MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for 1,1-Dichloroethane (CAS # 75-34-3)

FROM: Robert Sills, AQD Toxics Unit Supervisor

SUBJECT: 1,1-Dichloroethane ITSL change in the averaging time from 24 hrs to annual

DATE: December 6, 2016

The current ITSL for 1,1-dichloroethane (500 ug/m^3) was established on August 27, 1997 (see attached). The averaging time (AT) assigned to the ITSL at that time was 24 hours, as per the default methodology at that time (Rule 232(2)(b)). The ITSL was based on and consistent with an EPA Reference Concentration (RfC) of the same value, which EPA derived from a subchronic (13 week) animal bioassay. As described in the attached, EPA (1995) applied a total uncertainty factor (UF) = 1000, which consisted of a UF = 10 for interspecies extrapolation, UF = 10 for intraspecies variability, and UF = 10 to extrapolate from subchronic to chronic exposure duration. The current file review concludes that the AT for the ITSL may appropriately be set at annual, based on the nature and duration of the key study and the ITSL value derivation, as allowed under Rule 229(2)(b). Therefore, the AT is being changed from 24 hours to annual at this time.

Also attached is an August 29, 2012 memo describing a re-evaluation of the possible carcinogenicity of 1,1-dichloroethane, which found that the data were inconclusive.

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for 1,1-Dichloroethane (CAS No. 75-34-3)

FROM: Cathy Simon, Toxics Unit, Air Quality Division

DATE: August 29, 2012

SUBJECT: Updated Carcinogenicity Assessment for 1,1-Dichloroethane

An updated evaluation of the data relating to the carcinogenic potential of 1,1-dichloroethane has been completed. Based on this evaluation, the conclusion made in 1997 on this issue is still appropriate. Specifically, the finding in 1997 was that there was no conclusive evidence for carcinogenicity of 1,1-dichloroethane, and therefore no cancer potency or unit risk value was derived pursuant to the requirements of the Michigan Air Toxic Rules. The background information, relevant data, and basis for this conclusion are summarized below.

Background

In August 1997, the Air Quality Division (AQD) of the Michigan Department of Environmental Quality (MDEQ) established an initial threshold screening level (ITSL) of 500 ug/m^3 (24-hour averaging time) for 1,1-dichloroethane (MDEQ, 1997). At that time it was also found that there was no conclusive evidence for the carcinogenicity of 1,1-dichloroethane, and therefore, no risk assessment was done to establish an initial risk screening level (IRSL) or secondary risk screening level (SRSL).

As part of the AQD's evaluation of 1,1-dichloroethane in 1997, the US Environmental Protection Agency's (US EPA) Integrated Risk Information System (IRIS) database was reviewed for relevant information. At that time, no inhalation reference concentration (RfC) or oral reference dose (RfD) was available in the IRIS database. With regards to assessment of carcinogenicity data, the IRIS database identified 1,1-dichloroethane as a Group C or possible human carcinogen, however no quantitative risk assessment had been done to establish a cancer potency factor or unit risk value.

Currently, the status of the IRIS database for 1,1-dichloroethane is the same as in 1997, with no RfC, RfD, or quantitative cancer risk assessment available, and a Group C classification with regards to the qualitative assessment of the carcinogenicity data (EPA, 2012a). While the current IRIS database indicates the carcinogenicity assessment was last revised in December 1996, it also contains a note that states as of September 2002 a screening level review of the more recent toxicology literature related to the carcinogenic assessment of 1,1-dichloroethane did not identify any critical new data. It should also be noted that other past reviews by the US EPA have also found that the carcinogenicity data for 1,1-dichloroethane were considered inconclusive and not adequate for quantitative risk assessment (EPA, 1980; 1982; 1984; 2006).

More recently, the US EPA's Office of Air Quality Planning and Standards (OAQPS) has tabulated dose response assessments for use in risk assessments for hazardous air pollutants (EPA, 2012b). For 1,1-dichloroethane, the US OAQPS has identified a unit risk value of 1.6×10^{-6} $(\mu g/m^3)^{-1}$ (EPA, 2012b). This unit risk value was derived by the California Environmental Protection Agency's (Cal/EPA) Office of Environmental Health Hazard Assessment (OEHHA) (Cal/EPA, 2009).

An evaluation of the risk assessment done by the Cal/EPA (2009) was undertaken to determine the appropriateness of using the unit risk value derived by this agency for setting an IRSL and SRSL. This evaluation focused only on review of information related to the cancer risk assessment for 1,1-dichloroethane, and did not include any update of the existing ITSL. Furthermore, this evaluation did not include an independent review of all relevant scientific literature, but relied primarily on reviews done by various organizations such as the National Toxicology Program (NTP), Agency for Toxics Substances and Disease Registry (ATSDR), World Health Organization (WHO), US EPA, and Cal/EPA. Information from these and other sources, as well as the result of the risk assessment evaluation are presented below.

Carcinogenicity Data

The only lifetime carcinogenicity bioassay available for 1,1-dichloroethane is one performed by the National Cancer Institute (NCI, 1978), that was previously summarized and reviewed by the MDEQ (1997). In this study, groups of Osborne-Mendel rats and B6C3F1 mice were administered 1,1-dichloroethane by gavage at two dose levels for 78 weeks, followed by an observation period of 33 weeks for rats, and 13 weeks for mice. A high mortality rate was observed in both species of treated and control animals, but was especially marked in the male and female rats. No tumors were significantly increased in male or female rats, although there was a significant dose related trend for mammary adenocarcinomas and hemangiosarcomas in female rats. In male mice, no tumors were significantly increased, while in female mice there was a statistically significant increased incidence of endometrial stromal polyps of the uterus in the high dose group. Because of poor survival in all animal groups the statistical analyses were repeated to include only those animals surviving at least 52 weeks. These analyses showed a significant dose related trend in the incidence of hepatocellular carcinomas in male mice, but no statistically significant increased incidence in either dose group. Other findings were not changed by these further analyses. The authors of this study concluded that the results are indicative of the "possible carcinogenic potential" of 1,1-DCE; however, under the conditions of the bioassay, there was no conclusive evidence of carcinogenicity for rats or mice (NCI, 1978).

The IRIS database includes a summary and evaluation of a drinking water study in mice to determine if 1,1-dichloroethane could act as a tumor promoter or complete carcinogen. Mice were exposed for up to 52 weeks to two dose levels of 1,1-dichloroethane in drinking water, followed by 4 weeks of treatment with either an initiator (diethyl nitrosamine) or deionized water (non-initiated groups). Animals were held for another 24 or 52 weeks. The authors concluded that 1,1-dichloroethane was not carcinogenic to mice and did not act as a tumor promoter following initiation with diethyl nitrosamine. The US EPA found that these conclusions may not have been "entirely justified" as the study duration may not have been adequate, and the high response in the diethyl nitrosamine treated groups would have required a marked response in the 1,1-dichloroethane only groups in order to be detectable (EPA, 2012a).

Genotoxicity Data

The genotoxicity data for 1,1-dichoroethane has been summarized and evaluated by the Cal/EPA (2003). The results of this data are equivocal, with positive and negative results seen in various systems. Positive results for mutagenicity have been observed in *S. typhimurium* TA 98, TA100, and TA1535 both with and without metabolic activation; however, negative results have also been obtained in those same strains, as well as in TA1537. Negative results were found in yeast mutation assays using *S. cerevisiae*, whereas positive results for chromosomal effects were observed in the fungi, *Aspergillus nidulans.* In mammalian cells *in vitro*, 1,1-dichloroethane induced viral transformations in Syrian hamster cells and unscheduled DNA synthesis in rat and mouse cells, but did not induce transformations in BALB/C-3T3 cells. Binding to nucleic acids and proteins of the liver, lung, kidney, and stomach was observed after *in vivo* exposure in rats and mice administered 1,1-dichloroethane by intraperitoneal injection; however, no DNA single strand breaks were found in the liver DNA of mice exposed in a similar manner (CalEPA, 2003). In another *in vivo* study available as an abstract and not reviewed by CalEPA, chromosomal aberrations and micronuclei were observed in the bone marrow cells of Swiss Webster mice administered 1,1-dichloroethane by intraperitoneal injection (Patlolla et al, 2005).

Reviews by Other Agencies

No review of the data for 1,1-dichoroethane has been done by the International Agency for Research on Cancer. The ATSDR published a Toxicological Profile for 1,1-dichloroethane in 1990, and found that there was inconclusive evidence that 1,1-dichloroethane may be carcinogenic in humans (ATSDR, 1990). In addition, the ATSDR has not set any minimal risk levels for 1,1-dichloroethane. The WHO has reviewed the toxicological data for 1,1-dichloroethane for the purpose of establishing guidelines for drinking-water quality. The WHO found no conclusive evidence of carcinogenicity for 1,1-dichloroethane, and due to the limited data for this chemical, concluded no guideline value should be proposed (WHO, 2003).

The US EPA has conducted several reviews of the toxicological data for 1,1-dichloroethane over the years. In 1980, the US EPA concluded that there was insufficient data to establish any ambient water quality criterion for 1,1-dichloroethane. This included the finding that the data were not adequate for a carcinogenic risk assessment (EPA, 1980). A review by the US EPA in 1982 found that the NCI bioassay study was inconclusive due to poor survival and that risks could not be evaluated (EPA, 1982). A review two years later came to a similar conclusion regarding the NCI bioassay, and further identified 1,1-dichloroethane as a Group D carcinogen, defined as not classifiable with regards the carcinogenic potential (EPA, 1984). In 1989, 1,1-dichloroethane was listed as a probable human carcinogen (Group B2) in the US EPA's Health Effects Assessment Summary Tables (HEAST), noting hemangiosarcomas in rats as the tumor of concern (Cal/EPA, 1999). This classification was changed to Group C, possible human carcinogen, in 1990 and posted on IRIS in October of that year. According to a personal communication between Cal/EPA and the US EPA, the change was based on a change in professional judgment rather than significant new information Cal/EPA (1999). The last revision of HEAST from 1997 contains only a reference to IRIS for the carcinogenicity classification of 1,1-dichloroethane (EPA, 1997).

Under the US EPA Superfund program, the toxicological data for 1,1-dichloroethane was evaluated for the purpose of establishing a Provisional Peer Reviewed Toxicity Value (PRRTV) in 2006 (EPA, 2006). This evaluation included a review of the scientific literature through September 2004. Based on this evaluation, the US EPA concluded that "...1,1-dichloroethane

is considered to show suggestive evidence of carcinogenic potential;" however, a unit risk value was not derived because the available data were considered insufficient to support such a quantitative risk assessment (EPA, 2006). The US EPA went on to state that, "This is in accordance with the U.S. EPA (2005) cancer guidelines, which state it is generally not appropriate to derive quantitative estimates of cancer risk for chemicals where the weight-of-evidence for carcinogenicity provides only *suggestive evidence of carcinogenic potential*" (EPA, 2006).

The State of California first listed 1,1-dichloroethane "as causing cancer" under its Proposition 65 program on January 1, 1990. This listing was based upon the US EPA classification of 1,1-dichloroethane as a probable human carcinogen (Group B2) in its 1989 HEAST (Cal/EPA, 1999). In 1990, the US EPA published a health assessment evaluation of 1,1-dichlorothane on its IRIS database, classifying it as a possible human carcinogen (Group C). According to a personal communication between the Cal/EPA and US EPA, the reclassification appeared "to be due to change in professional judgment, rather than being based on significant new information" (Cal/EPA, 1999).

As a result of the change in the US EPA carcinogen classification of 1,1-dichloroethane, the Cal/EPA undertook a review of this chemical to determine if it should be delisted from the list of compounds causing cancer developed under the Proposition 65 program. This review did not identify any new, significant data to change previous interpretations of the data; however, Cal/EPA cited an analysis of the NCI bioassay (NCI, 1977) by other researchers that appeared to have weight in their final decision on whether or not to delist 1,1-dichloroethane. According to Cal/EPA, survival analysis of the NCI bioassay data conducted by Gold and Zeiger in a 1997 publication, included positive findings of "liver tumors ($p<0.05$) and lung tumors ($p<0.04$) in male mice compared to matched controls" (Cal/EPA, 1999).

The final conclusion by Cal/EPA was to not delist 1,1-dichloroethane from the list of compounds identified as "causing cancer" under Proposition 65. The basis for this conclusion appeared to be the findings by NCI (1977), including dose related increases of mammary gland adenocarcinomas and hemangiosarcomas in female rats and significantly increased incidences of endometrial polyps in female mice; the analysis by Gold and Zeiger of the NCI bioassay data, the positive mutagenicity findings, and the structural similarity to 1,2-dichloroethane, a probable human carcinogen (Cal/EPA, 1999).

Cancer Risk Assessment

The only quantitative cancer risk assessment available for 1,1-dichloroethane has been done by the Cal/EPA (1992). For this assessment, Cal/EPA derived an oral cancer potency value of 5.7×10^{-3} $(mg/kg/day)^{-1}$ using the data from the NCI bioassay (NCI, 1978). No details are available regarding how this value was derived, except for the following:

> Gold et al list the results of the NCI (1977) gavage studies in male and female B6C3F1 mice and Osborne Mendel rats. Cancer potency is based on mammary gland adenocarcinomas observed in female rats, the most sensitive of the species/sex combinations tested. Because survival was poor for the study in female rats, the potency was derived using a time-to-tumor analysis (Crump et al., 1991). (Cal/EPA, 1992)

Cal/EPA derived an inhalation unit risk value of 1.6×10^{-6} $(\mu g/m^3)^{-1}$ from the above oral cancer potency factor assuming a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day (Cal/EPA, 2009).

Conclusion

No new, significant data was found since the review done in 1997, at which time the AQD found that the data were inconclusive regarding the carcinogenic potential of 1,1-dichloroethane, and therefore no cancer potency value should be derived for the purpose of determining an IRSL and SRSL. No international, federal, or state agency other than Cal/EPA has found the data conclusive enough to warrant a quantitative carcinogenic risk assessment for 1,1-dichloroethane. The only lifetime cancer bioassay available was the NCI (1978) study, whose authors concluded that the results of this study were indicative of the "possible carcinogenic potential" of 1,1-DCE; however, under the conditions of the bioassay there was no conclusive evidence of carcinogenicity for rats or mice (NCI, 1978). The US EPA OAQPS in the only EPA program office to identify a cancer potency factor or unit risk value for 1,1-dichloroethane; however, it appears the only basis for doing this, is a policy to adopt a California based unit risk value, if one hasn't been developed by the US EPA (EPA, 2012b). It does not appear that the US EPA OAQPS conducted any independent review or evaluation of Cal/EPA's rationale for its conclusions regarding the carcinogenic potential of 1,1-dichloroethane or the derivation of the unit risk value. While the information reviewed for this evaluation is suggestive of the carcinogenic potential of 1,1-dichloroethane, it is not adequate to conclude that it meets the definition of carcinogen in Rule 103(c) of the Michigan Air Pollution Control Rules. Therefore the finding in 1997 by the MDEQ AQD that no carcinogenic potency value be derived to establish an IRSL or SRSL is still appropriate.

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CS:lh

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

August 27, 1997

TO: File for 1,1-Dichloroethane (CAS# 75-34-3)

FROM: Michael Depa, Toxics Unit, Air Quality Division

SUBJECT: Screening Level Determination

The initial threshold screening level (ITSL) for 1,1-dichloroethane is 500 µg/m³ based on a 24-hour averaging time.

The following references or databases were searched to identify data to determine the ITSL: IRIS, RTECS, ACGIH Threshold Limit Values, NIOSH Pocket Guide to Hazardous Chemicals, Environmental Protection Bureau Library, IARC Monographs, CAS Online (1967 - December 30, 1995) National Library of Medicine, Health Effects Assessment Summary Tables, and NTP Status Report. Review of these sources found that an RfC or RfD are not listed in IRIS for 1,1-dichloroethane. An RfC and an RfD are listed in EPA's HEAST as 0.5 mg/m³ and 0.1 mg/kg/day (respectively). The ACGIH and NIOSH established occupational exposure limits (OELs) of 405 and 400 mg/m³ (respectively). NIOSH considers 1,1-dichloroethane a potential occupational carcinogen. The molecular weight of 1,1-dichloroethane is 98.96g.

Background

At one time 1,1-dichloroethane was used as an anesthetic (EPA, 1984). The ability of 1,1-dichloroethane to induce cardiac arrhythmia caused discontinuation of its use as and anesthetic. It is probable that human exposure to sufficiently high levels would cause CNS depression and respiratory tract and skin irritation, since many other chlorinated aliphatics do. No dose-response data concerning these phenomena are available (EPA, 1984).

Animal Toxicological Studies

The US EPA (1984) summarized a German publication by Hofmann et al. (1971). In this subchronic inhalation study, groups of 10 rats, 4 cats, 4 rabbits and 10 guinea pigs were exposed to 500 ppm (~2025 mg/m³) 1,1-dichloroethane 6 hrs/day, 5 days/wk for 13 weeks. Since no effects were reported in any of the animals tested, the exposure was increased to 1000 ppm (~4050 mg/m³) for an additional 13 weeks (6 hrs/day, 5 days/wk). The EPA (1984) stated:

> The most sensitive animal tested appeared to be the cat, the only animal in which adverse effect were noted. Blood urea nitrogen levels were immediately elevated and rose steadily to week 24, at which time they peaked at ~3 times the control levels. Blood creatinine levels showed a parallel but less dramatic increase. No increase of SGOT or SGPT was noted. Histopathological examination of the cats revealed renal tubular dilation and degeneration, indication of renal damage.

EPA (1984) summarized an unpublished subchronic inhalation study by Torkelson and Row (1981) of the Dow Chemical Company in which unspecified numbers of rats, guinea pigs, rabbits and dogs were exposed to 500 or 1000 ppm (2025 or 4050 mg/m³, respectively) 1,1-dichloroethane for 7 hours/day, 5 days/week for 6 months. The EPA (1984) reported:

> Blood chemistries, necropsy and histological examinations revealed no changes attributed to the exposure. Based in the studies of Torkelson and Rowe (1981) and Hoffman et al. (1971), and NOEL of 500 ppm (2035 mg/m³) can be suggested for subchronic inhalation exposure to 1,1-dichloroethane in rats, cats, rabbits, guinea pigs and dogs.

In a range finding study, groups of rats (number and strain not given) were exposed to 1,1-dichloroethane for various amounts of time (Dow Chemical, 1960). Table 1 contains information on the acute toxicity of 1,1-dichloroethane obtained from this report.

Table 1. Results from Acute Exposure to 1,1-dichloroethane

Concentration of 1,1-dichloroethane	Exposure Duration(hrs)	No. Killed/ No. Exposed	Comments and Observations
64,000 ppm	0.5	9/9	All rats were dead on removal.
64,000 ppm	0.2	5/9	All deaths occurred during exposure. The survivors recovered rather quickly and had either shown increase in weight or very slight decrease when weighed the following day.
25,000 ppm	2.5	9/9	All rats died during exposure.
25,100 ppm	1	1/9	One rat died shortly before the end of the exposure. The survivors recovered quickly and regained their weight.
14,350 ppm	7	3/9	Three animals died during exposure the balance recovered quickly. Only a slight transitory weight loss occurred. Moderate kidney pathology was noted on several of the animals killed for pathological examination.
7,000 ppm	6-7	0/27	Rats lost only a slight amount of weight which they quickly recovered. Pathology was slightly more consistent with less lung pathology than was noted at the higher concentrations. Slight to moderate liver and kidney pathology was seen on several animals sacrificed after exposure.

In a developmental study, groups of pregnant Sprague-Dawley rats were exposed to 0 (n=43), 3800 ppm (n=16), and 6000 ppm (n=19) 7 hours/day on days 6 - 15 of gestation (Schwetz et al., 1974). These exposure concentrations correspond to 0, 15,382, and 24,287 mg/m³ (respectively). There were no effects on the incidence of fetal resorptions, fetal body measurements or on the incidence of gross or soft tissue anomalies. A significantly increased incidence of delayed ossification of sternebrae was

associated with exposure to the 6000 ppm dose ($p<0.05$). The incidence of vertebrae with bipartite centra was significantly lower in fetuses of rats exposed to 3800 ppm than in control fetuses. Maternal food consumption and weight gain were slightly decreased among rats exposed to 3800 or 6000 ppm ($p<0.05$). Exposure had no effect on the conception rate, the number implantations or litter size, SGPT activity or the gross appearance of the liver. A developmental NOAEL of 3800 ppm (15,382 mg/m^3) was identified from this study.

In a study performed by the National Cancer Institute (1978), groups of 50 male and 50 female Osborne-Mendel rats and B6C3F1 50 male and 50 female mice were dosed by gavage with 1,1-dichloroethane 5 days/week for 78 weeks, followed by an observation period of 33 weeks for rats and 13 weeks for mice. Twenty animals of each sex and species were used as non-treated controls and another 20 animals of each sex and species were gavaged with corn oil (designated vehicle controls). The dose levels varied with time over the course of the experiment. The time-weighted average dosages for the male rats were 0, 0, 382, and 764 mg/kg for untreated control, vehicle control, low dose and high dose, respectively. The time-weighted average dosages for the female rats were 0, 0, 475, and 950 mg/kg for untreated control, vehicle control, low dose and high dose, respectively. The time-weighted average dosages for the male mice were 0, 0, 1442, and 2885 mg/kg for untreated control, vehicle control, low dose and high dose, respectively. The time-weighted average dosages for the female mice were 0, 0, 1665, and 3331 mg/kg for untreated control, vehicle control, low dose and high dose, respectively. The authors concluded that under the conditions of the bioassay there was no conclusive evidence for the carcinogenicity of 1,1-dichloroethane in Osborne-Mendel rats or B6C3F1 mice. Pneumonia was observed in 80 percent of the rats in this bioassay. The authors stated that high mortality rates of rats and mice during the course of this study complicated the interpretation of the results of this bioassay. The final survivorship in the untreated control, vehicle control, low dose and high dose groups was, respectively, 30, 5, 4, and 8 percent in the male rats; 40 20, 16, and 18 percent in the female rats; 35, 55, 62, and 32 percent in the male mice; and 80, 80, 80, and 50 percent in the female mice. There was no difference in body weight compared to the control in any dose group. There was a statistically significant increase in the incidence of endometrial stromal polyps among dosed female mice as compared to controls. The authors stated that these findings are indicative of the possible carcinogenic potential of 1,1-dichloroethane; however, it must be recognized that under the conditions of this bioassay there was no conclusive evidence for the carcinogenicity of 1,1-dichloroethane. Because the increase in mammary adenocarcinomas among female rats was not significantly different from controls, a cancer potency value was not developed from this study.

Determination of ITSL

As mentioned above, the ACGIH and NIOSH have set occupational exposure limits for 1,1-dichloroethane (405 and 400 mg/m^3 respectively). A NIOSH Criteria Document was not available; however, the ACGIH TLV documentation was analyzed in order to determine the adequacy of the TLV. The ACGIH stated that the TLV was based on the animal studies with repeated inhalations; however, the exact study or calculation was not provided. It was deemed inappropriate to use an OEL to develop the ITSL since the EPA has developed an RfC.

As noted above, the EPA (1984) evaluated and summarized the German toxicological study by Hoffman et al. (1971). The EPA (1984) also performed a risk assessment on 1,1-dichloroethane. The EPA designated the dose level of 2025 mg/m^3 as a 13-week (subchronic) NOAEL. The RfC was calculated as follows:

RfC = [NOAEL x (cat inhalation rate)/(cat body weight) x (6 hrs)/(24 hrs) x (5 day)/(7 days)

x (average weight of human)/(average human inhalation rate)] ÷ (UF_1 x UF_2 x UF_3)

Where UF_1, U_{F2}, and UF_3 were used to account for interspecies variability, intraspecies variability and to convert from subchronic to chronic exposure periods, respectively. The RfC then becomes:

RfC = (2025 mg/m³ x (1.26 m³/day)/(3.3 kg) x 6/24 x 5/7 x 70kg/20m³)/(10 x 10 x 10)

RfC = (483 mg/m³)/(1000)

RfC = 0.48 mg/m³

RfC = 0.5 mg/m³

RfC = 500µg/m³

Since an RfC was developed by the EPA and no information was found to indicate that it would not be appropriate, the RfC was used to set the ITSL. According to Rule 230(1)(a) the ITSL shall equal the RfC. The ITSL for 1,1-dichloroethane is 500 µg/m³ based on a 24-hour averaging time.

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