the primary study used by USEPA as the basis for the HCB cancer slope factor was Erturk et al. (1986), which dosed with 4 and 8 mg/kg/day. A cancer slope factor of 1.6 $(mg/kg/day)^{-1}$ has been developed for HCB in the rat by USEPA (1996). If dacthal provided no additional carcinogenicity, the presence of 0.13% HCB contamination would nevertheless result in an apparent cancer slope for dacthal of 0.0021 $(mg/kg/day)^{-1}$ (1.6 $(mg/kg/day)^{-1}$ x 0.0013). This apparent slope factor for dacthal based on the HCB which present as a contaminant is very close to the slope factor calculated by USEPA (1998b) for dacthal from the ISK Biotech (1993) data, 0.00149 $(mg/kg/day)^{-1}$, suggesting that HCB impurities could account for the observed liver tumor potency. However, the increased incidence of renal carcinoma seen in male Sprague-Dawley rats treated with HCB at higher doses was not seen in the rats treated with the HCB-contaminated dacthal.

The cancer potency contributed by dioxin contamination (USEPA, 2003) was calculated using the 10^{-9} weight-to-weight proportion of contamination, based on total toxic equivalence (USEPA, 2003) for the reported contamination by the dioxin-like compounds, which was multiplied by the current range of draft cancer slope factors for dioxin (USEPA, 2003). Thus, the apparent cancer potency from dioxin would be 0.0001 – 0.001 $(mg/kg/day)^{-1}$ (1 x 10^5 to 1 x 10^6 $(mg/kg/day)^{-1}$ x $1x10^{-9}$). This slope factor is lower than the observed cancer slope factor for dacthal.

It is less likely that the increased incidence of thyroid tumors seen in the ISK Biotech (1993) study results from HCB contamination of the dacthal. An increased incidence of thyroid tumors (14% in males and 5% in females) was seen with HCB in Golden Hamsters (Cabral et al., 1977), but this was only statistically significant at the highest dose (16 mg/kg/d). HCB did not cause thyroid tumors in any of the tested strains of rats (USEPA, 1996).

The non-cancer health effects of HCB and dioxins in rats were notably different than the effects observed in the chronic technical grade dacthal study, although they might not be expected to occur from the low concentrations found in the technical grade dacthal. Additionally, lung, thyroid, and ocular effects seen with dacthal were absent in studies of HCB and dioxin, and the liver histopathology from dacthal differed from that seen with HCB and dioxin. The animals dosed with 1 mg/kg/d dacthal in the ISK Biotech (1993) studied would have been exposed to dioxin at a dose equivalent to the current draft RfD, 10^{-9} mg/kg/d, and to HCB at a dose 160% higher than the current RfD of 0.0008 mg/kg/d.

The dose-related decreases in T4 and increases in TSH caused by dacthal suggest that the increased incidence of thyroid tumors, primarily adenomas except for carcinomas among high dose males, may result from a threshold mode of action related to endocrine effects, although this mode of action has not been fully proven for dacthal. Decreased levels of T4 are often due to increased hepatic

metabolism of T4 resulting from liver hypertrophy. Secretion of TSH is increased in response to the decrease in T4, and chronic over-stimulation of the thyroid gland by TSH, as evidenced by the observed goitrogenic histopathological changes, is known to increase the risk of developing follicular thyroid adenomas in rats (see Chronic and Sub-chronic Laboratory Animal Studies, above).

Because of the unique nature of the variety of modes of action for thyroid tumor causation, many of which are threshold endocrine phenomena rather than non-threshold genotoxic phenomena, a technical panel of the USEPA Risk Assessment Forum (1998a) provided guidance on how best to apply thyroid tumors data in risk assessment, as follows:

Using the current understanding of thyroid carcinogenesis, the EPA adopts the following science policy for interpreting data on this process in experimental animals:

1. It is presumed that chemicals that produce rodent thyroid tumors may pose a carcinogenic hazard for the human thyroid.

2. In the absence of chemical-specific data, humans and rodents are presumed to be equally sensitive to thyroid cancer due to thyroid-pituitary disruption. This is a conservative position when thyroid-pituitary disruption is the sole mode of action, because rodents appear to be more sensitive to this carcinogenic mode of action than humans. When the thyroid carcinogen is a mutagenic chemical, the possibility that children may be more sensitive than adults needs to be evaluated on a case by case basis.

3. Based on data and mode of action information on a chemical that has produced thyroid tumors, a judgment will be made concerning the applicability of the generic EPA presumption that dose and response maintain linearity from high dose to zero dose as follows:

a. A linear dose-response procedure should be assumed when needed experimental data to understand the cause of thyroid tumors are absent and the mode of action is unknown.

b. A linear dose-response procedure should be assumed when the mode of action underlying thyroid tumors is judged to involve mutagenicity alone.

c. A margin of exposure dose-response procedure based on nonlinearity of effects should be used when thyroid-pituitary disruption is judged to be the sole mode of action of the observed thyroid and related pituitary tumors. Thyroid-pituitary perturbation is not likely to have carcinogenic potential in short-term or highly infrequent exposure conditions. The margin of exposure procedure generally should be based on thyroid-pituitary disruptive effects themselves, in lieu of tumor effects, when data permit. Such analyses will aid in the development of combined noncancer and cancer assessments of toxicity. Results of the margin of exposure procedure will be presented in a way that supports risk management decisions for exposure scenarios of differing types (e.g., infrequent exposure, short durations).

d. Consistent with EPA risk characterization principles, both linear and margin of exposure considerations should be assumed when both mutagenic and thyroid-pituitary disruption modes of action are judged to be potentially at work. The weight of evidence for choosing one over the other should also be presented. The applicability of each to different exposure scenarios should be developed for risk management consideration.

e. When supported by available data, biologically based dose-response modeling may be conducted. This is the preferred approach when detailed data are available to construct such a model.

As discussed above, the balance of evidence leans toward a thyroid-pituitary mode of action for thyroid tumor causation (3c above) which is a threshold phenomenon. Decreased thyroxine and elevated TSH were observed in this long-term study. However, stronger and more complete evidence for this mode of action would include characterization of the reason for reduced T4 (e.g., greater metabolism of T4 by the liver or reduced synthesis of T4 in the thyroid) and demonstration of reversal of the thyroid effects following supplementation with thyroxine or cessation of dacthal exposure.

Additionally, contributions from other modes of action for carcinogenicity which may be linear (3d above) not been ruled out, since the liver tumors seen in the ISK Biotech (1993) study could result from dacthal rather than from the contaminants present in the technical grade dacthal.

In the two year study of CD-1 mice (Fermenta Plant Protection Co., 1988) a dose-related increase of liver adenomas was found in females (3%, 0%, 3%, 5%, and 11% in the 0, 10, 50, 500, and 1000 mg/kg/d groups), but the incidence at the high dose was only slightly elevated above the range for historical controls (2-8%). The incidence of adenomas in males did not exceed that of the historical controls, except at the highest dose, and the incidence of carcinomas in males did not exceed historical controls at any dose.

Tumors were not observed in the two year dacthal feeding study in rats conducted by Diamond Alkali Co. (1963) at dosage levels of 5, 50 and 500 mg/kg/d.

There is no cancer assay data available for the metabolites, TPA and MTP, but structural analysis (Klopman et al., 1996) strongly suggests that no cancer effect would be found.

Quantitative Risk Assessment

Studies Useful for Risk Assessment

The ISK Biotech Corp. (1993) 2-year dietary study of rats has been used by USEPA for determination of an RfD (USEPA, 1994) and a cancer slope factor (USEPA, 1998b). This study was of sufficient size, used the oral dietary exposure route, and was sufficiently well conducted to also be the most suitable for use in developing a New Jersey Health-based MCL (HBMCL).

Weight of Evidence for Carcinogenicity and Risk Assessment Approach

As discussed above, an increased incidence of liver and thyroid tumors was observed in the ISK Biotech (1993) chronic oral rat study. The liver carcinogenicity of dacthal has not been definitively established because of two carcinogenic impurities in the dacthal used in the ISK Biotech Corp (1993) rat study, HCB and dioxin. However, the renal cancers seen with exposure to HCB were not observed in the dacthal study, complicating the attribution of the liver tumors to HCB. These impurities have also not previously been associated with thyroid tumors in rats. The chronic study does show evidence that dacthal disrupted the pituitary-thyroid endocrine feedback mechanism, which can cause thyroid tumors in a threshold-dependent manner. While the evidence is strong, it is not complete enough to definitively identify this as the mode of action for thyroid gland tumors.

Based on these conclusions, it is recommended that dacthal be considered a suggestive carcinogen, under the USEPA (2005a) cancer risk assessment guidelines. It is New Jersey policy to base the risk assessment for suggestive carcinogens on a slope factor at a risk level of 10^{-6} if there is sufficient data to warrant the development of a slope factor. If development of a slope factor is not warranted, the risk assessment is based on a Reference Dose with an additional uncertainty factor of 10 to protect for possible carcinogenic effects.

For dacthal, the development of a slope factor is not warranted because of possible contributions of the contaminants, HCB and dioxin, to the observed carcinogenic effects and because the thyroid tumors may occur through a threshold mechanism. Thus, the incorporation of an additional uncertainty factor of 10 into the Reference Dose is recommended.

Development of Reference Dose

Based on a NOAEL of 1 mg/kg/d from ISK Biotech (1993) and a combined uncertainty factor of 1000 (10 for intraspecies variability, 10 for animal to human extrapolation, and 10 for possible carcinogenicity), the RfD is 0.001 mg/kg/d.

Calculation of the Health-based Maximum Contaminant Level

The Drinking Water Equivalent Level (DWEL) derived from this Reference Dose is:

$$\frac{0.001 \text{ mg/kg/d} \times 70 \text{ kg average adult body weight}}{2 \text{ L /day}} = 0.035 \text{ mg/L.}$$

Where 70 kg is the assumed body weight of an adult and 2 L/day is the assumed daily drinking water consumption of an adult.

The availability of data on dietary exposure to dacthal allows for the development of a chemical-specific RSC to be used instead of the default RSC of 0.2. The decreased use of dacthal in food production since the mid-1990s suggests that an RSC higher than the default value of 0.2 is appropriate. Under NJDEP policy for drinking water HBMCLs, the guidance provided in the *USEPA (2000) Methodology for Deriving Ambient Water Quality Criteria for the Protection of*

Human Health is used to develop RSCs. Under this guidance, RSCs between a "floor" value of 0.2 and a "ceiling" value of 0.8 are recommended, with a default value of 0.2 in the absence of chemical-specific data. Data from 2003, the most recent available from the FDA Total Dietary Study, indicate that little dacthal is found in food. Dacthal was not detected in any fruits, meats, or grains, or in most vegetables, and was found in several vegetables at levels below 1 ug/g. The estimated total daily ingestion from foods is less than 0.01 ug/kg/d, which represents less than 1% of the RfD of 0.001 mg/kg/day (1 ug/kg/day). Additionally, exposure is not anticipated through routes other than diet and drinking water, such as inhalation from indoor air. As much less than 20% of exposure is expected to come from no-drinking water sources, an RSC of 0.8 is warranted for dacthal. Application of a Relative Source Contribution factor (RSC) of 0.8 to the DWEL of 0.035 mg/L yields an HBMCL of 0.028 mg/L.

The HBMCL is expected to be protective against health effects from the dacthal metabolites, TPA and MTP, as well as dacthal. It is further recommended that the HBMCL be applied to the total of the parent compound and degradates.

Comparison with HBMCL based on cancer slope factor

For the sake of comparison, the HBMCL based on the cancer slope factor of 1.49×10^{-3} $(mg/kg/day)^{-1}$ developed by USEPA (1998b) from the combined liver adenoma and carcinoma in female rats (ISK Biotech Corp, 1993) is presented. The daily dose of dacthal at the 10^{-6} risk level is equal to 0.0067 mg/kg/day ($10^{-6}/1.49 \times 10^{-3}$ $(mg/kg/day)^{-1}$). The HBMCL based on this daily dose and standard assumptions of 70 kg body weight and 2 L/day water ingestion would be:

$$\frac{0.00067 \text{ mg/kg/d} \times 70 \text{ kg average adult body weight}}{2 \text{L/d}} = 0.023 \text{ mg/L}.$$

This HBMCL is very close to the recommended HBMCL of 0.028 mg/L based on a Reference Dose with incorporates an additional uncertainty factor for possible carcinogenicity.

Conclusions

A Health-based MCL (HBMCL) of 0.028 mg/L for dacthal is recommended. This HBMCL is based on the RfD derived from a chronic rat study (ISK Biotech Corp, 1993) that includes an additional uncertainty factor of 10 to account for possible carcinogenic effects. A chemical-specific RSC of 0.8 was used to develop the HBMCL for dacthal. Based on the available data, the HBMCL for dacthal is anticipated to be protective from potential health effects of the dacthal degradates, TPA and MTP. It is recommended that the HBMCL for dacthal be applied to the total concentration of dacthal and its degradates.

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Health-Based MCL Support Documents
1,2,3-Trichloropropane

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Executive Summary

1,2,3-Trichloropropane is a contaminant of nematocides/fumigants applied to soil and has also been used for other industrial purposes. It is stable in the environment and has been detected in public water systems, private wells, and in ground water at contaminated sites in New Jersey and in other locations. There is no federal MCL for 1,2,3-trichloropropane. In 1999, NJDEP developed a drinking water guidance value of 0.025 ug/L for 1,2,3-trichloropropane based on the analytical practical quantitation limit (PQL). The health-based guidance value developed at that time was 0.005 ug/L, based on carcinogenic effects and the 10^{-6} risk level.

After absorption into the body, 1,2,3-trichloropropane is metabolized to reactive intermediates which are mutagenic, genotoxic, and carcinogenic. It is a potent carcinogen and caused tumors in male and female rats and mice in multiple organs in a 2-year chronic gavage study (NTP, 1993). In this study, tumors began to be detected within a year of the start of dosing, associated with high mortality rates of treated animals. Forestomach tumors were the most frequent tumor type in male and female mice and rats.

Because the incidence of forestomach tumors was so high even at the lowest dose, a time-to-tumor model appropriate for modeling dose-response data from studies with early fatal tumor occurrence was used to develop cancer slope factors from the NTP (1993) data. Modeling of forestomach tumors in female mice gave the highest slope factor, 26 $(mg/kg/day)^{-1}$, and these data were judged appropriate for the basis of the Health-based MCL. The recommended Health-based MCL developed from this slope factor is 0.0013 ug/L.

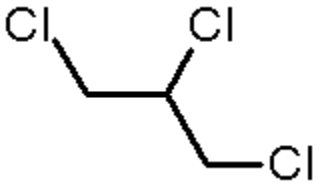
Background Information and Properties

Chemical Properties (ATSDR, 1992: NTP, 1999; WHO, 2003)

Chemical Name: 1,2,3-Trichloropropane

Synonyms: Allyl trichloride, glycerol trichlorohydrin, glyceryl trichlorohydrin, NCI-C60220, trichlorohydrin, trichloropropane, 1,2,3-TCP

CAS #: 96-18-4
Chemical Formula: C3H5Cl3
Chemical Structure:



Molecular Weight:	147.43
Physical State:	liquid
Melting Point:	-14.7 ° C
Boiling Point:	156.8 ° C
Vapor Pressure:	3.1 torr at 25 ° C
Density	1.38 g/cm3
Water Solubility	1750 mg/L at 20 ° C
Log octanol / water partition coefficient	1.98
Taste Threshold (water)	No data
Odor Threshold (water)	No data
Odor Threshold (air)	No data

Production and Use

1,2,3-Trichloropropane is a known contaminant of nematocides and soil fumigants including D-D (1,2-dichloropropane and 1,3-dichloropropene [mixed isomers]) and Telone (1,3-dichloropropene) (NTP, 2005). Telone has been reported to contain up to 0.17% 1,2,3-trichloropropane by weight (WHO, 2003), and has been used in the majority of counties in New Jersey (New Jersey Department of Health, 1979). Application of these fumigants to soil is thought to be a source of 1,2,3-trichloropropane contamination of rural wells in New Jersey and other locations. When 1,2,3-trichloropropane was detected in Galloway Township, Atlantic County, New Jersey, in 1999, three other chemicals with use as soil fumigants were also found at the sampling sites: dibromochloropropane, 1,2-dichloropropane, and ethylene dibromide (NJDEP, 1999). The occurrence of 1,2,3-trichloropropane in the environment is discussed in more detail below.

1,2,3-Trichloropropane was extensively used in the past as a solvent, cleaning and degreasing agent, and as a paint and varnish remover. It is used as intermediate in the synthesis of several organic

compounds including polysulfone liquid polymers, dichloropropene, hexafluoropropylene, and polysulfides (NTP, 1999).

1,2,3-Trichloropropane is a byproduct produced in significant quantities in the manufacture of other chlorinated compounds, including epichlorohydrin. It is listed as a component which is present at greater than 0.01% (a reporting threshold) on the Right to Know lists of New Jersey, Pennsylvania, and Massachusetts, as well as the California Proposition 65 list. According to the SPI Epichlorohydrin Task Force, the majority of 1,2,3-trichloropropane produced as a byproduct of epichlorohydrin production today is incinerated on-site (WHO, 2003). 1,2,3-TCP is also a byproduct of dichloropropene, propylene dichlorohydrin, dichlorohydrin, and glycerol (NTP, 1999).
A polymer used as a coagulant in the treatment of potable water and wastewater is produced by reacting epichlorohydrin with dimethylamine. Epichlorohydrin is a known contaminant of these polymers, and it may be present in finished drinking water due to its use in the coatings of drinking water pipes (USEPA, 1985). Since 1,2,3-trichloropropane is a contaminant in epichlorohydrin, it might also be present in drinking water, especially since 1,2,3-trichloropropane is more stable in water than epichlorohydrin.

In an NSF International (2000) report prepared for Health Canada on impurities in drinking water treatment, 1,2,3-TCP was identified as a contaminant in an unidentified well drilling aid. However, the Action Level (target drinking water level based on health effects) used by Health Canada was 5 ug/L, which is much higher than the health based drinking water level based on carcinogenic effects or the analytical practical quantitation limit (see below).

Guidelines, Regulations and Standards
USEPA does not currently have an MCL for 1,2,3-trichloropropane, but it is one of the contaminants listed on the draft Contaminant Candidate List of chemicals being considered for MCL development by USEPA (2008a).

1,2,3-Trichloropropane has been classified as reasonably anticipated to be a human carcinogen by the National Toxicology Program (2004) and as probably carcinogenic to humans (Group 2A) by IARC (1995).

The current USEPA Lifetime Drinking Water Health Advisory (USEPA, 1989) of 40 ug/L is not up-to-date, as it does not reflect the results of the NTP (1993) chronic bioassay of 1,2,3-trichloropropane. As discussed below, the NTP (1993) chronic study in rats and mice and other supporting data have shown that 1,2,3-trichloropropane is a potent genotoxic carcinogen which causes tumors at multiple sites in rat and mice. According to USEPA Office of Water Policy, a Lifetime Health Advisory is not provided for known or likely carcinogens (USEPA, 2006).

The Lifetime Health Advisory for 1,2,3-trichloropropane is based on a Reference Dose (RfD) for non-carcinogenic effects of 0.006 mg/kg/day. The RfD is based on a No Observed Adverse Effect Level (NOAEL) of 5.71 mg/kg/day for alterations in clinical chemistry and reduction in red blood cell mass in the subchronic rat gavage study conducted by NTP (1983) as a range finding study for its subsequent chronic study (see below). An uncertainty factor of 1000 appropriate for a NOAEL from a subchronic study was applied to derive the RfD of 0.006 mg/kg/day.

The current USEPA IRIS RfD was posted on IRIS in 1990 and is identical to the RfD used for the Lifetime Drinking Water Health Advisory, 0.006 mg/kg/day. The current IRIS entry for 1,2,3-trichloropropane does not consider carcinogenic effects. USEPA is currently in the process of developing a slope factor based on the NTP (1993) study for incorporation into a cancer risk assessment in its IRIS database (USEPA, 2007). However, the basis (e.g. species and tumor type) used to derive the final USEPA slope factor will not necessarily be the same that presented in the draft IRIS Toxicological Review (USEPA, 2007).

A health-based drinking water guidance of 0.005 ug/L was developed by NJDEP in 1999 based upon the cancer slope factor of 7 $(mg/kg/day)^{-1}$ in the USEPA HEAST (1995) tables and a 10^{-6} lifetime cancer risk. This slope factor was developed by USEPA using the linearized multistage model and was based on the combined incidence of benign and malignant tumors in various organs in rats. Standard exposure factors for body weight (70 kg) and drinking water ingestion (2 L/day) were used. Based on the practical quantitation limit determined by New Jersey Department of Health and Senior Services laboratories, a guidance value of 0.025 ug/L was applied (NJDEP, 1999). The practical quantitation limit of 0.025 ug/L was determined by multiplying the method detection limit of 0.005 ug/L by a multiplier of 5.

A survey of state guidelines and standards for drinking water contaminants (USEPA, 1999) indicates that Hawaii has adopted a standard of 0.8 ug/L, while other states have the following guidance values: Connecticut 0.05 ug/L, Washington – 21 ug/L, Maine, Minnesota – 40 ug/L, Arizona, Florida – 42 ug/L, and Wisconsin – 60 ug/L. New York's MCL is 5 ug/L, based on the New York MCL for Principal Organic Contaminants, a generic value used for organic contaminants when there is no information indicating that a lower value is warranted (ATSDR, 2004).

California EPA has proposed a Public Health Goal of 0.0007 ug/L for 1,2,3-trichloropropane based on time-to-tumor modeling of forestomach tumors in female mice (California EPA, 2009). The California Department of Public Health (CDPH) has set a Notification Level of 0.005 ug/L, which is the method detection limit. Notification Levels are health-based advisory levels for chemical without MCLs. CDPH recommends that drinking water utilities inform consumers of the presence of a chemical above its Notification Level, and about health concerns associated with exposure to it (California EPA, 2009).

Environmental Exposure

As recently reviewed by California EPA (2009), 1,2,3-trichlopropane volatilizes from water to air and has a short half life in surface water, estimated to be about 7 hours in a river and 6 days in a lake due to evaporation. It is resistant to hydrolysis or biodegradation in soil or water, and it is not expected to bind to sediment or soil or to bioconcentrate in aquatic organisms.

1,2,3-Trichloropropane has been found in both public water supplies (including in USEPA Unregulated Contaminant Monitoring, USEPA, 2001a,b) and private wells in New Jersey and other states. As discussed above, it is known to be present in soil fumigants including D-D (mixed isomers of 1,2-dichloropropane and 1,3-dichloropropene) and Telone (1,3-dichloropropene), and there are also other potential sources of contamination. Because the health-based drinking water concentration based on carcinogenic effects at the 10^{-6} risk level for 1,2,3-trichloropropane is so low (see below), less sensitive analytical methods, such as those used in UCMR Round 1 monitoring (USEPA,

2001a,b), will not detect occurrences at some levels of concern. Reporting limits given by each state for the UCMR Round 1 monitoring ranged from 0.5 ug/L to 5 ug/L.

In 2005, NJDEP conducted a review of occurrence of 1,2,3-trichloropropane in New Jersey drinking waters. 1,2,3-Trichloropropane was detected at levels above the NJDEP health-based drinking water guidance of 0.005 ug/L (see below) in 30 of the 2,640 private wells (1.1%) sampled during contaminated site investigations overseen by NJDEP's Site Remediation Program between 1999 and 2004. In addition, as part of NJDEP's Synthetic Organic Compound (SOC) Waiver Program sampling, 1,2,3-trichloropropane was detected at levels above the health-based drinking water guidance of 0.005 ug/L developed by NJDEP in 11 of approximately 260 community water systems (4%) sampled between 1999 and 2004.

In unregulated contaminant monitoring of public water supplies in California from 1989 through the 1990s, fewer than 20 sources reported detections, reflecting the less sensitive analytical methods available at that time, with a reporting limit of 0.5 µg/L. However, more recent monitoring in California with a more sensitive analytical method reported 1,2,3-trichloropropane detections in 303 sources, at levels up to 57 µg/L. Of the 303 detections, 2 were below the detection limit of 0.005 ug/L, 171 between 0.005 and 0.05 ug/L, 104 between 0.05 and 0.5 ug/L, 20 between 0.5 and 5 ug/L, 4 between 5 and 50 ug/L, and 1 above 50 ug/L. This dataset is not yet complete (CDPH, 2007). California Department of Public Health (CDPH, 2007) states on its fact sheet that the primary possible contaminating activity for 1,2,3-TCP in drinking water appears to be hazardous waste sites. No further information is provided as to the reason for believing that this is the primary source of 1,2,3-trichloropropane in drinking water.

1,2,3-Trichloropropane is considered to be an emerging contaminant by the USEPA Office of Solid Waste and Emergency Response (USEPA, 2008b), and numerous Internet web sites provide information on many sites with drinking water and ground water contamination by 1,2,3-trichloropropane. 1,2,3-Trichloropropane is the main contaminant at a Superfund site, MacKenzie Chemical Works in Suffolk County, New York (ATSDR, 2004). ATSDR conducted an evaluation of this site in 2004 and used New York's MCL of 5 ug/L to evaluate the significance of the contamination. The cancer risk level at 5 ug/L is about 10^{-3} (see below). Analytical methods used in this investigation were chosen with the belief that a detection limit below 5 ug/L was not needed. Concentrations of 1,2,3-trichloropropane of up to 34,000 ug/L were detected in off-site groundwater, at 10,000 ug/L one block from the site, and above 100 ug/L more than 0.25 miles from the site.

Concentrations of 1,2,3-trichloropropane up to 210 ug/L were found in ground water at the Ciba–Geigy Superfund site in Dover Township, New Jersey (NJDHSS, 2001), and it has been detected above the New Jersey guidance level at contaminated sites in Cumberland and Gloucester counties.

Metabolism and Pharmacokinetics

Absorption

Mahmood et al. (1991) found that 1,2,3-trichloropropane is well absorbed orally. They studied the oral disposition and metabolism of ^{14}C-labelled 1,2,3-trichloropropane in male and female rats given 30 mg/kg by gavage and male mice given 30 or 60 mg/kg by gavage. Excreted ^{14}C was measured in the urine, feces, and as exhaled CO_2. USEPA (2007) estimated the absorption as $\geq$ 75% in male

rats, 68% in female rats, and 84% in male mice by totaling the amount found in urine and exhaled ^{14}C. The portion found in feces was not included, as it may include both absorbed and unabsorbed 1,2,3-trichloropropane. Information on inhalation or dermal absorption is not available.

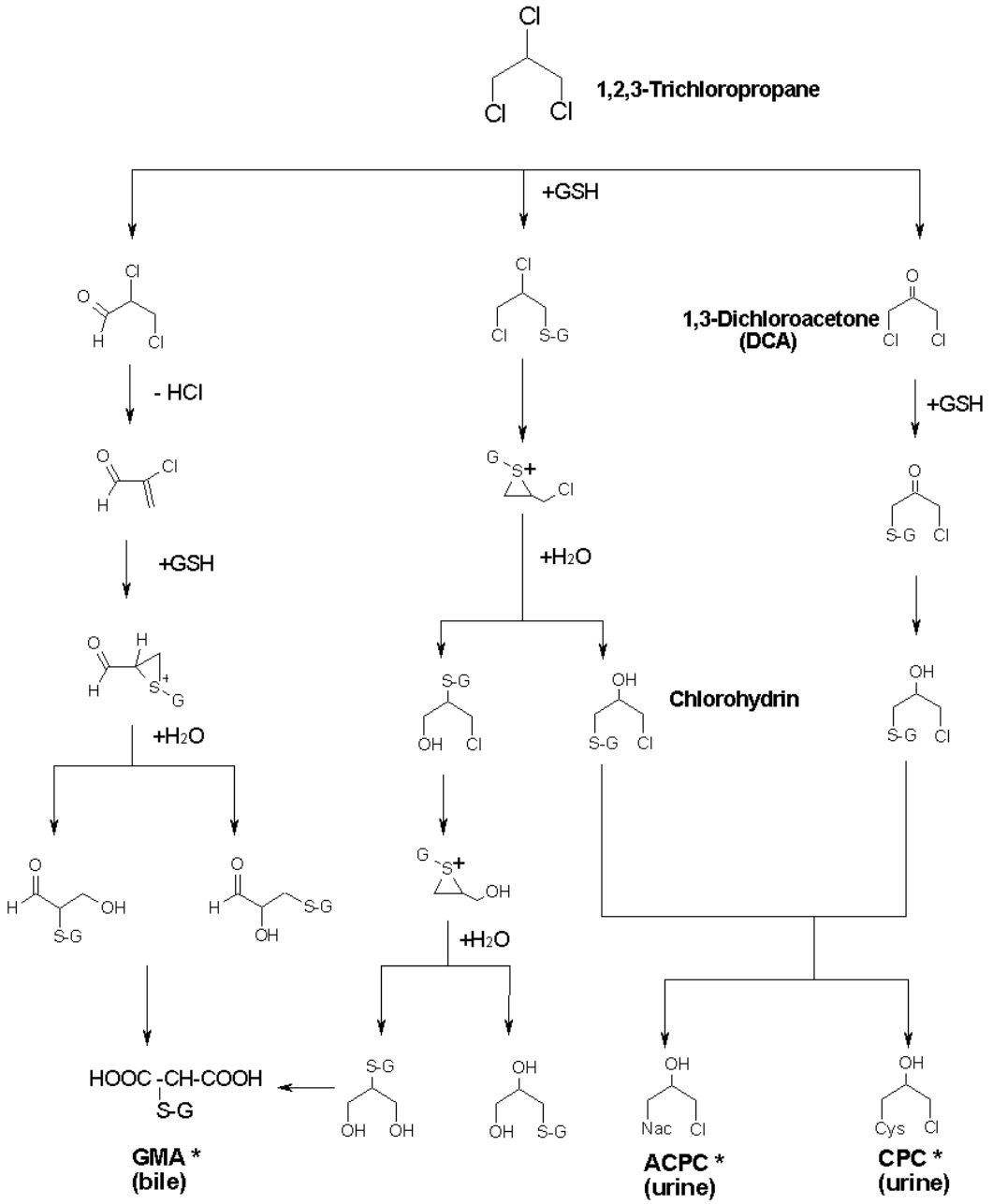
Distribution

Mahmoud et al. (1991) studied the disposition of ^{14}C-labelled 1,2,3-TCP to rats and mice after oral administration. After 6 hours, most of the radiolabel was found in the forestomach and glandular stomach, with smaller amounts in the intestines, adipose tissue, liver, and kidney. At 60 hours, after most radiolabel was excreted, most residual radiolabel was covalently bound in liver, kidney, skin, muscle, and adipose tissue.

Fifteen minutes after intravenous administration to rats, adipose tissue was the tissue with the largest percentage of 1,2,3-trichloropropane. After 4 hours, most was found in liver, primarily as metabolites (Volp et al., 1984)

Metabolism

1,2,3-Trichloropropane must be metabolized in order to covalently bind to macromolecules *in vivo* or *in vitro* and to cause mutagenicity. Metabolism also may serve to detoxify 1,2,3-trichloropropane. The metabolic pathways for 1,2,3-trichloropropane have not been fully characterized, but have been shown to involve both oxidation by cytochrome P-450 and reactions with glutathione. Based on metabolites detected in vivo (N-acetyl-S-(3-chloro-2-hydroxypropyl)-L-cysteine, S-(3-chloro-2-hydroxypropyl)-L-cysteine, and 2-(S-glutathionyl)malonic acid) and knowledge of the metabolism of the related compound, dibromochloropropane, Mahmoud et al. (1991) postulated the metabolic pathways shown in Figure 1.



S-G	*S*-glutathione	Nac	*N*-acetyl-L-cysteine
GSH	reduced glutathione	Cys	L-cysteine
*	detected *in vivo*		

Fig. 1: Possible metabolic pathways in rats (Mahmood et al., 1991)
[ACPC = N-acetyl-S-(3-chloro-2-hydroxypropyl)-L-cysteine; CPC = S-(3-chloro-2-hydroxypropyl)-L-cysteine;
GMA = 2-(S-glutathionyl)malonic acid]

After intraperitoneal administration to rats, 1,2,3-trichloropropane was found to bind to DNA, RNA, and protein in the liver (Weber and Sipes, 1990). In this study, 1,2,3-trichloropropane administration depleted hepatic glutathione, while administration of a glutathione-depleting compound decreased DNA binding and increased protein binding by 1,2,3-trichloropropane. In contrast, induction of cytochrome P-450 by phenobarbital decreased binding to DNA and protein, while inhibition of cytochrome P-450 increased binding to both DNA and protein. These findings were interpreted as indicating that glutathione is involved with activation of 1,2,3-trichloropropane to an intermediate that binds to DNA, while cytochrome P-450 causes detoxification of 1,2,3-trichloropropane.

The major DNA adduct formed from 1,2,3-trichloropropane in rats and mice has been identified as S-[l-(hydroxymethyl)-2-(N^7-guanyl)ethyl]glutathione (Figure 2). This is the same adduct formed from the related carcinogen, 1,2-dibromo-3-chloropropane (DBCP, La et al., 1995) and is closely related to the major DNA adduct formed from 1,2,-dibromoethane (EDB, Ozawa and Guengerich, 1983). The adduct was detected in many organs, including organs where tumors did and did not occur in the chronic carcinogenesis bioassay of 1,2,3-trichloropropane (see below). It was postulated that the adduct forms through conjugation with glutathione followed by rearrangement to an episulfonium ion which binds to DNA. This pathway is shown in the center of Figure 1.

In *in vitro* studies in human and rat liver microsomes, 1,2,3-trichloropropane was metabolized to the known mutagen, dichloroacetone (Weber and Sipes, 1992). Cytochrome P-450 was shown to be responsible for formation of this metabolite and for covalent binding to protein, while addition of glutathione prevented the protein binding. These findings suggest that the metabolic pathways responsible for binding to protein in this *in vitro* system differ from the pathways involved with DNA binding and adduct formation *in vivo*.

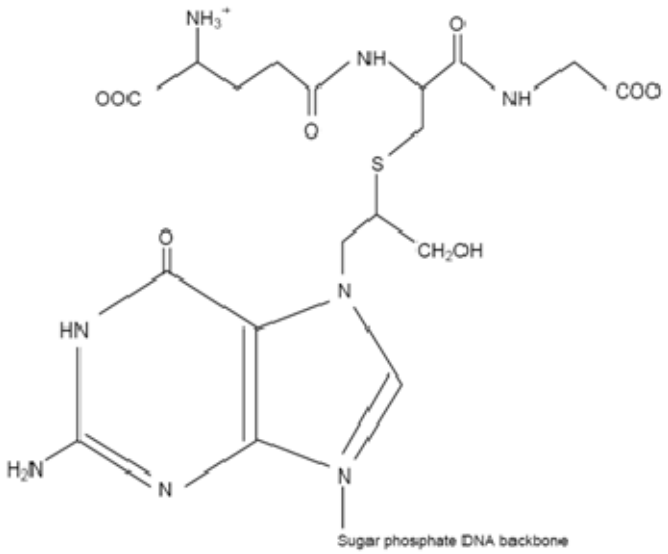


Figure 2. Major DNA adduct of 1,2,3-trichloropropane: S-[l-(hydroxymethyl)-2-(N7-guanyl)ethyl]glutathione

Elimination
Excretion of metabolites in the urine is the major route of elimination of of 1,2,3-trichloropropane (Volp et al., 1984, Mahmood et al., 1991). Both unmetabolized 1,2,3-trichloropropane and CO^2 resulting from degradation of 1,2,3-trichloropropane metabolites are exhaled from the lungs (Volp et al., 1984, Mahmood et al., 1991).

Human Exposure and Body Burden

No data on human body burden have been reported

Health Effects

Overview
After absorption into the body, 1,2,3-trichloropropane is metabolized to reactive intermediates which are mutagenic, genotoxic, and carcinogenic. It is a potent carcinogen and caused tumors in male and female rats and mice in multiple organs in a 2-year chronic gavage study (NTP, 1993). In this study, tumors began to be detected within a year of the start of dosing, associated with high mortality rates of treated animals. Forestomach tumors were the most frequent tumor type in male and female mice and rats. Subchronic, reproductive, and developmental effects are discussed below and are summarized in Table 1.

Human Studies
No human occupational, epidemiology, or case study data have been reported for 1,2,3-trichloropropane (USEPA, 2007).

Acute Laboratory Animal Studies
Oral LD_{50} values ranging from 150 mg/kg to 500 mg/kg have been reported in the rat (reviewed by ATSDR, 1992; WHO, 2003).

Subacute and Subchronic Laboratory Animal Studies

Oral
Three subchronic oral studies of 1,2,3-trichloropropane have been conducted (Villeneuve et al., 1985; Merrick et al., 1991; NTP, 1993).

Villeneuve et al. (1985) gave rats (10/sex/group) 1,2,3-trichloropropane in their drinking water at concentrations of 0, 1, 10, 100, or 1000 mg/L for 13 weeks. Emulphor (0.5%) was used to solubilize the 1,2,3-trichloropropane, and an additional control group given the Emulphor solution was included. Based on body weight and water consumption, the high dose males and females received 113 mg/kg/day and 149 mg/kg/day, respectively, and the 100 mg/L females received 13 mg/kg/day. Body weight was measured weekly throughout the study, and brain, liver, kidney, heart, and spleens were weighed at sacrifice. At sacrifice, blood samples were evaluated for clinical chemistry and hematology, gross and microscopic pathology examinations were conducted, and liver homogenates were assayed for mixed function oxidase activity.

Body weight gain was decreased in high dose males and females. Organ to body weight ratios were increased for liver, kidney, and brain in the high dose males and females, and for kidney and liver in females given 100 mg/L, but it was not reported whether these effects were statistically significant. Serum cholesterol was increased in high dose females. In liver homogenates, aminopyrine demethylase was increased in high dose males and females, and aniline hydroxylase was increased in high dose males. Neutrophils and lymphocyte counts were decreased in high dose males, but were in the normal range. Histological changes described as mild were seen in liver, kidneys, and thyroid of high dose males and females. The authors concluded that the NOEL in this study was 100 mg/L (15-20 mg/kg/day) and the LOEL was 1000 mg/L (113-149 mg/kg/day).

Table 1. NOAELs and LOAELs for Subchronic and Reproductive/Developmental Studies of 1,2,3-Trichloropropane

Study	NOAEL and/or LOAEL	Most Sensitive Endpoints
Villeneuve et al. (1985). Male and female rats. 13 weeks, Drinking water.	NOEL – 100 mg/L (15-20 mg/kg/day) LOEL – 1000 mg/L (113-149 mg/kg/day)	↓ Growth rate, males and females. ↑ Serum cholesterol, females. ↑ Aminopyrine demethylase and aniline hydroxylase. ↑ Mild histological changes in liver, kidney, and thyroid.
Merrick et al. (1991). Male and female rats. 90 days, Gavage.	NOAEL – not identified. LOAEL – 1.5 mg/kg/day	Inflammation and necrosis of the cardiac myocardium
NTP (1993) Male and female rats. 17 weeks, Gavage	Males: NOAEL –Not established LOAEL – 8 mg/kg/day Females: NOAEL – 8 mg/kg/day LOAEL – 16 mg/kg/day	Males: ↑ Absolute liver weight Females: ↑ Absolute and relative liver weight Anemia at 8 weeks of exposure.
NTP (1993) Male and female mice. 17 weeks, Gavage	NOAEL – 63 mg/kg/day LOAEL – 125 mg/kg/day	Liver – necrosis and karyomegaly. Lung/bronchiole – regeneration. Forestomach – hyperkeratosis.
Johannsen et al. (1988). Male and female rats. 13 weeks, Inhalation. (6 hr/day, 5 days/wk)	NOAEL – 1.5 ppm. LOAEL – 5 ppm	Peribronchial lymphoid hyperplasia. Hepatocellular hypertrophy (males) Hematopoiesis in the spleen (females)
NTP (1990) Mice. Continuous breeding.	NOAEL – not identified. LOAEL – 30 mg/kg/day	↓ Proportion of male pups at 5th breeding. Lengthened estrous cycle.
Johannsen et al. (1988). Male and female rats. Inhalation. 10 weeks pre-mating, up to 40 days mating, and gestation days 0-14.	NOAEL – 15 ppm (reproductive and developmental endpoints) LOAEL – 15 ppm (body weight)	↓ Body weight gain. No effects on reproductive or developmental endpoints evaluated.

Merrick et al. (1991) exposed male and female rats (10/sex/group) to 1,2,3-trichloropropane by corn oil gavage for 10 days at 1.5, 7.4, 30, or 118 mg/kg/day, or 90 days at 1.5, 7.4, 15, or 60 mg/kg/day.

Weight gain was significantly reduced in the high dose males and females in both the 10 day and 90 day studies. Decreased thymus weight relative to body weight and thymic atrophy occurred in the high dose rats after 10 days, but these effects were not seen in the 90 day study. Bile duct hyperplasia was seen in 4/10 high dose males and 8/10 females, but in only one control male rat. Several other neoplastic lesions were seen in a single animal in the high dose groups at sites including mammary gland, liver, lung, and stomach. The primary finding in this study was inflammation and necrosis of the cardiac myocardium. In the 10 day study, this was seen in all high dose animals, but not in the other groups. In the 90 day study, a dose related increase in severity and incidence was seen, with some animals affected in all treated groups, while none of the control animals had these cardiac changes.

NTP (1993) conducted a subchronic study in which 1,2,3-trichloropropane was administered by corn oil gavage 5 days per week to rats and mice (30/sex/control group and 20/sex/treated group) at doses of 0, 8, 16, 32, 63, 125, and 250 mg/kg/day. Half of the animals were sacrificed after 8 weeks and half after 17 weeks of dosing.

In the rat study, all 250 mg/kg/day females died by week 2, and all 250 mg/kg/day males died by week 5. These deaths were attributed to severe renal and hepatic toxicity. One male and four females receiving 125 mg/kg/day died during the study. Body weight gain was decreased in 125 mg/kg/day females and in 63 and 125 mg/kg/day males. In males, absolute liver weight was increased in all dose groups, and relative liver weight was increased at 32 mg/kg/day. In females, absolute and relative liver weight was increased at 16 mg/kg/day and above. Absolute and relative kidney weights were increased in males at 32 mg/kg/day and above, and in females receiving 63 mg/kg/day and 125 mg/kg/day.

Effects related to clinical chemistry were generally related to liver toxicity. At 8 weeks, bilirubin was increased in 63 and 12 5 mg/kg/day males and females, and 125 mg/kg/day females had notable increases in liver enzymes. Decreased pseudocholinesterase activity was found in all dosed females and was attributed to decreased synthesis due to liver toxicity, since 1,2,3-trichloropropane is not an inhibitor of cholinesterase. Urea nitrogen and creatinine were decreased in 63 mg/kg/day and 125 mg/kg/day females. Anemia occurred in rats receiving doses of 16 mg/kg/day or greater. Similar effects were observed at 17 weeks, with decreased urea nitrogen in females receiving 32 mg/kg/day or greater and in males receiving 125 mg/kg/day, and decreased pseudocholinesterase in males receiving 63 and 125 mg/kg/day as well as all groups of treated females.

Lesions were mainly seen in the liver, kidney, and nasal epithelium in the rat subchronic study. High dose rats that died early in the study had severe hepatic necrosis which was more severe in females. Hepatic necrosis, as well as hemorrhage and bile duct hyperplasia, were seen in 125 mg/kg/day females sacrificed at 8 weeks. Severe kidney toxicity was seen in rats that died during the study, with females affected to a greater extent than males. Kidney damage was also observed in 125 mg/kg/day rats sacrificed at 8 and 17 weeks. Nasal lesions, including necrosis of the epithelium and acute inflammation, were seen in animals that died early in the study. Nasal lesions were also seen in females given 125 mg/kg/day at 8 week sacrifice, and males and females given this dose at 17 week sacrifice.

Other lesions seen in treated rats included depletion of lymphocytes from the thymus, bone marrow

hypocellularity, uterine hypoplasia, atrophy of the spleen, vacuolation of cells of the adrenal cortex, and chronic myocardial inflammation. One female rat treated with 125 mg/kg/day had a carcinoma of the nasopharynx.

Based on the results of this study, 30 mg/kg/day was chosen as the high dose for the two year rat study, with 3 mg/kg/day and 10 mg/kg/day selected as the lower dose levels.

In the mouse subchronic study, 16 high dose males died during the first four weeks, seven high dose females died during the first two weeks, and one high dose female died at the end of the study immediately prior to scheduled sacrifice. Body weight gain was reduced only in high dose males. No hematology or clinical chemistry-related effects were seen. Absolute and relative liver weights were increased at 17 weeks in males receiving 125 mg/kg/day and in females in the two highest dose groups.

The principal organs where lesions related to toxicity occurred were liver, lung, and forestomach. Liver and lung lesions were seen in high dose mice that died during the study and in the 125 mg/kg/day and 250 mg/kg/day males and females that were sacrificed. Liver changes included necrosis and hepatocellular degeneration, and lung changes included necrosis, regeneration, and hyperplasia of the bronchiolar epithelium. Hyperplasia and hyperkeratosis of the forestomach were also observed in surviving animals in the two highest dose groups. One high dose female died of malignant lymphoma near the end of the study.

Based on results of this study, 60 mg/kg/day was chosen as the high dose for the two year mouse study, with 6 mg/kg/day and 20 mg/kg/day selected as the lower dose levels.

Inhalation

Johannsen et al. (1988) conducted 4 week and 13 week inhalation studies of 1,2,3-trichloropropane in rats. In the 4 week study, rats (5/sex/group) were exposed to target concentrations of 0, 100, 300, 600, or 900 ppm 1,2,3-trichloropropane, 6 hours/day, 5 days/week. All but one of the rats in the high dose group died after one exposure, and three animals in the 600 ppm group and one in the 300 ppm group died during the study. Weight gain was reduced in all groups, but this was not significant in the low dose group. Relative and absolute liver weight was significantly increased in all groups of males and in 300 ppm females. In 600 ppm females, only relative liver weight was increased significantly. Absolute and relative were increased for brain and kidney and were decreased for ovaries in the 300 and 600 ppm groups. In the 600 ppm group, spleen and testis weights were decreased. No histopathology was performed in this part of the study.

In the 13 week study, rats (15/sex/group) were exposed to target concentrations of 0, 5, 15, or 40 ppm 1,2,3-trichloropropane 6 hours per day, 5 days per week. Statistically significant body weight reductions at the conclusion of the study were seen in females exposed to 15 and 40 ppm. Absolute and relative liver weight were increased in all groups of exposed males and in high dose females, while relative liver weights were increased in 15 ppm females. Relative lung weights were increased in 15 and 50 ppm females, and relative kidney weights were increased in high dose males. Histopathological examination revealed peribronchial lymphoid hyperplasia in all groups of treated animals, hepatocellular hypertrophy in all groups of treated males but not in females, and hematopoiesis in the spleen in all groups of females but only in high dose males. A follow-up 13

week study involving exposure of rats (15/sex/group) for 6 hours per day, 5 days per week to 1,2,3-trichloropropane at 0, 0.5, or 1.5 ppm showed no treatment related gross or histopathological effects.

Two unpublished inhalation studies of 1,2,3-trichloropropane were conducted in rats and mice by Miller et al. (1987a,b). These studies are described in the USEPA (2007) Draft Toxicological Profile for 1,2,3-trichloropropane. Rats and mice (5/sex/group) were exposed to 0, 13, 40, or 132 ppm 1,2,3-trichloropropane 6 hours/day, 5 days/week for 9 days (Miller et al., 1987a).

In rats, body weights were decreased in the high exposure group, and liver weights were increased in both sexes in the 40 and 132 ppm groups. Very slight hepatocellular necrosis and very slight depletion of lymphoid elements of the spleen occurred in all high dose male rats. Degeneration and decreased thickness, and inflammation, of the nasal epithelium occurred in all treated animals, and the severity of these effects increased with dose.

In mice, no effects on weight gain were seen. Absolute and relative liver weights were increased in males and females in the high dose group, and testis weight was decreased in high dose males. Increased hepatocyte size and depletion of lymphoid elements in the spleen were seen in all high dose mice. As was seen in the rats, degeneration and decreased thickness, and inflammation, of the nasal epithelium occurred in treated animals, and the severity of these effects increased with dose.

A follow up study in rats and mice using the same protocol as the previous study, but with lower concentrations of 1,2,3-trichloropropane (0, 1, 3, and 10 ppm), was conducted by Miller et al. (1987b). No effects on body weight or organ weight were seen. Very slight degeneration and decreased thickness of the nasal epithelium occurred in all rats exposed to 3 and 10 ppm, and in all mice exposed to 10 ppm.

Behavioral and Central Nervous System
No studies examining behavioral or CNS effects of 1,2,3-trichloropropane have been reported.

Reproductive, Embryonic and Teratogenic
Reproductive toxicity of 1,2,3-trichloropropane given by corn oil gavage was studied in CD-1 mice using the Reproductive Assessment by Continuous Breeding Protocol (NTP, 1990). This protocol involves four tasks: Task 1- range finding, Task 2 – continuous breeding study, Task 3 – crossover mating study to determine affected sex; and Task 4 – assessment of F1 generation offspring.

In the range finding study, mice (8/sex/group) were dosed with 0, 12.5, 25, 50, 100, or 200 mg/kg/day. No effects on weight gain or signs of toxicity were noted.

Based on these results, the doses chosen for the continuous breeding study (Task 2) were 0, 30, 60, and 120 mg/kg/day. Forty breeding pairs per control group and 20 breeding pairs per treated group were dosed for 126 days. Endpoints monitored in this study included body weight, water consumption, fertility, litters per pair, live pups per litter, proportion of pups born alive, sex of live pups, and pup weight at birth, but abnormalities or malformations in the pups were not evaluated. Dose-related decreases in number of litters per fertile pair and number of live pups per litter were observed. The number of litters per fertile pair was significantly reduced in the high dose group, and the number of live pups per litter was reduced for the 2nd to 5th litters in the high dose group and for

the 5th (final) litter in the middle dose group. In the high dose group, the average number of pups per litter decreased over time, from 11.5 in the first litter to 2.9 and 2.5 in the fourth and fifth litters, while in the control groups, the first, fourth, and fifth litters had averaged 11.1, 11.8, and 12.8 pups.

The crossover study (Task 3) was conducted after the last Task 2 litters were weaned, using control and high dose animals from Task 2. Twenty breeding pairs per group (control male x control female, 120 mg/kg/day male x control female, and control male x 120 mg/kg/day females) were evaluated for fertility, organ weights, and for effects on reproductive organs. The purpose of this part of the study is to determine if effects on fertility result from toxicity to males, females, or both sexes. Fertility did not differ among groups, but treated females delivered fewer live pups, male pups which were lighter than control pups, and fewer males per litter than controls. Treated male and female mice had increased absolute and relative liver weights compared to controls. The weight of the epididymis and cauda epididymis was significantly reduced in treated mice, but sperm parameters and sperm counts were not affected. No effects were seen on the length of the estrous cycle in treated mice.

In Task 4, offspring assessment, the last litter born in Task 2 was weaned on postnatal day 21 and kept until sexual maturity while being treated at the same dose as the parents. Males and females from different litters of the same dose group were then mated. Indices of mating and fertility were significantly reduced in the high dose group. The number of live pups per litter was also decreased in the high dose group, but this was not significant. No effects were seen on proportion of pups born alive, or on sex or weight of live pups.

The authors concluded that 1,2,3-trichloropropane can impair fertility and reproduction in mice, with reproductive endpoints affected in both sexes, and fertility primarily decreased in females. USEPA (2007), in its review of this study, concluded that the LOAEL for the most sensitive endpoints in this study is 30 mg/kg/day, the lowest dose tested.

The rat inhalation study conducted by Johannsen et al. (1988) included a single-generation reproductive study as well as the subchronic study described above. In the first part of the reproductive study, rats (10 male and 20 female per group) were exposed to 5 or 15 ppm for a 10 week pre-mating period, a mating period of up to 40 days, and for gestation days 0-14 for females. One male rat was housed with two female rats, and females that did not become pregnant in 10 days were housed with another male for 10 days, until they became pregnant. In the second part of the study, target concentrations were 0.5 and 1.5 ppm, and the mating period did not exceed 30 days.

In the first study, there was poor mating performance in all groups, including the controls. Based on severe head tilt observed in several animals, they were possibly infected with *Mycoplasma*, but this was not confirmed through serological studies. Mating performance and pregnancy rate did not differ between treated and control groups, and body weight was decreased in the 15 ppm group. There were no treatment-related histopathological changes in reproductive organs, pup viability at birth, pup body weight, or pup survival in this study. The second study with exposure to lower 1,2,3-trichloropropane concentrations evaluated similar parameters as the first study, and did not identify any effects related to treatment.

Genotoxicity

Mutagenicity studies of 1,2,3-trichloropropane were comprehensively reviewed by USEPA (2007),

and this information is summarized below. In several different studies, 1,2,3-trichloropropane was positive for mutagenicity in several strains of *Salmonella typ*himurium (Ames test) with metabolic activation by the S9 fraction from rat and hamster liver, but was not positive in any study in the absence of metabolic activation. The S9 fraction includes the cytosolic and microsomal fractions, and contains both Phase I and Phase II xenobiotic metabolizing enzymes. In these studies, some negative results in the presence of S9 were also reported. Results of mutagenicity tests in other microbial systems were mixed. 1,2,3-Trichloropropane was also positive for mutagenicity in two studies in the presence, but not the absence, of S9 in L5176Y mouse lymphoma cells.

1,2,3-Trichloropropane was also positive for a variety of other genotoxic effects in cultured mammalian cells, both with and without metabolic activation. Studies with negative results have also been reported. Effects observed in various types of cells include chromosomal aberrations in Chinese hamster ovary (CHO) cells with metabolic activation, formation of micronuclei in CHO cells and other cell lines without activation, DNA strand breaks in human lymphocytes with and without activation, sister chromatic exchange in CHO and Chinese hamster lung cells with activation, and enhanced DNA viral transformation in Syrian hamster embryo cells.

Some in vivo studies of 1,2,3-trichloropropane's genotoxic potential were positive, while other studies gave negative results. In *Drosophila melanogaster*, exposure to larvae induced the formation of wing spots, indicative of genotoxic effects such as somatic mutations, chromosomal rearrangements, or non-disjunction. Exposure of male albino rats by inhalation to 0.8 or 2.16 mg/L for one week was reported to increase the incidence of polyploidy in hepatic cells. Intraperitoneal injection of 1,2,3-trichloropropane caused strand breaks in hepatic and kidney DNA in rats. Negative results of in vivo studies were reported for micronucleus formation in bone marrow of CD-1 mice, dominant lethal mutations in rats, and unscheduled DNA synthesis in rat hepatocytes.

The formation of DNA adducts from 1,2,3-trichloropropane after metabolic activation, which is considered part of genotoxicity, is discussed under **Metabolism** above. As discussed above, the major DNA adduct formed from 1,2,3-trichloropropane in rodents has been identified as S-[l-(hydroxymethyl)-2-(N^7-guanyl)ethyl]glutathione (Figure 2) and is thought to form through conjugation with glutathione followed by rearrangement to an episulfonium ion which binds to DNA.. The adduct was detected in many organs, including organs where tumors did and did not occur in the chronic carcinogenesis bioassay of 1,2,3-trichloropropane (see below).

The effect of route of administration on DNA adduct formation and cell proliferation was investigated in male mice by La et al. (1996). The mice (15 for each exposure route) were given (^{14}C)-labelled-1,2,3-trichloropropane at a target dose of 6 mg/kg/day for 5 days. For gavage dosing, 1,2,3-trichloropropane was dissolved in 0.15 ml of corn oil. For drinking water dosing, 1,2,3-trichloropropane was dissolved in water containing 0.5% Emulphor 620L to increase its solubility. It is stated that 1,2,3-trichloropropane concentrations were adjusted to account for evaporation, but no information is given on how frequently the drinking water solutions were prepared. It is also stated that animals were monitored daily to ensure that they received the proper (6 mg/kg) dose. However, no information on the drinking water consumption rate and actual dose received through drinking water is provided. Without this information, the actual dose received is not known, and this information is crucial to the accuracy of the conclusions made in this study.

Animals were sacrificed 24 hours after the last gavage dose, while animals were exposed through drinking water until immediately before sacrifice. DNA was isolated from forestomach, glandular stomach, kidney, and liver. For forestomach and glandular stomach, tissues from five animals were pooled. DNA was hydrolyzed, the adducts were separated by HPLC, and the adduct levels were calculated based on radioactivity in adduct fractions compared to the measured guanine content of the DNA. Adduct concentrations in kidney and liver DNA from the animals dosed by gavage were about twice those in the DNA from animals dosed by drinking water, while the adduct concentrations were not significantly different in glandular stomach or forestomach from the two groups.

Additional studies on the effect of exposure route on cell proliferation were conducted using non-radioactive 1,2,3-trichloropropane given for 5 or 10 days. Cell proliferation in the liver, forestomach, glandular stomach, and kidney was measured in mice given 6 or 60 mg/kg/day 1,2,3-trichloropropane for 5 days by immunohistochemical measurement of proliferating cell nuclear antigen to determine the percent of cells in S-phase. Cell proliferation was increased in a dose-related fashion in the liver in animals treated by gavage, but not by drinking water. It was not possible to evaluate the effect of 1,2,3-trichloropropane on cell proliferation in glandular stomach or forestomach with this method.

In a subsequent study, 6 mg/kg/day of 1,2,3-trichloropropane was given by gavage or drinking water 5 days per week over a two week period. Cell proliferation was assayed in the four organs mentioned above by measuring the incorporation of bromodeoxyuridine given intraperitoneally one hour before sacrifice. Cell proliferation was increased significantly in all four organs in the animals dosed by gavage, but was not increased significantly in those dosed by drinking water.

The authors suggest that, based on the results of these studies, the cancer risk from drinking water exposure to 1,2,3-trichloropropane may be lower than that from gavage exposure. However, such conclusions do not seem to be supported from these results due to uncertainties about the actual doses received through drinking water and other aspects of the study, as well as the relatively small difference in adduct formation between the two exposure routes. Additionally, in this study, neither adduct formation nor cell proliferation appear to correlate with the sites of tumor formation in the NTP (1993) cancer bioassay (discussed below).

Carcinogenicity

NTP (1993) conducted a two year study of the toxicity and carcinogenicity of 1,2,3-trichloropropane in F-344/N rats and B6C3F1 mice. The chemical was administered by corn oil gavage 5 days per week to 60 animals/sex/group, starting at 16 weeks of age, for up to 104 weeks. Rats received 0, 3, 10, or 30 mg/kg/day and mice received 0, 6, 20, or 60 mg/kg/day. Doses were selected based on effects observed in the 17 week study described above.

After 15 months (65–67 weeks), 8 to 10 rats or mice per group were sacrificed to allow an interim evaluation of all toxicological parameters and histopathology. Absolute and relative liver and kidney weights of dosed rats were significantly greater than those of the controls, while hematocrit and hemoglobin concentrations were reduced, especially in the intermediate dose group. Chemical-related non-neoplastic lesions and neoplasms of the forestomach, oral mucosa, pancreas (males), kidney, mammary gland (females), preputial gland, and clitoral gland were observed in dosed rats. Chemical-related non-neoplastic lesions and neoplasms of the forestomach and liver (females) were observed in dosed mice, as well as reduced hematocrit and hemoglobin concentrations. Endometrial

hyperplasia was elevated in a dose-response manner.

Survival of male and female rats receiving 10 or 30 mg/kg 1,2,3-trichloropropane was significantly lower than that of controls. Two-year survival rates of male rats were: control, 34/50; 3 mg/kg, 32/50; 10 mg/kg, 14/49; 30 mg/kg, 0/52; and of females were: 31/50, 30/49, 8/52, 0/52. At 30 mg/kg, survival was markedly reduced due to chemical-related neoplasms, and survivors were sacrificed in weeks 67 (females) or 77 (males). Final mean body weights of 30 mg/kg rats were 13% lower for males and 12% lower for females than those of controls; mean body weights of 3 and 10 mg/kg rats were similar to controls. Increased nephropathy, thickening of the glomerulus and tubule basement membranes, glomerulosclerosis, and degeneration, atrophy, and regeneration of the tubular epithelium were observed in dosed rats.

Survival rates of mice receiving 6, 20, or 60 mg/kg 1,2,3-trichloropropane were also significantly lower than those of controls. Two-year survival rates of male mice in the 0, 6, 20, and 60 mg/kg dose groups were: 42/52, 18/51, 0/54, 0/56; and of female mice were: 41/50, 13/50, 0/51, 0/55. Because of reduced survival in mice given 20 and 60 mg/kg due to chemical-related neoplasms, survivors were sacrificed in weeks 73 (60 mg/kg females), 79 (60 mg/kg males), or 89 (20 mg/kg males and females). Final mean body weights were 16% lower for 60 mg/kg males, 18% lower for 60 mg/kg females, and 13% lower for 20 mg/kg males than those of controls. Final mean body weights of 6 mg/kg males and females and 20 mg/kg females were similar to controls.

An increased incidence of tumors occurred at all doses in multiple organs in both sexes of mice and rats exposed to 1,2,3-trichloropropane at all doses (see attached tables). Steady occurrence of tumors was observed starting shortly after one year of exposure. Organs affected in rats were oral cavity, forestomach, pancreas, kidney, preputial gland, clitoral gland, mammary gland, and Zymbal gland. In mice, tumors occurred in the oral cavity, forestomach, liver, Harderian gland, and uterus/cervix. The forestomach was the most frequent site for tumors in male and female mice and rats. Tumors in many of the organs exhibited the characteristics of metastasized forestomach carcinomas. The National Toxicology Program concluded that there is *clear evidence for carcinogenicity* of 1,2,3-trichloropropane in male and female rats and mice.

Table 2. Summary of Treatment-Related Tumors in the 1,2,3-Trichloropropane Cancer Bioassay in the B6C3F1 Mice [1]

Male Mice	Female Mice
	Oral cavity: squamous cell carcinoma (0/50, 0/50, 1/51, 5/55)
Forestomach: squamous cell papilloma (3/52, 28/51, 22/54, 33/56)[2] squamous cell carcinoma (0/52, 40/51, 50/54, 51/56) papilloma and/or carcinoma (3/52, 50/51, 53/54, 55/56)	Forestomach: squamous cell papilloma (0/50, 23/50, 18/51, 29/55) squamous cell carcinoma (0/50, 46/50, 49/51, 49/55) papilloma and/or carcinoma (0/50, 48/50, 50/51, 54/55)
Liver: hepatocellular adenoma (11/52, 18/51, 21/54, 29/56) hepatocellular carcinoma (4/52, 11/51, 5/54, 3/56) adenoma and/or carcinoma (13/52, 24/51, 24/54, 31/56)	Liver: hepatocellular adenoma (6/50, 9/50, 8/51, 31/55) hepatocellular carcinoma (1/50, 3/50, 0/51, 2/55) adenoma and/or carcinoma (7/50, 11/50, 8/51, 31/55)
Harderian gland: adenoma (1/52, 2/51, 10/54, 11/56)	
	Uterus: adenoma (0/50, 1/50, 0/51, 3/54) adenocarcinoma (0/50, 4/50, 3/51, 6/54) adenoma and/or carcinoma (0/50, 5/50, 3/51, 9/54)

[1] Adapted from NTP (1993). Doses were 0, 6, 20, or 60 mg/kg/day.
[2] Number of tumor-bearing mice/number of mice necropsied in each dose group

Table 3. Summary of Treatment-Related Tumors in the 2-Year 1,2,3-Trichloropropane Cancer Bioassay in the F-344 Rat[1]

Male Rats	Female Rats
Oral cavity: squamous cell papilloma (0/50, 4/50, 9/49, 19/52)[2] squamous cell carcinoma (1/50, 0/50, 11/49, 25/52) papilloma and/or carcinoma (1/50, 4/50, 18/49, 40/52)	Oral cavity: squamous cell papilloma (1/50, 5/49, 10/52, 18/52) squamous cell carcinoma (0/50, 1/49, 21/52, 21/52) papilloma and/or carcinoma (1/50, 6/49, 28/52, 32/52)
Forestomach: squamous cell papilloma (0/50, 29/50, 33/49, 38/52) squamous cell carcinoma (0/50, 9/50, 27/49, 13/52) papilloma and/or carcinoma (0/50, 33/50, 42/49, 43/52)	Forestomach: squamous cell papilloma (0/50, 13/49, 32/51, 17/52) squamous cell carcinoma (0/50, 3/49, 9/51, 4/52) papilloma and/or carcinoma (0/50, 16/49, 37/51, 19/52)
Pancreas: acinar adenoma (5/50, 21/50, 36/49, 29/52) adenocarcinomas (0/59, 0/50, 2/49, 1/52) papilloma and/or adenocarcinoma (5/50, 21/50, 36/49, 29/52)	
Kidney: renal tubule adenoma (0/50, 2/50, 20/49, 21/52)	
	Clitoral gland: adenoma (5/46, 10/46, 13/50, 10/51) carcinoma (0/46, 0/46, 4/50,6/51) papilloma and/or carcinoma (5/46, 10/46, 17/50, 15/51)
	Mammary gland: adenoma (1/50, 0/40, 3/52, 0/52) adenocarcinoma (1/50, 6/49, 12/52, 21/52)
Preputial gland: adenoma (5/49, 3/47, 5/49, 11/50) carcinoma (0/49, 3/47, 3/49, 5/50) papilloma and/or carcinoma (5/49, 6/47, 8/49, 16/50)	
Zymbal's gland: carcinoma (0/50, 0/50, 0/49, 3/52)	Zymbal's gland: carcinoma (0/50, 1/49, 0/52, 3/52)

[1] Adapted from summary table in NTP (1993). Doses were 0, 3, 10, or 30 mg/kg/day.
[2] Number of tumor bearing rats/number of rats necropsied in each dose group

Quantitative Risk Assessment

Studies Useful for Risk Assessment

The NTP (1993) 2-year toxicity and carcinogenicity study of rats and mice is the only chronic study of 1,2,3-TCP. It is a well conducted study based on oral exposure and is appropriate for use as the basis for quantitative risk assessment. Tumors were found in multiple organs, even at the lowest dose.

Weight of Evidence for Carcinogenicity and Risk Assessment Approach

1,2,3-TCP is DNA-reactive, clearly genotoxic and mutagenic, caused tumors in a number of tissues in both the rat and the mouse, and metastatic forestomach tumors were found in variety of locations. Thus, the risk assessment of this chemical should be based on low-dose extrapolation of the NTP (1993) carcinogenicity data.

The most frequently occurring tumors were found in the forestomach in both the rat and the mouse. IARC (2003) provides an extensive discussion of the issues related to human relevance of forestomach tumors. They state that forestomach tumors from genotoxic chemicals usually arise through a genotoxic mechanism. Thus, forestomach tumors from genotoxic chemicals such as 1,2,3-trichloropropane should be treated like tumors of other organs for the purposes of risk assessment. In contrast, oral exposure to some nongenotoxic chemicals results in tumors only of the forestomach (but not of other organs distant from the point of contact) which appear to arise through a sequence of cytotoxicity, cell proliferation, and hyperplasia, rather than through a genotoxic mechanism.

Although humans do not have a forestomach, tumors of the forestomach are considered relevant to humans because the squamous epithelial tissue of the oral cavity and the tissue of the upper two thirds of the esophagus is similar to the tissue of the forestomach (IARC, 2003). Also, in cancer risk assessment, it is assumed that carcinogens may target different sites in different species.

Because 1,2,3-TCP is DNA-reactive, clearly genotoxic and mutagenic, and caused tumors in a number of other tissues in both the rat and the mouse, it is appropriate to base the cancer slope on the forestomach tumors. As discussed below, the drinking water Public Health Goal developed by California EPA (2009) is based on mouse forestomach tumors.

Development of Slope Factor

The data from the NTP (1993) two year study provides an appropriate basis for development of a cancer slope factor for 1,2,3-trichloropropane. As noted above, the most frequently occurring tumors were found in the forestomach in both the rat and the mouse, and it is appropriate to base the cancer slope factor on them because 1,2,3-TCP is DNA-reactive, clearly genotoxic and mutagenic, and caused tumors in a number of other tissues in both the rat and the mouse.

The incidence of the forestomach tumors was high even in the low dose group, and the average lifespan was shortened due to significant numbers of animals with early mortality or found moribund. For data of this type, the multistage model used by USEPA and New Jersey for low dose extrapolation for carcinogens, is not the most appropriate model (See Appendix A for more detailed explanation.) Instead, a multistage Weibull (MSW) time-to-tumor model (see Appendix A) was

used to generate a benchmark dose (BMD) and the lower 95th percentile confidence limit of the BMD (BMDL). The MSW time-to-tumor model was used previously in the development of the New Jersey Health-based MCL for vinyl chloride (NJDWQI, 1987) and has been used by USEPA IRIS for several chemicals, including 1,3-butadiene and bromate.

In order to use the MSW model, it is necessary to make certain assumptions as to whether malignant and benign tumors contributed to the cause of death and whether or not to include interim sacrifice group data. Many of the animals in the NTP (1993) study of 1,2,3-trichloropropane had tumors at multiple sites and the causes of deaths for individual animals were not provided. For these reasons, it was judged appropriate in the assignment of data from animals which died prior to sacrifice and in moribund animals to consider carcinomas to be fatal, while papillomas and adenomas were assumed to be incidental to the cause of death. These assumptions provide a better approximation of the potential causes of death than either of the extreme assumptions (i.e., all tumors fatal or all tumors incidental to the cause of death). Animals exhibiting both adenomas and carcinomas at a site were evaluated based on the occurrence of the carcinoma. In addition, all tumors found at scheduled interim sacrifices (data from NTP, 2007) and the final sacrifice were considered incidental. This approach is also used by California EPA (2009) in the risk assessment of 1,2,3-trichloropropane.

Because mice were more sensitive to the carcinogenic effects of 1,2,3-trichloropropane than were rats, the data from mice were selected as most appropriate to use as the basis for the slope factor for 1,2,3-trichloropropane.

The doses administered to mice were converted to human equivalent doses by adjusting for the number of days per week dosed, and by using allometric scaling (assuming toxicologic equivalence in terms of animal-to-human body weight to the ¾ power) as follows:

Human Equivalent Dose (HED) =

Animal dose x [(Human Weight / Animal Weight)$^{3/4}$ /Human Weight].

This simplifies algebraically to:

HED = Animal dose x (Animal Weight/Human Weight)$^{1/4}$.

This adjustment is made to approximately account for metabolic differences between laboratory animals and humans and is recommended in the USEPA (2005a) Guidelines for Cancer Risk Assessment. For the purposes of this equation, the average weight of the mice was taken as approximately 30 grams, which is considered a typical value for the weight of adult laboratory mice.

MSW analysis was conducted by California EPA (2009) using the Tox_Risk software (ICF, Fairfax, VA; Crump, 2000), version 5.2, with inputs and assumptions judged appropriate as the basis for the New Jersey slope factor proposed herein. The analysis was run to calculate the slope factor for tumor incidence. The model was run to test the assumption of 1, 2, or 3 stages, and the 2-stage model was selected as the most parsimonious with the greatest statistical significance. The detailed documentation of the inputs and assumptions, and the results of the analysis are presented in Appendix B. Additionally, identical results were obtained by USEPA NCEA (Dr. K Hogan,

personal communication) using the same software with inputs and assumptions supplied by Dr. P. Cohn, NJDHSS.

The forestomach tumors in female mice, which were much more numerous at all doses than tumors in the other organs, gave the highest slope factor, 26 $(mg/kg/day)^{-1}$. The slope factor based on forestomach tumors in male mice was 19 $(mg/kg/day)^{-1}$. The next highest slope factors, from liver and uterine tumors, were approximately an order of magnitude lower. Slope factors from rats were an order of magnitude or more lower than those from mice.

The most sensitive endpoint or tumor type is used as the basis for quantitative risk assessment unless there is a reason that it is not considered relevant or appropriate. Thus, the slope factor derived from the data on female mouse forestomach tumors was used as the basis for the Health-based MCL for 1,2,3-trichloropropane.

In addition, sensitivity analyses of the tumors of the forestomach in female mice were performed (California Environmental Protection Agency, 2009) to measure the impact of the following assumptions: 1) all forestomach tumors considered to be incidental to the cause of death of the animal, and 2) forestomach tumors presumed to be the cause of death of the animal. Using these assumptions results in a range of slope factors; categorization of all tumors as fatal or as incidental gave rise to slope factors of 11 and 180 $(mg/kg/day)^{-1}$, respectively. Thus, the approach used herein, in which some tumors are considered fatal and others are considered incidental, results in a slope factor, 26 $mg/kg/day^{-1}$, which is intermediate between these two values. In addition, results from the linearized multistage model yielded a lower-bound estimate of the slope factor of 6.7 (mg/kg/day)-1, which is identical (after rounding) to the slope factor of 7 $(mg/kg/day)^{-1}$ from USEPA HEAST (1995) which was the basis for the health-based drinking water guidance of 0.005 ug/L developed by NJDEP in 1999.

Calculation of Health-based Maximum Contaminant Level

The daily dose of 1,2,3-trichloropropane resulting in a one-in-one-million lifetime cancer risk is calculated from the slope factor of 26 $(mg/kg/day)^{-1}$ as:

$$10^{-6} / 26\ (mg/kg/day)^{-1} = 0.038 \times 10^{-6}\ mg/kg/day$$

The Health-based Maximum Contaminant Level for 1,2,3-trichloropropane based on this slope factor is:

$$\frac{0.038 \times 10^{-6}\ mg/kg/day \times 70\ kg}{2\ L/day} = 1.3 \times 10^{-6}\ mg/L, \text{ or } 0.0013\ ug/L$$

Where: 70 kg is the assumed body weight of an adult and 2 L day is the default value for daily water consumption of an adult.

It should be noted that the both the California EPA Public Health Goal of 0.0007 ug/L and the proposed New Jersey Health-based MCL of 0.0013 ug/L are based on the same slope factor, 26 $mg/kg/day^{-1}$. The two-fold difference arises because California considers non-ingestion exposures to volatile organic chemicals in deriving its Public Health Goals and assumes exposure to the

equivalent of 4 liters of water per day, while New Jersey Health-based MCLs are based on the assumption of ingestion of 2 liters of water per day.

Conclusions

Tumor formation in the female mouse forestomach in the NTP (1993) chronic toxicity and carcinogenicity study serves as the basis for establishing a cancer slope factor on which to base a Health-based Maximum Contaminant Level for 1,2,3-trichloropropane. The recommended Health-based Maximum Contaminant Level is 0.0013 ug/L.

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Appendix A: Time-to-Tumor Modeling

Cancer slope factors are usually developed using models, most commonly the multistage model by default, based solely on the response to dose. The modeled data consist of a pair of numbers for each dose group: the number of animals at risk and the number of animals found, upon necropsy, to have the tumor being modeled at any time up to the end of the study (cumulative incidence). The time at which the tumor is observed is not considered. According to the USEPA Guidelines for Carcinogen Risk Assessment, finalized in 2005, the models are used to generate a benchmark dose (BMD) and the lower confidence limit on it (BMDL). The BMD (and its lower confidence limit, the BMDL) is the estimation, based directly on the experimental data, of a certain level of response, typically 5% or 10%. The BMDL is used as a "point of departure" for further extrapolation to a much lower dose at the risk level of interest, such as 10^{-6}, using linear extrapolation unless available information suggests otherwise. Prior to the publication of the USEPA guidelines in 2005, the multistage model was used in a linearized form that directly extrapolated to very low doses.

However, when the incidence of tumors is high even in the low dose group and the average lifespan is shortened due to significant numbers of animals with early mortality or found moribund, the multistage model discussed above is not appropriate for low dose extrapolation of carcinogen risk. Instead, a multistage Weibull (MSW) time-to-tumor model (see Appendix) is used to generate a benchmark dose (BMD) and the lower 95^{th} percentile confidence limit of the BMD (BMDL).

The multistage Weibull (MSW) time-to-tumor model is multistage in dose and models time with a Weibull-type equation. It describes the probability of a test subject exhibiting a specific carcinogenic response by observation time *t*, when the subject is exposed to a carcinogen at dosage rate *d* (Krewski et al., 1983). The tumor can be a malignant cancer or a relevant benign tumor (e.g., an adenoma that can progress to a malignant tumor). Tumors are modeled by specific tissue or organ in a specific sex and strain of animal (e.g., hepatocellular carcinomas and adenomas in female B6C3F1 mice).

Time-to-tumor data consist of dose, tumor response category (below), and time of the observation, for individual animals.

The test subject's response is classified within one of the following four outcome categories (Peto et al., 1980):

- Censored response (*C*). The subject is removed from the study at time *t* because of sacrifice, or death from some cause other than the tumor being modeled.

- Death from fatal tumor (*F*). The subject dies at time *t*, a tumor is detected when the subject is examined, and death is attributed to this rumor.

- Incidental tumor (*I*). The subject is removed from the study at time *t* (because of sacrifice, or death from a cause other than the tumor being modeled), and a tumor is detected when the subject is examined. In such cases, the lesion is judged to not be the cause of death. The MSW time-to-tumor model assumes that incidental tumors have no influence over probability of death or time of death.

• Unknown response observed (*U*). The presence or absence of tumors cannot be determined when the subject is examined at time *t,* usually due to decomposition or inconclusive necropsy. They contribute no information about time of tumor onset.

The multistage-Weibull model has the form:

$$P(d) = 1 - exp[-(q_0 + q_1 d + q_2 d^2 + ... + q_k d^k) \times (t \pm t_0)^c],$$

where P(*d*) represents the lifetime risk (probability) of cancer at dose d (i.e., human equivalent exposure in this case). Polynomial parameters (or coefficients) $q_i \geq 0$, for i = 0, 1, ..., k, determine the curvature of the dose-response curve; t is the time at which the tumor was observed; t_0 represents the model estimated time between when a potentially fatal tumor becomes observable and when it causes death; c is a parameter estimated in fitting the model, which characterizes the change in response with age. The model parameters are constrained to satisfy the restrictions $c \geq 1$, $t > t0 \geq 0$, and $qi \geq 0$, $i = 0, 1, ..., k$ stages (or steps) of carcinogenesis. The user selects the maximum number of stages, generally empirically determine by what provides the best fit. Some of the polynomial parameters may be set to zero (because of the constraint $qi \geq 0$) during maximum likelihood estimation.

By setting the parameter t_0 to be constant across all test subjects, the multistage Weibull model makes some implicit, and perhaps unrealistic, assumptions. In particular, the model assumes that:

a. The time between "onset" and death from the tumor is the same across all subjects. As currently specified, the multistage Weibull model does not allow for subjects to die from the cancer at varying time intervals after "onset". This may be a reasonable approximation if the distribution of t_0 is narrow compared with the distribution of times of onset or of death, but there are no studies examining the consequences of this assumption.

b. A tumor onset inevitably leads to death from the tumor. The model implicitly assumes that the tumor is eventually fatal.

The model computes benchmark doses (BMDs) and their confidence intervals. It represents the lowest reliable measure of experimental dose-response. The BMD_{10}, which is usually used in carcinogenicity dose-response modeling, is equivalent to the dose causing a 10% effect (ED_{10}). The linear cancer slope represents a line connecting the lower confidence limit for the BMD_{10}, the $BMDL_{10}$, with zero. Zero is used since the evidence weighs strongly that 1,2,3-TCP is a non-threshold carcinogen. Since the $BMDL_{10}$ is the estimate of the lower statistical bound on the dose causing a 10 percent tumor incidence, the linear slope between the $BMDL_{10}$ and zero is $0.1/BMDL_{10}$.

In the time-to-tumor model, as in the more commonly used multistage model for low dose extrapolation for carcinogens, human equivalent doses are derived by using allometric scaling, as recommended by USEPA (2005). This adjustment is made to account for metabolic differences, which are generally proportional to the ratio of animal and human body weights raised to the ¾-power, as follows:

Human Equivalent Dose =

Animal dose x [(Human Weight / Animal Weight)$^{3/4}$ /Human Weight] =

Animal dose x (Animal Weight/Human Weight)$^{1/4}$.

Appendix Citation

Krewski, D; Crump, KS; Farmer, J; et al. (1983) A comparison of statistical methods for low dose extrapolation utilizing time-to-tumour data. Fundam Appl Toxicol 3:140-160.

Appendix B: Tox_Risk Output for Female Mouse Forestomach Tumor and Explanation

The setup of Tox_Risk requires a statement of the experimental exposure parameters and the human exposure parameters to be assessed for risk, as well as a database of tumor incidence and/or fatality by time of detection in the experiment. This first page of output presents the summary of the exposure parameters and the summary of the number of incidental (I) and fatal (F) tumors by dose. (As noted in the text, carcinomas (C) are fatal, while adenomas (A) are incidental. Interim and terminal tumors are considered incidental.) The method for conversion of animal dose to human dose uses the ratio of body weights raised to the ¾ power and the factor of 7/5 to account for human exposure for 7 days/week versus the exposure to the experimental animals on 5 of 7 days/week.

The analysis statement shows that multistage Weibull with the incident extra risk (multiplicative) model was chosen and that a suitable level of statistical significance was achieved. The model with k=2 is the most appropriate since it is parsimonious and Q3 in the 3-stage model was zero. The lower bound of the dose estimate at 0.1 incidental extra risk (i.e., $BMDL_{10}$) is used to calculate the cancer potency slope factor, as noted in Development of Slope Factor, as follows: $0.1 / BMDL_{10} = 0.1 / 0.0039$ mg/kg/d = 26 $(mg/kg/day)^{-1}$.

Generating Protocol ---

TITLE: Female Mouse forestomach

Avg Dose (mg/kg/day)	#fatal	#incidental	#animals
0	0	0	60
6	46	8	60
20	49	10	60
60	49	10	60

	MOUSE		HUMAN	
Body Weight	0.03	kg	70	kg
LifeSpan	104	weeks	70	years
Breathing Rate	0.0347	l/min	0.833	m^3/hr
Food Consumption	3.9	g/day	1400	g/day
Drinking Rate	6	ml/day	2	l/day
Route	WATER (mg/kg/day)		N/A	
Dosing: Hrs/Day	24		N/A	
Days/Week	5		N/A	
Weeks	104		N/A	
Weeks of Study	104		N/A	
Averaging Factor	1		1	

Model: Multistage Weibull Risk Type: Incid Extra Risk Confidence limit: 95%
Animal to human conversion method: MG/KG BODY WEIGHT(3/4)/DAY

Generating Model Fit Table ---
TITLE: Female Mouse forestomach

Dataset: C:\TCP Fem mouse forestomach C=F A=I with interim+terminal sacrifice = I.ttd

Functional form: 1 - EXP[(-Q0 - Q1 * D - Q2 * D^2 ... - Qk * D^k) * (T - T0)^Z]

Maximum Log-Likelihood = -5.423465e+002

Parameter Estimates : k = 2
Q 0 = 0.000000E+000
Q 1 = 7.457934E-016
Q 2 = 9.832566E-017
Z = 7.505444E+000
T0 = 2.360316E+001

Avg Dose (mg/kg/day)	#fatal	#incidental	#animals
0	0	0	60
6	46	8	60
20	49	10	60
60	49	10	60

Generating Extrapolated Doses Table ---

TITLE: Female Mouse forestomach

Dataset: C:\TCP Fem mouse forestomach C=F A=I with interim+terminal sacrifice = I.ttd

Exposure Pattern
Model: Multistage Weib Age Begins: 0 Age Ends: 70
Target Species: Human Weeks/Year: 52 Days/Week: 7
Route: Food Hours/Day : 24

Dose Estimates (ug/kg/day)

Incid Extra Risk	Time	95.00 % Lower Bound	MLE	95.00 % Upper Bound
1.0000E-006	70.00	3.7108E-005	9.2044E-005	Not Reqstd
1.0000E-005	70.00	3.7108E-004	9.2044E-004	Not Reqstd
0.0001	70.00	3.7110E-003	9.2047E-003	Not Reqstd
0.0010	70.00	3.7126E-002	9.2076E-002	Not Reqstd
0.01	70.00	3.9005E-001	9.2366E-001	Not Reqstd
0.10	70.00	3.9064E+000	9.5469E+000	Not Reqstd