MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for 2-Nitropropane (CAS No. 79-46-9)

FROM: Cathy Simon, Toxics Unit, Air Quality Division

DATE: July 30, 2012

SUBJECT: Evaluation of Cancer Risk Screening Levels for 2-Nitropropane

Background

In July 1991, the Michigan Department of Environmental Quality (MDEQ), Air Quality Division (AQD) established an acceptable ambient concentration (AAC) of 3.7×10^{-4} µg/m^3 for 2-nitropropane, representing a concentration in air corresponding to an increased cancer risk of 1×10^{-6}. Following promulgation of the Michigan Air Toxic Rules in April 1992, new terminology was introduced, and this AAC became the initial risk screening level (IRSL). At that time, a secondary risk screening level (SRSL) of 3.7×10^{-3} µg/m^3, corresponding to an increased cancer risk of 1×10^{-5}, was also established, as well as an initial threshold concentration (ITSL) of 20 µg/m^3 (24 hour averaging time). The ITSL was derived from the United States Environmental Protection Agency (US EPA) reference concentration (RfC) available in the EPA's Integrated Risk Information System (IRIS) database at that time.

When the IRSL and SRSL were established by the AQD, there was no cancer risk assessment for 2-nitropropane in the IRIS database, although an inhalation unit risk value of 2.7×10^{-3} (µg/m^3)$^{-1}$ was listed in the version of the US EPA's *Health Effects Assessment Summary Tables* (HEAST) available at that time (MDEQ, 1991). This unit risk value is also listed in the last updated version of HEAST (EPA, 1997). The unit risk value from HEAST was essentially identical to the unit risk value of 2.8×10^{-3} (µg/m^3)$^{-1}$ derived by the AQD in 1991. Both unit risk values were derived from the same key study, using similar methodologies. The inhalation unit risk value from HEAST (EPA, 1997) is also the same value provided in the January 2000 version of the *Hazard Summary for 2-Nitropropane* available on the EPA's web site (EPA, 2012a).

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 2-nitropropane, the US EPA OAQPS has selected a unit risk value of 5.6×10^{-6} (µg/m^3)$^{-1}$, a value developed by the Health Council of the Netherlands (HCN, 1999). The US EPA OAQPS stated the basis for selecting the HCN unit risk value over the value in HEAST, was that HEAST value did not "reflect the most recent studies and analysis methods." (EPA, 2012c).

It should also be noted that as of the current date, the US EPA IRIS database contains no evaluation of the carcinogenic potential of 2-nitropropane. The most recent entry in this data-base for 2-nitropropane, is the inhalation RfC which was established in 1991 (EPA, 2012d).

An evaluation of the risk assessment done by the HCN, as well as a re-evaluation of the AQD and US EPA HEAST risk assessments was undertaken to determine if any change to the currently established IRSL and SRSL was warranted. This evaluation focused only on review of information related to the cancer risk assessments for 2-nitropropane, 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 International Agency for Research on Cancer (IARC), National Toxicology Program (NTP), US EPA, World Health Organization (WHO) and the HCN.

While no independent comprehensive update of the scientific literature was performed as part of this review, the US EPA did undertake a fairly recent review of the scientific literature for 2-nitropropane as part of the High Production Volume (HPV) Challenge Program (EPA, 2011). Under this program, producers and importers of HPV chemicals voluntarily sponsored chemicals. Sponsorship included preparing summaries of existing toxicity data, and developing test plans where data were determined to be inadequate to evaluate the hazards associated with exposure to each chemical. The data summary for 2-nitropropane was submitted to the US EPA in 2005, by Dow Chemical Company, the sponsoring company. The US EPA's Office of Pollution Prevention and Toxics (OPPT) prepared a screening level hazard characterization based on the submittal of this data, which also included an update of the scientific literature from one year prior to the HPV submission to around 2011 (EPA, 2011). The hazard characterization revealed no new animal cancer bioassays or epidemiological studies to evaluate the carcinogenic potential of 2-nitropropane, since the IRSL and SRSL were established in 1992 by the AQD.

Carcinogenicity Data

Two published studies are available that show 2-nitropropane to be carcinogenic in rats, one by oral exposure (Fiala et al, 1987), and the other via inhalation (Lewis et al, 1979). In both studies, 2-nitropropane caused hepatocellular carcinomas in exposed animals. In the oral study, hepatocellular carcinomas occurred in 22/22 rats administered 2-nitropropane by gavage at a dose level of 1 mmol/kg three times per week for 16 weeks, compared to 0/29 control animals (Fiala et al, 1987). One control animal in this study did develop a benign liver tumor (adenoma). In the inhalation study, groups of 50 male Sprague-Dawley rats were exposed to 2-nitropropane at concentrations of 0, 27, or 207 ppm for 7 hours/day, 5 days/week for up to 6 months. Interim sacrifices of 10 animals per group were made at 2 days, 10 days, 1 month, 3 months, and 6 months (final sacrifice). For the animals exposed the full 6 months, the incidence of hepatocellular carcinomas was 0/10, 0/10, and 10/10 for the controls, low dose, and high dose groups, respectively (Lewis et al, 1979).

In a series of experiments conducted for ANGUS Chemical Company, Sprague-Dawley rats (125/sex/group) were exposed to 0, 25, 100, or 200 ppm of 2-nitropropane for 7 hours/day, 5 days/week for up to 22 months depending on the exposure concentration. Only the results from the 25 ppm exposure regime have been published (Griffin et al, 1980; 1981), whereas limited results from the 100 and 200 ppm exposure groups have been briefly summarized elsewhere (Griffin et al, 1980; HCN, 1999; EPA, 2012d; Dow Chemical Company, 2005). In the study in which rats were exposed to 25 ppm, interim sacrifices of 10 animals per group occurred at 1 month, 3 months, 6 months, and 12 months of exposure. In addition, at 3 months and 12 months, 10 animals per group were removed from exposure and remained exposure free until the end of the study. All surviving animals were sacrificed 22 months after the beginning of exposure. A similar protocol was supposedly used for the higher dose animals in the unpublished studies, although total exposure duration was 18 months for the 100 ppm group,

and 6 months for the 200 ppm group. (EPA, 2012d). In the 25 ppm dose group, no increased incidence of tumors was observed; however, focal areas of hepatic, cellular nodules were observed in 3/250 animals in the control group, and 13/249 animals in the exposed group. No breakdown by sex or duration of exposure for the incidence of these lesions was provided (Griffin et al, 1980). In the 200 ppm group exposed for 6 months to 2-nitropropane, and then held for 6 months without exposure, it was reported that 9/10 rats developed liver tumors (Griffin et al, 1980), although again the details of this study have not been published. Griffin et al (1980) also reported that in the rats exposed to 2-nitropropane at 100 ppm, hepatocellular carcinomas occurred in males after 12 months of exposure, and females after 18 months of exposure, although no details on specific incidences were provided.

One retrospective epidemiological study of mortality of 1481 workers involved in the manufacture of 2-nitropropane in the US was available to the IARC (1982; 1999) for review as an abstract. No excess mortality from any specific cancer site was observed; however, the IARC found several shortcomings with this study and concluded that it was inadequate for the evaluation of carcinogenic potential for humans.

Genotoxicity

The genotoxicity of 2-nitropropane has been reviewed by the IARC (1999), the WHO (1992), the HCN (1999), and Environment Canada and Health Canada (EC/HC, 2010). Positive results have been obtained for several different endpoints in a number of different test systems. Gene mutations have been observed *in vitro* in bacterial systems with and without metabolic activation, as well as in Chinese hamster cells and rat hepatoma cells. Unscheduled DNA synthesis occurred in human, rat, and mouse hepatocytes *in vitro*. Chromosomal aberrations and sister chromatid exchanges were seen in cultured human lymphocytes. Micronuclei were also produced in three separate rat hepatoma lines *in vitro* and in rat hepatocytes *in vivo*. Other positive *in vivo* findings include DNA strand breaks in the liver and bone marrow of rats, as well as the formation of 8-amino- and 8-hydroxydeoxyguanosine in rat liver DNA, and 8-amino- and 8-hydroxyguanosine in rat liver RNA.

Carcinogenicity Summary

The overall carcinogenic potential of 2-nitropropane has been evaluated by several US and international organizations. The IARC (1999) has concluded that 2-nitropropane is possibly carcinogenic to humans (Group 2B), based on inadequate evidence in humans and sufficient evidence in animals. Similarly, the Organization for Economic Co-operation and Development (OECD, 2010) concluded that "2-nitropropane possesses properties indicating a hazard for the human health endpoints, carcinogenicity and genotoxicity." The National Toxicology Program concluded that 2-nitropropane is "reasonably anticipated to be a human carcinogen" in the *Report on Carcinogens, Twelfth Edition* (NTP, 2011). The US EPA has classified 2-nitropropane as a Group B2, probable human carcinogen (EPA, 2012a). Based on the positive findings in the laboratory animal studies (Lewis, 1979 and Fiala, 1987), 2-nitropropane meets the definition of carcinogen found in Rule 103(c) of the Michigan Air Pollution Control Rules.

Review of Cancer Risk Assessments

As mentioned above, inhalation unit risk values have been developed by the MDEQ AQD, the US EPA, and the HCN, all based upon the results from animal bioassays. These values are summarized in Table 1.

Table 1. Unit Risk Values for 2-Nitropropane

Unit Risk $(\mu g/m^3)^{-1}$	Source
$2.8x10^{-3}$	MDEQ, 1991
$2.7x10^{-3}$	EPA, 1997
$5.6x10^{-6}$	HCN, 1999[a]

[a]This value is also used by the US EPA OAQPS for risk assessments of hazardous air pollutants (EPA,2012b).

The unit risk value of 2.8×10^{-3} $(\mu g/m^3)^{-1}$ developed by the MDEQ AQD is based upon the study by Lewis et al (1979). A linearized multistage model was fit to the dose response data from this study to derive the cancer potency or unit risk value. Since the tumor incidence in the highest dose group was 100% (10/10), and the multistage model cannot be adequately fit with such dose response data, an incidence of 9/10 was used for this dose group. Prior to modeling, doses were adjusted to a time weighted average value to take into account a less than continuous exposure regime by multiplying each dose by a factor of 5 days/7 days and 7 hours/24 hours. After modeling, adjustments were made to the cancer potency value by multiplying by a factor of 64 to account less than lifetime exposure (6 months exposure) for the test animals, and by a species scaling factor of 5.85 to account for differences between humans and rats (MDEQ, 1991). These factors were determined as follows:

$$\left(L/Le\right)^3 = 64$$

$$\sqrt[3]{W_h/W_a} = 5.85$$

Where:

$L =$ Average lifespan of the test animal (24 months)

$Le =$ Experiment duration (6 months)

$W_h =$ Average weight of a human (70 kg)

$W_a =$ Weight of the test animal (0.35 kg)

The US EPA unit risk value of 2.7×10^{-3} $(\mu g/m^3)^{-1}$ was also derived from the study by Lewis et al (1979). Unfortunately, HEAST (EPA, 1997) does not provide specific information as to the methodology used in the derivation of the unit risk value. Considering the similarity to the MDEQ AQD value, and that the cancer risk assessment methodology used by the AQD was consistent with the US EPA methodology at the time, it is likely both unit risk values were derived in a similar manner. Supporting this conclusion is the US EPA's derivation of an oral unit risk value for 2- nitropropane (EPA, 1985), which was based upon the same study (Lewis et al, 1979) used for the inhalation unit risk value. For this assessment, after transforming the inhalation doses to oral doses, the US EPA used the same methodology as the MDEQ AQD, with one other adjustment. In addition to using an adjusted response rate of 9/10 for the high dose group, the US EPA also adjusted the dose by a factor of 9/10.

In contrast to the unit risk values derived by the US EPA (1985, 1997) and the MDEQ AQD (1991), which used the study by Lewis et al (1979), the HCN used the study by Griffin et al (1980;1981) as the starting point for derivation of a unit risk value. As discussed above, the Griffin et al study did not result in any increased tumor incidence in rats exposed to 25 ppm of 2-nitropropane. Instead, the HCN used the combined incidence of focal areas of hepatic cellular

nodules in male and female rats at 25 ppm (78 mg/m^3) as the basis for developing a unit risk value. The HCN (1999) assumed a simple linear dose response relationship and calculated the unit risk value as follows:

$$I = \frac{I_e - I_c}{C \times \left(X_{po}/L\right) \times \left(X_{pe}/L\right) \times \left(\exp osure\ hours\ per\ day/24\right) \times \left(esposure\ days\ per\ week/7\right)}$$

$$I = \frac{\left(13/249\right) - \left(3/250\right)}{\left(78\ mg/m^3\right) \times \left(665/1000\right) \times \left(665/1000\right) \times \left(7/24\right) \times \left(5/7\right)} = 5.6 \times 10^{-3}\ (mg/m^3)^{-1}$$

$I = 5.6 \times 10^{-6}\ (\mu g/m^3)^{-1}$

Where:

I = the carcinogenic activity attributable to the exposure to the substance per unit daily dose under lifespan conditions, assuming a linear dose response relationship.

I_e and I_c = incidence of tumor bearing animals in exposed and control animals, respectively.

X_{po} = exposure period, X_{pe} = experimental period

L = standard lifespan for the animals in question (assumed to be 1000 days for the rat).

Evaluation of Cancer Risk Assessments

In reviewing the unit risk value derived by the HCN, three issues were identified that needed further evaluation. These included: 1) the appropriateness of using lesions described as "focal areas of hepatic, cellular nodules;" 2) the extrapolation model; and 3) model inputs and adjustments.

The HCN used the incidence of hepatic cellular nodules from the study by Griffin et al (1980; 1981) to derive a unit risk value. Griffin et al (1980) stated that, "Gross and microscopic examination of liver tissue did not reveal any malignancies or significant pathologic changes in any of the male or female rats which could be attributed to exposure by inhalation of 25 ppm of 2-NP in a chronic regimen of 7 hrs. per day for 5 days per week, over a period of 22 months." With regards to a description of the focal areas of hepatic cellular nodules, Griffin et al (1980) further stated, "The cells in the nodular areas were generally hypertrophied, but nuclei were normal." Lesions described in such a manner have not typically been used in cancer risk assessments by federal or Michigan regulatory agencies.

It should be further noted that the study by Griffin et al (1980; 1981) has also been used by the US EPA to derive a reference concentration (RfC) for 2-nitropropane (EPA, 2012d). The US EPA identified the 25 ppm dose level as a lowest observable adverse effect level (LOAEL), based upon the finding of an increased incidence of slight hepatic congestion and focal areas of hepatocellular nodules in exposed animals.

Over the years, various terms have been used to describe proliferative lesions of the rat liver. This issue has been reviewed by the US EPA (1986) and the National Toxicology Program (Maronpot et al, 1986). Considering these reviews by the US EPA and the NTP, the author's description of the lesions (Griffin et al, 1980), and the identification of 25 ppm as a LOAEL for deriving an RfC (EPA, 2012d), it appears the focal areas of hepatic cellular nodules would not be considered cancerous, but may be considered pre-neoplastic lesions. While the use of such lesions in cancer risk assessment has not typically been done, this issue has been addressed by the US EPA in their *Guidelines for Carcinogen Risk Assessment* (EPA, 2005)*:*

> Cancer is a collection of several diseases that develop through cell and tissue changes over time. Dose-response assessment procedures based on tumor incidence have seldom taken into account the effects of key precursor events within the whole biological process due to lack of empirical data and understanding about these events. In this discussion, response data include measures of key precursor events considered integral to the carcinogenic process in addition to tumor incidence. These responses may include changes in DNA, chromosomes, or other key macromolecules; effects on growth signal transduction, including induction of hormonal changes; or physiological or toxic effects that include proliferative events diagnosed as precancerous but not pathology that is judged to be cancer. Analysis of such responses may be done along with that of tumor incidence to enhance the tumor dose-response analysis. If dose-response analysis of nontumor key events is more informative about the carcinogenic process for an agent, it can be used in lieu of, or in conjunction with, tumor incidence analysis for the overall dose-response assessment. (p. 3-2)

Other relevant sections from the EPA *Guidelines for Carcinogen Risk Assessment* (EPA, 2005) include the following:

> Quantitative data on precursors can be used in conjunction with, or in lieu of, data on tumor incidence to extend the dose-response curve to lower doses. Caution is used with rates of molecular events such as mutation or cell proliferation or signal transduction. Such rates can be difficult to relate to cell or tissue changes overall (emphasis added) (p. 3-15).

> *When good quality precursor data are available and are clearly tied to the mode of action of the compound of interest*, models that include both tumors and their precursors may be advantageous for deriving a POD. Such models can provide insight into quantitative relationships between tumors and precursors (see Section 3.2.2), possibly suggesting the precursor response level that is associated with a particular tumor response level. The goal is to use precursor data to extend the observed range below what can be observed in tumor studies. EPA is continuing to examine this issue and anticipates that findings and conclusions may result in supplemental guidance to these cancer guidelines. If the precursor data are drawn from small samples or if the quantitative relationship between tumors and precursors is not well defined, then the tumor data will provide a more reliable POD (emphasis added) (pp. 3-17-18).

With regard to proliferative lesions in the rat liver, the EPA (1986) has found that analysis of foci of cellular alteration are useful as part of the "…hazard identification step of the of the carcinogenic risk assessment. Dose-response and time-to-occurrence parameters are useful in this qualitative (emphasis added) analysis." Regarding neoplastic nodules in the rat liver, the EPA (1986) also states:

> Neoplastic nodules are increased in animals receiving carcinogens, and that occurrence is almost always associated with an increase in hepatocellular carcinoma. However, it appears that there is not a one-to-one relationship between nodules and carcinomas. Although some nodules may have "malignant potential," others may only be "hyperplastic" lesions. Still other nodules may regress following cessation of carcinogenic administration.
>
> Therefore, the exact contribution of neoplastic nodules to the overall incidence of hepatocellular tumors in the rat is unclear at this time. (p. 16)

Considering the above information, and the unclear quantitative relationship between the focal areas of hepatic, cellular nodules observed in rats exposed to 2-nitropropane and the development of hepatocellular carcinomas, the use of the pre-neoplastic data from Griffin et al (1980; 1981) is less supported than the tumor data from Lewis et al (1979).

Other problems with use of the Griffin et al (1980; 1981) study, is that no specific details are given as to the timeframe of development for the focal areas of hepatic, cellular nodules. The derivation of a unit risk value by the HCN (1999) assumed all animals (125 per sex per group) were at equal risk and exposed for the full 22 months of the experiment. Based on the study protocol, which involved both interim sacrifices, and stop exposure-recovery groups, the maximum number of animals that could have been exposed the full 22 months would be 65 per sex per group. Based on the number of animals for which liver weight was determined at 22 months, the actual numbers of animals surviving this full exposure regime were as follows: male control group (63); male exposed group (27); female control group (48); female exposed group (29). Modeling the dose response data based on the number of animals at the start of the experiment, rather than those alive at the end, would result in an underestimation of the unit risk value.

The HCN used a simple linear model in which a straight line was drawn from a single dose response data point to the origin. The slope of this line provided the unit risk value of 5.6×10^{-6} $(\mu g/m^3)^{-1}$. Similarities of this approach, to that in the US EPA *Guidelines for Carcinogenic Risk Assessment* (EPA 2005), include the straight line extrapolation from a point of departure (POD). This approach, however, lacks other important elements of the EPA methodology, including the use of more than one data point to provide a better estimate of the dose response curve, and the use of some statistical upper bound on risk or lower bound on dose to account for uncertainties related to experimental variability, and to provide an appropriate measure of confidence that risk is not underestimated. EPA's *Guidelines for Carcinogenic Risk Assessme*nt and the *Benchmark Dose Technical Guidance* address this issue as follows:

> The POD for extrapolating the relationship to environmental exposure levels of interest, when the latter are outside the range of observed data, is generally the lower 95% confidence limit on the lowest dose level that can be supported for modeling by the data. (EPA, 2005, p. 1-14)
>
> This document recommends use of the 95% lower bound on a BMD (i.e., the BMDL) as the POD for noncancer effects, as described by U.S. EPA (2002a). Using the lower bound accounts for the experimental variability inherent in a given study and assures (with 95% confidence for the experimental context) that the selected BMR is not exceeded (see Section 2.2 6 for discussion of the BMR). The use of a 95% bound is also consistent with what has traditionally been used for cancer risk estimates, and the

general use of the BMDL as the POD is noted in U.S. EPA's cancer guidelines. (EPA, 2012e, p.5-6):

Conclusion

Considering all of the above information, the unit risk value developed by the HCN is not recommended for use in deriving the IRSL and SRSL for 2-nitropropane. The current IRSL and SRSL were derived pursuant to the methodologies specified in Rule 231 of the Michigan Air Pollution Control Rules. Rule 229(1)(c) allows the use of any other alternative methodology which can be demonstrated to be more appropriate based on biological grounds and which is supported by the scientific data. The methodology used by the HCN (1999) does not meet the provisions of this rule, and therefore the existing IRSL of 3.7×10^{-4} µg/m^3 and the existing SRSL of 3.7×10^{-3} µg/m^3 are recommended for continued use at this time until additional data become available to support alternative values determined pursuant to Rule 229(1) of the Michigan Air Pollution Control Rules.

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