MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for 1,2-Dichloropropane (CAS No. 78-87-5)

FROM: Cathy Simon, Air Quality Division

DATE: Screening Level Update

SUBJECT: September 18, 2013

A review and evaluation of the carcinogenicity data for 1,2-dichloropropane has been completed. As a result of this review, an initial risk screening level (IRSL) for 1,2-dichloropropane has been established at 0.2 µg/m^3 (annual averaging time) and a secondary risk screening level (SRSL) at 2 µg/m^3 (annual averaging time). The background information, relevant data and basis for this conclusion are summarized below.

Background

In 1991, the Air Quality Division (AQD) of the Michigan Department of Natural Resources (MDNR) established an initial threshold screening level (ITSL) for 1,2-dichloropropane of 4 µg/m^3 (24-hour averaging time). This ITSL was derived from an inhalation reference concentration (RfC) of 4 µg/m^3, established by the U.S. Environmental Protection Agency (EPA). At that time, the EPA's Integrated Risk Information System (IRIS) database had no carcinogenicity assessment for 1,2-dichloropropane, nor had the AQD done any assessment of the carcinogenicity data for this compound. Therefore, no determination was made as to whether or not the data supported establishing an IRSL and SRSL.

The inhalation RfC in the IRIS database remains at 4 µg/m^3 as of the present date (EPA, 2013), and no update of the ITSL is being done at this time. The focus of this evaluation is on the review of the data relating to the carcinogenic potential of 1,2-dichloropropane.

No carcinogenicity assessment or inhalation unit risk value is currently available in the EPA's IRIS database (EPA, 2013a). In the last update of the Health Effects Assessment Summary Table (HEAST) in 1997, the EPA provided an oral cancer slope factor of 6.8 x 10^{-2} $(mg/kg/day)^{-1}$ for 1,2-dichloropropane, but no inhalation unit risk value (EPA, 1997). The oral slope factor was derived from the National Toxicology Program (NTP) cancer bioassay, in which an increased incidence of liver tumors was observed in B6C3F1 mice administered 1,2-dichloropropane by gavage (NTP, 1986). In 2003, the EPA assessed the available carcinogenicity data for its Superfund program, and concluded that the data were not adequate to derive a provisional inhalation unit risk value for 1,2-dichloropropane (EPA, 2003). For the 2005 National Air Toxics Assessment (NATA), the EPA derived an inhalation unit risk value of 1.9 x 10^{-5} $(\mu g/m^3)^{-1}$, based on a conversion from the oral cancer slope factor derived from the NTP study, and assuming a 70 kg person inhales 20 m^3 of air per day (EPA, 2011). Other than the 2005 NATA, no other

EPA program or study was identified that utilized or derived an inhalation unit risk value for 1,2-dichloropropane.

The International Agency for Research on Cancer (IARC) last evaluated the carcinogenicity data for 1,2-dichloropropane in 1999, and found, at that time, there was limited evidence in animals for the carcinogenicity of this compound, and no human epidemiological data relevant to the carcinogenicity. Overall, the IARC concluded that "1,2-dichloropropane is not classifiable as to its carcinogenicity to humans (Group 3)" (IARC, 1999).

In addition to the above EPA and IARC references, data summaries prepared by the Agency for Toxic Substances and Disease Registry (ATSDR, 1989), World Health Organization (WHO, 2003), and Organization for Economic Cooperation and Development (OECD, 2003) were also reviewed for relevant information related to the carcinogenicity assessment of 1,2-dichloro-propane.

Review of Relevant Data

The NTP conducted an oral carcinogenesis bioassay in which groups of 50 male and 50 female F344 rats and B6C3F1 mice were administered 1,2-dichloropropane by gavage 5 days/week for two years. Dose levels for rats were 0, 62, and 125 mg/kg/day, whereas mice received doses of 0,125, and 250 mg/kg/day. The NTP concluded that there was some evidence of carcinogenicity for male and female mice, based on the increased incidence of hepatocellular neoplasms. The NTP also found that there was no evidence of carcinogenicity for male rats, and equivocal evidence in female rats based on a marginally increased incidence of adenocarcinomas in the mammary gland (NTP, 1986). The IARC based its finding of limited evidence of carcinogenicity in animals based on this NTP study, and the EPA derived an oral cancer slope factor from the same study, utilizing the liver tumor incidence data for male mice (EPA, 1997). No other oral carcinogenicity data was identified for 1,2-dichloropropane.

Two recent studies (Umeda et al, 2010; Matsumoto et al, 2013) were identified that evaluated the carcinogenicity of 1,2-dichloroproane by inhalation exposure. In the study by Umeda et al (2010), groups of 50 male and 50 female F344 rats were exposed to 1,2-dichloropropane at concentrations of 0, 80, 200, or 500 ppm. Animals were exposed 6 hours per day, 5 days per week for two years. Exposure to 1,2-dichloropropane resulted in a significant increase in non-neoplastic and neoplastic lesion of the nasal cavity in both sexes of rats. The incidences of the following non-neoplastic lesions of the nasal cavity were significantly increased at all dose levels in both male and female rats: hyperplasia of the transitional epithelium, squamous cell metaplasia of the respiratory epithelium, inflammation of the respiratory epithelium, and atrophy of the olfactory epithelium. In addition, the incidence of squamous cell hyperplasia of the nasal cavity was significantly increased in male rats exposed to 200 and 500 ppm, and in female rats exposed to 500 ppm. The incidences of nasal papillomas and total nasal tumors were significantly increased in both male and female rats exposed to 1,2-dichloropropane at 500 ppm. The incidences of these tumors are shown in Table 1. No other exposure related lesions were observed in any other organs of either sex of rats.

Table 1: Incidence of nasal tumors in male and female rats exposed to 1,2-dichloropropane (Umeda et al, 2010)

	Dose (ppm)			
Nasal Tumor Type/Sex	**0**	**80**	**200**	**500**
Papilloma – Male	0/50	0/50	3/50	15/50[a]
Esthesioneuroepithelioma - Male	0/50	2/50	1/50	0/50
Total nasal tumors - Male	0/50	2/50	4/50	15/50[a]
Papilloma - Female	0/50	0/50	0/50	9/50[a]
Esthesioneuroepithelioma - Female	0/50	0/50	0/50	0/50
Total nasal tumors - Female	0/50	0/50	0/50	9/50[a]
[a] Significantly increased at $p \leq 0.01$ by Fisher's Exact test				

In the second inhalation study (Matsumoto et al, 2013), groups of 50 male and 50 female B6D2F1 mice were exposed to 1,2-dichloropropane at concentrations of 32, 80, or 200 ppm. Animals were exposed 6 hours per day, 5 days per week for two years. In female mice, the incidence of bronchiolo-alveolar carcinomas alone, and in combination with bronchiolo-alveolar adenomas, increased in a dose dependent manner. Additionally, the combined incidence of bronchiolo-alveolar adenoma and carcinoma was significantly increased in the 200 ppm dose group. In male mice, the combined incidence of bronchiolo-alveolar adenoma and carcinoma was significantly increased in the 32 and 200 ppm dose groups, but did not increase in a dose dependent manner. For this reason, the authors concluded that the relation between the increased incidence of lung tumors in male mice and exposure to DCP is not clear. Exposure to DCP also resulted in a dose related increase in the incidence of Harderian gland adenomas in male mice, and the incidence in the 200 ppm dose group was significantly increased for this tumor. Lastly, the incidence of splenic hemangiosarcoma alone or combined with hemangioma was significantly increased in the 200 ppm dose group for male mice, however, these incidences were within the maximum incidences of historical controls. Therefore, the authors concluded that the relation between splenic tumors and exposure to DCP is not clear (Matsumoto et al, 2013). Table 2 provides the incidence of tumors that were increased in male or female mice exposed to DCP.

Table 2: Tumor incidence in male and female mice exposed to 1,2-dichloropropane (Matsumoto et al, 2013).

	Dose (ppm)			
Tumor Type/Sex	**0**	**32**	**80**	**200**
Bronchiolo-alveolar adenoma - Male	5/50	14/50[a]	9/50	12/50
Bronchiolo-alveolar carcinoma - Male	4/50	6/50	6/50	8/50
Bronchiolo-alveolar adenoma and/or carcinoma - Male	9/50	18/50[a]	14/50	18/50[a]
Haderian gland adenoma - Male[b]	1/50	2/50	3/50	6/50
Spleen hemangioma – Male	0/50	1/50	0/50	1/50
Spleen hemangiosarcoma	0/50	3/50	3/50	5/50[a]
Spleen hemangioma and/or hemangiosarcoma	0/50	4/50	3/50	6/50[a]
Bronchiolo-alveolar adenoma - Female	1/50	4/50	4/50	4/50
Bronchiolo-alveolar carcinoma - Female[b]	1/50	1/50	1/50	4/50
Bronchiolo-alveolar adenoma and/or carcinoma - Female[b]	2/50	4/50	5/50	8/50[a]
[a] Significantly increased at $p<0.05$ by Fisher's Exact test [b] Significant dose related trend at $p<0.05$ by Peto's test				

As mentioned above, previous reviews (ATSDR, 1989; IARC, 1999; EPA, 2003) regarding the potential carcinogenicity of 1,2-dichloropropane have found no human epidemiological data relevant to this evaluation. More recently, Kumagai et al (2013), reported the findings of their investigation on the incidence of cholangiocarcinoma among 62 male workers (51 proof-printing workers and 11 front room workers) exposed to 1,2-dichlorpropane and/or dichloromethane in a small printing company in Osaka, Japan. The 51 proof printing workers were exposed to 1,2-dichloropropane for 1 – 17 years (mean, 6 years). Additionally, 27 of these 51 workers were also exposed to dichloromethane for 1 – 12 years (mean, 4 years). Table 3 provides estimated exposure concentrations for these two chemicals, based on measured concentrations during an experiment to reproduce the working environment of the proof printing room, and chemical usage data for the various time periods. Other chemicals the workers may have been exposed to included gasoline, kerosene, 1,1,1-trichloroethane, and petroleum hydrocarbons (not specified).

Table 3: Estimated exposure concentration of 1,2-dichloropropane and dichloromethane for the proof-printing workers (Kumagai et al, 2013).

Years	Estimated Exposure Concentration (ppm)	
	1,2-Dichloropropane	Dichloromethane
1991 – 1992/1993	120 – 430 (mean: 220)	80 – 120 (mean: 140)
1992/1993 – 1997/1998	100 – 360 (mean: 190)	190 – 540 (mean: 360)
1997/1998 – 2006	150 – 670 (mean: 310)	Not used in this time period

Among the 62 workers (proof printing and front room), 11 of them were diagnosed with cholangiocarcinoma. All 11 of the workers with cholangiocarcinoma had been exposed to 1,2-dichloropropane for 7 – 17 years (mean, 10 years) and 10 of the 11 workers had been exposed to dichloromethane for 1 – 13 years (mean, 7 years). Standard mortality ratios (SMR) for cholangiocarcinoma are provided in Table 4.

Table 4: Cholangiocarcinoma SMR for workers exposed to 1,2-dichloropropane and/or dichloromethane (Kumagai et al, 2013)

Worker Classification	SMR	Expected Deaths	Confidence Interval
Proof printing	5000	0.00100	1,600 – 12,000
Front room	960	0.00104	24 – 5,400
All workers	2900	0.00204	1,100 – 6,400

As a result of the significant number of cholangiocarcinoma cases identified at this printing plant, the Japanese Ministry of Health Labor and Welfare (JMHLW) convened an expert panel in September 2012 to look into the causal relationship between occupational exposures at the plant and the development of this type of cancer. Five additional cancer cases presumably were discovered at this plant, as the expert panel report identifies 16 biliary tract cancer cases. The following conclusions were made by the expert panel (JMHLW, 2013):

- The Standardized Incidence Ratio (SIR) for biliary tract cancer of male workers at the printing room compared to the Japanese male population was found to be about 1200 (95% CI 714 – 1963).

- 1,2-dichloropropane and dichloromethane, used in large quantities in the ink cleaning process, were likely causative agents.

    - All 16 cases were exposed to 1,2-dichloropropane used in ink cleaner from March 1991 to October 2006.

    - Out of 16 cases, 11 were exposed to a mixture of equal parts of dichloromethane and 1,2-dichloropropane used from April 1991 – April 1996.

- The possible metabolic pathway for development of the biliary tract cancer could be activation of the glutathione-s-transferase (GST) pathway after the cytochrome P450 pathway is saturated. The biliary tract cancer could develop by repetitive DNA lesions caused by GST-mediated metabolites in biliary epithelial cells.

- Considering the fact that all 16 cases were exposed to 1,2-dichloropropane, it was highly probable that the biliary tract cancer was caused by long term exposure to 1,2-dichloro-propane at high concentrations.

A 17th case of biliary tract cancer has also been identified at this printing plant and is being investigated by the JMHLW (Kamae, 2013).

The IARC (1999) has evaluated the genotoxicity of 1,2-dichloropropane. The only data available were using *Drosophila* and various in vitro assays. The review by IARC (1999) indicated that 1,2-dichloropropane was mutagenic for *Salmonella typhimurium* strains TA 100 and 1535, both with and without metabolic activation, but negative for strains TA 1537, 1538, 98, and 1978. These results show 1,2-dichloropropane induces base-pair substitutions, but not frameshift mutations in this assay system. The IARC also reported that 1,2-dichloropropane was negative in a forward mutation assay with *Streptomyces coelicolor*, weakly positive in a forward mutation assay with *Aspergillus nidulans*, and negative in a genetic crossing over assay with *Aspergillus nidulans*. Lastly, 1,2-dichloropropane was reported to cause sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells, but did not induce sex linked recessive lethal mutations in *Drosophila melanogaster* (IARC, 1999).

In summary, 1,2-dichloropropane has caused an increased incidence of liver tumors in male and female mice and mammary adenocarcinoma in female rats through the oral route of exposure (NTP, 1986); an increased incidence of nasal tumors in male and female rats exposed via inhalation (Umeda et al, 2010); and an increased incidence of bronchiolo-alveolar adenomas and carcinomas in male and female mice, and hemangiosarcoma of the spleen and Harderian gland adenomas in male mice exposed by inhalation (Matsumoto et al, 2013). In addition, the extremely high SMRs and SIRS for cholangiocarcinomas in workers at a printing plant in Japan have been linked to exposure to 1,2-dichloropropane (Kumagai et al, 2013; JMHLW, 2013; Kamae, 2013). Lastly, 1,2-dichloropropane has been shown to be genotoxic in several *in vitro* assays.

Considering the above information, 1,2-dichloropropane meets the definition of carcinogen in Rule 103(c) of the Michigan Air Pollution Control Rules.

Cancer Risk Assessment

The mode of action by which 1,2-dichloropropane causes cancer is not known. When the mode of action cannot be established, the U.S. EPA *Guidelines for Carcinogen Risk Assessment* (EPA, 2005) recommends a linear extrapolation approach to estimate cancer risks. The point of departure for the linear extrapolation is the $BMCL_{10}$, derived from fitting experimental cancer bioassay dose response data to the multistage model. The $BMCL_{10}$ represents the lower 95% confidence limit on the concentration associated with a 10% extra cancer risk. This 10% extra

risk is defined as the benchmark response (BMR = 0.1). The inhalation unit risk (IUR), which represents the slope of the linear extrapolation, is then derived as follows:

$$IUR = BMR/BMCL_{10}$$

The IUR expresses the slope in terms of $\mu g/m^3$ or ppm air, and is used to estimate cancer risk at low concentrations.

The studies by Umeda et al (2010) and Matsumoto et al (2013) were used to derive inhalation unit risk values, consistent with the EPA *Guidelines for Carcinogen Risk Assessment* (EPA, 2005). The multistage model, available with the EPA's benchmark dose software (BMDS) (Version 2.4), were fit to the incidence data for tumors types occurring with a significantly increased incidence to determine the degree of the multistage model that best fit the data. Prior to running the BMDS, the experimental exposure concentrations were converted from units of ppm to mg/m^3, and adjusted to continuous exposure as follows:

$$AdjConc_{(mg/m3)} = EC_{(ppm)} \times MW/24.45 \times (6 \text{ hours})/(24 \text{ hours}) \times (5 \text{ days}/7\text{days})$$

Where:
AdjConc = Adjusted concentration for continuous exposure.
$EC_{(ppm)}$ = Experimental concentration in ppm.
MW = Molecular weight of 1,2-dichloropropane = 112.99.

Consistent with the U.S. EPA's *Benchmark Dose Technical Guidance* (EPA, 2012), all feasible orders of the multistage model up to three (number of dose groups less one) were evaluated for fit. Model fits with goodness-of-fit *p* values >0.1 were considered acceptable. Models that met this criterion were evaluated further considering visual fit of the data, statistical evaluation using Akaike's Information Criterion (AIC), and standardized residuals. The best fitting model was selected based on the criteria described in the U.S. EPA's guidance document (EPA, 2012).

With regards to the data for male rats from Umeda et al (2010), the one parameter multistage model was selected over the two and three parameter models. While all three models met the goodness of fit criterion of $p>0.1$, the one parameter model had the lowest AIC and $BMCL_{10}$. With regards to the data for female rats from Umeda et al (2010), the one parameter model was considered unacceptable with regards to fit ($p=0.0193$). The three parameter model was chosen over the two parameter model, based on the lowest AIC. With regards to the data for male and female mice from Matsumoto et al (2013), the one, two, and three parameter models gave the same results.

Using the selected models, the $BMCL_{10}$ was determined to use in calculation of the IUR. Before calculating the IUR, the $BMCL_{10}$ was converted to a human equivalent concentration by applying a dosimetric adjustment factor (DAF). The DAF was determined according to the EPA (1994) reference concentration (RfC) methodology. Under this methodology, 1,2-dichloro-propane would be considered a Category 2 gas, as it is moderately soluble and causes respiratory and systemic effects. Currently, dosimetry equations for Category 2 gases provided in the RfC methodology are undergoing re-evaluation by the EPA, and are not being used at this time. For

cross species scaling on extrarespiratory effects, the EPA's current practice is to treat Category 2 gases as Category 3 gases. For Category 3 gases, responses across species are considered equivalent on a ppm basis, unless the air:blood partition coefficient for the experimental animal species is less than that for humans. In this case, an adjustment is made based on the ratio of the animal to human blood:air partition coefficients. If partition coefficients are not available for humans and the experimental species, they are considered equivalent.

For Category 2 gases which cause respiratory effects, there is no clear guidance on the approach to use for determining a DAF. In deriving an RfC for 1,2-dibromoethane, which is considered a Category 2 gas, the U.S. EPA used the Category 1 gas methodology for the portal of entry effects, and the Category 3 gas methodology for the systemic effects (EPA, 2004). Likewise, for determining the inhalation unit risk value for 1,2-dibromo-3-chloropropane, another Category 2 gas, the EPA used the Category 1 gas methodology for the nasal and lung tumors, and the Category 3 gas methodology for the adrenal tumors (EPA, 2006). In deriving an inhalation unit risk value for ethylene oxide, another Category 2 gas, the EPA suggested one approach would be to do cross-species scaling using both Category 1 and Category 3 gas equations and then decide which is most appropriate (EPA, 2013b). While the EPA identified the Category 3 gas equations as the preferred approach for ethylene oxide, dose equivalency based on Category 2 gas equations were also used to provide information as a bounding exercise (EPA, 2013b).

For the purpose of determining an inhalation unit risk value for 1,2-dichloropropane, both the Category 1 and Category 3 gas methodologies were used for an initial assessment of tumors in the respiratory tract. For the rat nasal tumors and mouse lung tumors, a regional gas dose ratio (RGDR) was determined, consistent with the Category 1 equations. The RGDR was determined using the ventilation rates (V_E) and surface area (SA) of the appropriate region of the respiratory tract for the experimental animals and humans as follows:

$$\text{RGDR} = \frac{V_E(animal)/SA(animal)}{V_E(human)/SA(human)}$$

Since Umeda et al (2010) and Matsumoto et al (2013) reported only final body weights, ventilation rates for rats and mice were calculated based on default body weights provided in the EPA RfC methodology (EPA, 1994). Human default ventilation rates, and default respiratory surface areas for rats, mice, and humans were also used to derive the RGDR. Table 5 provides these values and the resulting RGDRs

Table 5: Regional gas dose ratios (RGDR) and applicable parameters and associated values used in derivation of RGDR.

Species/Sex	Body weight (kg)	V_E (L/minute)	SA of Applicable Respiratory Region (cm^2)	RGDR
Rat - male	0.380	0.254	13.8 (extrathoracic)	0.25
Rat - female	0.229	0.167	13.8 (extrathoracic)	0.16
Mouse - male	0.0373	0.044	500 (pulmonary)	3.4
Mouse - female	0.0353	0.041	500 (pulmonary)	3.2
Human	NA	15	200 (extrathoracic) 540,000 (pulmonary)	NA
NA – Not applicable				

To derive the inhalation unit risk value, the human equivalent concentration (HEC) for the $BMCL_{10}$ was first determined by multiplying the animal $BMCL_{10}$ by the applicable DAF. For respiratory effects, two DAFs were used; one based on the applicable RGDR (Category 1 method) and the other assuming ppm equivalency between species (Category 3 method). For systemic effects, only the Category 3 approach was used, consistent with the EPA recommendations. The inhalation unit risk value (IUR) was then determined as follows:

$$IUR = 0.1/BMCL_{10(HEC)}$$

Table 6 provides a summary of the unit risk values derived for each tumor type that was significantly increased in the Umeda et al (2010) and Matsumoto et al (2013) studies, using the above methodology.

Table 6: Inhalation unit risk (IUR) values for animals exposed to 1,2-dichloropropane by inhalation (Umeda et al (2011); Matsumoto et al (2013))

Sex/ species	Tumor Type	DAF	$BMCL_{10}$ (mg/m^3)	Unit risk $(mg/m^3)^{-1}$	
				Category 1 gas dosimetry	Category 3 gas dosimetry
Female mice	Alveolar/bronchiolar adenoma/carcinoma	3.2 (Category 1) 1 (Category 3)	68	4.6×10^{-4}	1.5×10^{-3}
Male mice	Alveolar/bronchiolar adenoma/carcinoma	3.4 (Category 1) 1 (Category 3)	41	7.2×10^{-4}	2.4×10^{-3}
Male mice	Alveolar/bronchiolar carcinoma	3.4 (Category 1) 1 (Category 3)	80	3.7×10^{-4}	1.2×10^{-3}
Male mice	Haderian gland adenoma	1 (Category 3)	86	NA	1.2×10^{-3}
Male mice	Spleen hemangiosarcoma	1 (Category 3)	75	NA	1.3×10^{-3}
Male mice	Spleen hemangioma or hemangiosarcoma	1 (Category 3)	66	NA	1.5×10^{-3}
Male rats	Nasal	0.2 (Category 1) 1 (Category 3)	102	4.9×10^{-3}	9.8×10^{-4}

Female rats	Nasal	0.2 (Category 1) 1 (Category 3)	241	2.1×10^{-3}	4.1×10^{-4}
NA – Not applicable					

The unit risk values for the different species and tumor types in Table 6 range from 3.7×10^{-4} to 4.9×10^{-3} $(mg/m^3)^{-1}$. The data from nasal tumors in male rats using the Category 1 gas methodology provides the highest estimate of the unit risk value (4.9×10^{-3} $(mg/m^3)^{-1}$), and is selected to determine the IRSL and SRSL. This unit risk value is only two fold higher than the unit risk values for lung tumors in male mice, the highest unit risk determined from the Category 3 gas methodology. It is also approximately three fold higher than the unit risk based on lung tumors in female mice and spleen hemangiomas or hemangiosarcomas in male mice, both derived using the Category 3 gas dosimetry. Rounding to one significant figure the unit risk value based on nasal tumors in male rats is 5×10^{-3} $(mg/m^3)^{-1}$ or 5×10^{-6} $(\mu g/m^3)^{-1}$. It may be noted that this IUR is approximately four fold lower than the IUR (1.9×10^{-5} $(\mu g/m^3)^{-1}$) that was utilized by the EPA for the 2005 NATA, and based on a conversion from the oral cancer slope factor derived from the NTP study. Using the unit risk value from the nasal tumors in male rats, the IRSL and SRSL are determined as follows:

$$IRSL = \frac{1x10^{-6}}{5x10^{-6}\left(\mu g/m^3\right)^{-1}} = 0.2\,\mu g/m^3$$

$$SRSL = \frac{1x10^{-5}}{5x10^{-6}\left(\mu g/m^3\right)^{-1}} = 2\,\mu g/m^3$$

The above derivation of the IRSL and SRSL for 1,2-dichloropropane is based upon the methodology specified in Rule 229(1)(c) of the Michigan Air Pollution Control Rules.

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