MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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August 28, 2013

To: File for 2-Nitrophenol (CAS No. 88-75-5)

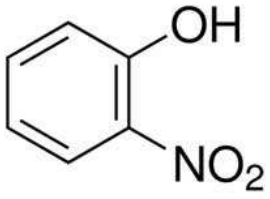
From: Michael Depa, Air Quality Division, Toxics Unit

Subject: Screening Level

The acute Initial Threshold Screening Level (ITSL) for 2-nitrophenol is 18 µg/m³ with 24-hr averaging time.

The following information sources were searched in order to support the development of screening levels for 2-nitrophenol: United States Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS), the Registry of Toxic Effects of Chemical Substances (RTECS, 2013), the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLV), National Institute of Occupational Safety and Health (NIOSH) Pocket Guide to Hazardous Chemicals, Environmental Protection Bureau Library, International Agency for Research on Cancer Monographs, National Library of Medicine, Health Effects Assessment Summary Tables, and National Toxicology Program Status Report. The EPA has not established a reference concentration (RfC) for 2-nitrophenol; however, there is a provisional peer review toxicity value (PPRTV) (see Appendix B). California Office of Environmental Health Hazard Assessment (Cal-OEHHA) has not established reference exposure levels for 2-nitrophenol. The U.S. Agency for Toxic Substances and Disease Registry (ATSDR) has not established minimal risk levels for 2-nitrophenol. The ACGIH has not established a TLV. See below for chemical and physical information for 2-nitrophenol.

Chemical and Physical Information for 2-nitrophenol



Physical Property	Value	Units
Melting Point	44.8	deg C
Boiling Point	216	deg C
Water Solubility	2500	mg/L @ 25°C
Vapor Pressure	0.113	mm Hg @ 25°C
Henry's Law Constant	1.28E-05	atm-m^3/mole @ 20°C

From: ChemID Plus (2013)

Inhalation Toxicity

Available information for repeated inhalation exposure is limited to results of a single 28-day study (Hazleton Laboratories, 1984). Groups of 7-week-old Sprague-Dawley rats (15/sex/group) were exposed to 2-nitrophenol vapors at target concentrations of 0, 5, 30 or 60 mg/m^3 for 6 hours/day, 5 days/week for 4 weeks. All rats were subjected to ophthalmoscopic examinations prior to initiation of exposures and immediately preceding terminal sacrifice. Each animal was observed twice daily (pre- and postexposure during the week; morning and afternoon on weekends) for mortality and morbidity. Clinical signs and body weights and weight gains were assessed throughout the study. Following the 11th and 20th exposures, blood was collected by orbital sinus puncture from 10 rats/sex/group and analyzed for methemoglobin concentrations. At termination of the study (day 29), blood was collected via the abdominal aorta from 10 anesthetized rats/sex/group for hematology and serum chemistry. At necropsy, all rats were subjected to comprehensive gross examinations and organ weights were recorded. Comprehensive histopathological examinations were performed on 10 rats/sex in the 0 and 60 mg/m^3 exposure groups. Nasal turbinates were examined histopathologically in 10 rats/sex of each exposure group.

Overall mean analytical concentrations deviated from the target concentrations by 0.0, +8.3 and +2.5% for the 5, 30 and 60 mg/m^3 exposure groups, respectively (Hazleton Laboratories, 1984). The aerosol content of the exposure chambers was not significantly different from that present in room air. No significant exposure-related ocular lesions were apparent in any of the rats. No animals died during the study. No apparent exposure-related trends in clinical signs were apparent with the exception of yellow stains on the fur of all 2-nitrophenol exposed animals. There were no statistically significant exposure-related effects on mean body weight or weight gain. A statistically significant increase in methemoglobin levels was noted in male and female rats of the 5 mg/m^3 group analyzed on day 15 of the study. However, when animals were analyzed on day 28, the methemoglobin levels were similar to controls. No statistically significant increases were found in the higher dose groups. The change, compared with controls, in methemoglobin levels in treated animals of the low dose groups, while exhibiting statistical significance, was not considered biologically significant. Hematology and clinical chemistry findings were unremarkable. Gross pathology revealed no consistent exposure-related trends. Small increases in liver weight, liver/brain weight ratio and spleen/brain weight ratio were seen in the 5 mg/m^3 group females, but were not observed in females at higher doses or in any of the treated males. Histopathological examinations revealed squamous metaplasia in epithelium of the nasoturbinates and maxilloturbinates in 1/10, 0/10, 10/10 and 10/10 male rats and 1/10, 1/10, 9/10 and 10/10 female rats of the 0, 5, 30 and 60 mg/m^3 exposure groups, respectively. No other apparent exposure-related effects were observed. On the basis of the nasal lesions, this study identified a no-observed-adverse-effect-level (NOAEL) of 5 mg/m^3 and a LOAEL of 30 mg/m^3 for 2-nitrophenol in rats.

Additional toxicological studies were performed using either oral or skin routes of exposure. These studies are summarized in Appendix B.

Derivation of the ITSL

The dose-response relationship observed in the 28-day rat inhalation study (Hazleton Laboratories, 1984) described above was used as input data for the Benchmark Dose Software (BMDS)(US EPA, 2013). The 10% extra risk was used as the Benchmark Response. The female rat incidence rates of 1/10, 1/10, 9/10 and 10/10 were used as

input for control, low, medium and high doses (0, 1.25, 7.5, and 15 mg/m³; respectively, for duration adjusted dose; 6hrs/24hrs). The results of the BMDS analysis are shown in Table 1. The complete BMDS Output Report is attached in Appendix A of this memo.

Table 1. Summary of Benchmark Dose Software Modeling Results

Model Type (comment includes graph)	BMDL	p-value	AIC	Model Warnings	BMDS Wizard* Bin Placement	BMDS Wizard* Recommendation
Gamma	**0.525**	1.	23.505	None	Viable	**Recommended (lowest BMDL)**
Dichotomous-Hill	4.79	1.	23.505	Warning: BMDL computation is at best imprecise for these data	Viable	Alternate
Logistic	0.841	0.859	23.808	None	Viable	Alternate
LogLogistic	0.739	1.	23.505	None	Viable	Alternate
Probit	error	error	error		Unusable	***Unusable***
LogProbit	error	error	error		Unusable	***Unusable***
Weibull	error	error	error		Unusable	***Unusable***
Quantal-Linear	error	error	error		Unusable	***Unusable***
Multistage 3°	error	error	error		Unusable	***Unusable***

*The "Wizard" is an excel spreadsheet, called the "BMDS Wizard," developed by ICF International (2013) in order to automate some of the steps involved in entering and processing dose-response data. The Wizard also evaluates how well the models fit the curve, and recommends the best model. The Wizard provides text for its recommendations. The BMDS Wizard is bundled with the most current BMDS software downloaded from U.S. EPA's Benchmark Dose website (http://www.epa.gov/ncea/bmds/).
**Best fitting model, chosen as the point of departure (POD).

Because the nasal effects were the only adverse effect observed, the human equivalent concentration (HEC) was assumed to be the same as the animal duration adjusted $BMDL_{10}$ (i.e., the dosimetric adjustment factor = 1). This approach follows the recommendation of EPA (2012), where extrarespiratory effects between humans and rats, "are close to or greater than 1:1."

Using the EPA (2011) guidance on using the benchmark dose methodology, the duration adjusted for continuous exposure (i.e., x 6hrs/24hrs) $BMDL_{10\text{-}ADJ}$ of 0.525 mg/m³ was chosen as the point of departure (POD). The acute ITSL is then calculated as follows:

$ITSL = POD/(UF_H \times UF_A)$

Where UF_H is an uncertainty factor of 10 for sensitive humans
UF_A is 3 for interspecies variability

$ITSL = (0.525\ mg/m^3)/30$

$ITSL = 0.0175\ mg/m^3 \times 1000\ \mu g/1mg$

$ITSL = 18\ \mu g/m^3$

A 10-fold UF_H is used to account for variation in sensitivity among members of the human population (i.e., interindividual variability).

An UF_A of 3 is used to account for uncertainty in extrapolating from laboratory animals to humans (i.e., interspecies variability). No information is available regarding the toxicity of 2-nitrophenol in humans. No comparative information is available regarding the toxicokinetics or toxicodynamics of 2-nitrophenol in animals and humans. However, the default dosimetric calculation for deriving an HEC accounts for the uncertainty in the variability in toxicokinetics of humans and rats. A 3-fold UF is applied to account for uncertainty in species differences for toxicodynamics (U.S. EPA, 1994).

Instead of using the $BMCL_{10\text{-}ADJ}$ as the POD it is possible to use the NOAEL of 5 mg/m³ from the Hazelton Labs (1984) study. The intermittent exposure was adjusted to account for a continuous exposure scenario as follows:

$NOAEL_{ADJ}$ = NOAEL x 6 hours/24 hours
$NOAEL_{ADJ}$ = 5 mg/m³ x 6/24 = 1.25 mg/m³

$NOAEL_{HEC}$ (human equivalent concentration) is calculated by multiplying the $NOAEL_{ADJ}$ by the dosimetric adjustment factor; in this case a value of 1 was used. Applying the same uncertainty factors as were used in the above equation using the BMCL, an ITSL can be calculated as follows:

$ITSL = NOAEL_{HEC}/UF_A \times UF_H$

ITSL = 1.25 mg/m³/(3 x 10)

ITSL = 0.0417 mg/m³ x 1000µg/mg

ITSL = 42 µg/m³

Since the ITSL was developed as an acute health benchmark, no uncertainty for duration extrapolation was necessary, since the acute ITSL averaging time is 24 hours. The toxicopharmacology of 4 weeks of exposure very likely over-estimates the toxic potential of a single 24-hr exposure. This increased confidence in the protectiveness of the acute ITSL is not specifically accounted for in its derivation. Still, an acute ITSL with a 24-hr averaging time is meant to be applicable to industrial air emissions which are permitted to occur indefinitely, including a likely scenario of long-term operations. Because of the lack of information regarding dose-response effects during a chronic exposure scenario, there remains some residual uncertainty in the protectiveness of the derived ITSLs above. However, the BMD method reduces this uncertainty because it employs statistical methods that fit a curve to the specific shape of the dose-response data, as well as using the 95% lower-bound confidence limit on the 10% response rate. For this reason, and that the BMDS is recommended by EPA as “state-of-the-art” risk assessment, the Benchmark Dose methodology was selected to derive the acute ITSL for 2-nitrophenol. Therefore, the acute ITSL for 2-nitrophenol is 18 µg/m³ with a 24-hour averaging time.

References

ChemID Plus. 2013. 2-Nitrophenol. RN: 88-75-5 (Full Record). National Library of Medicine, 8600 Rockville Pike, Bethesda, MD 20894. Queried via TOXNET. http://chem.sis.nlm.nih.gov/chemidplus/

Hazleton Laboratories. 1984. Subacute inhalation toxicity study in rats. o-Nitrophenol. Submitted to U.S. EPA under TSCA Section 8ECP. EPA Document No. 88-920007617.

ICF International (2013) ICF BMDS Wizard, Beta Version 1.7 March 18, 2013. http://www.icfi.com/insights/products-and-tools/bmds-wizard

U.S. EPA (Environmental Protection Agency). 1994. Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. U.S. Environmental Protection Agency, Office of Research and Development, Office of Health and Environmental Assessment, Washington, DC, EPA/600/8-90/066F.

U.S. EPA. 2007. Provisional Peer Reviewed Toxicity Values for 2-Nitrophenol (CAS 88-75-5) Superfund Health Risk Technical Support Center, National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Cincinnati, OH 45268. 9-20-2007. http://hhpprtv.ornl.gov/issue_papers/Nitrophenol2.pdf

U.S. EPA. 2012. Advances in Inhalation Gas Dosimetry for Derivation of a Reference Concentration (RfC) and Use in Risk Assessment (Final Report). ORD; NCEA-RTP, U.S. Environmental Protection Agency, Washington, DC, EPA/600/R-12/044. http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=508055.

U.S. EPA. 2013. Benchmark Dose Software (BMDS) Version 2.4 R70 [Build: 04/01/2013]. National Center for Environmental Assessment. Available from: http://www.epa.gov/NCEA/bmds/index.html

Appendix A
BMDS Output Report

Study and Design: 28-day inhalation study (Hazleton Laboratories, 1984). Groups of 7-week-old Sprague-Dawley rats (15/sex/group) were exposed to 2-nitrophenol vapors at target concentrations of 0, 5, 30 or 60 mg/m^3 for 6 hours/day, 5 days/week for 4 weeks.

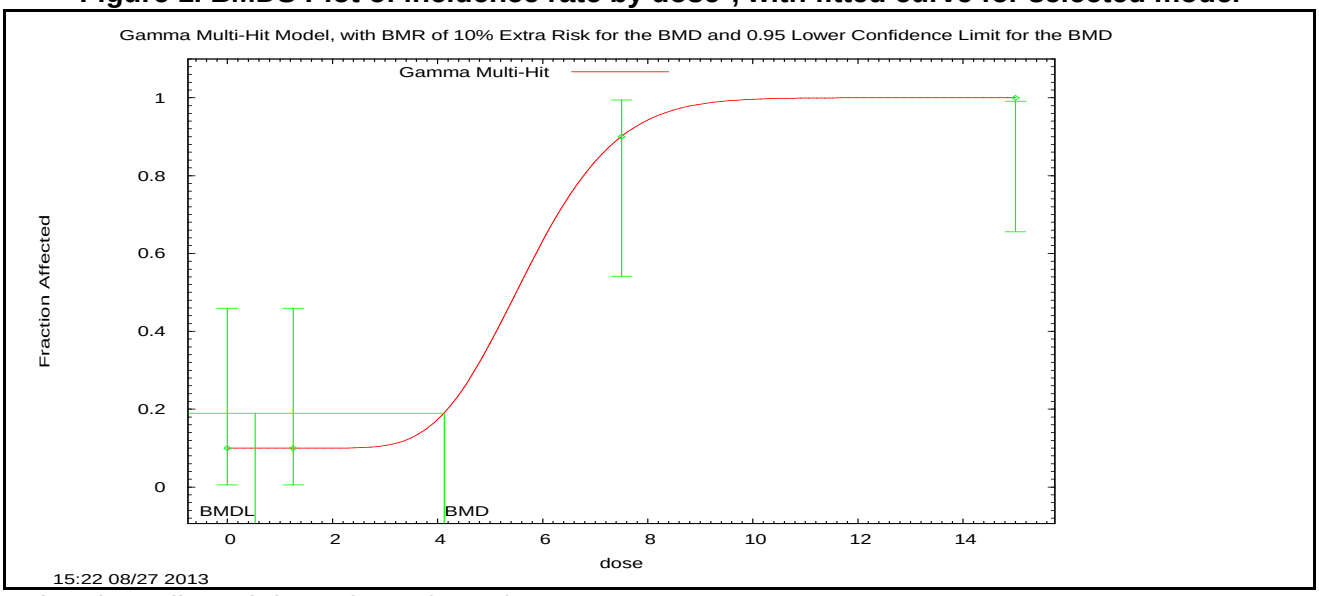
Benchmark Dose Software (BMDS)(EPA, 2013) Summary of Nasal Squamous Metaplasia (Hazleton Labs, 1984)

Table 1. BMDS Model predictions for Nasal Squamous Metaplasia (Hazleton Labs 1984)

Model[a]	Goodness of fit		$BMD_{10\%}$ (mg/m^3)	$BMDL_{10\%}$ (mg/m^3)	Basis for model selection
	p-value	AIC			
Gamma	**1.000**	**23.505**	**4.13**	**0.525**	**Lowest BMDL**
Dichotomous-Hill	1.000	23.505	5.91	4.79	
Logistic	0.859	23.808	1.53	0.841	
LogLogistic	1.000	23.505	5.91	0.739	
Probit[b] LogProbit[b] Weibull[b] Quantal-Linear[b] Multistage 3°[b]	Failed	Failed	Failed	Failed	

[a] Selected model in bold; scaled residuals for selected model for doses 0, 1.25, 7.5, and 15 mg/m^3 were -0.000, -0.000, -0.000, and 0.002, respectively.
[b] BMD or BMDL computation failed for this model.

Figure 1. BMDS Plot of incidence rate by dose*, with fitted curve for selected model



*duration adjusted dose shown in mg/m^3

Gamma Model. (Version: 2.16; Date: 2/28/2013)
The form of the probability function is: P[response]= background+(1-background)*CumGamma[slope*dose,power], where CumGamma(.) is the cummulative Gamma distribution function
Power parameter is restricted as power >=1

Benchmark Dose Computation.
BMR = 10% Extra risk
BMD = 4.1275
BMDL at the 95% confidence level = 0.524644

Parameter Estimates

Variable	Estimate	Default Initial Parameter Values
Background	0.1	0.166667
Slope	3.1064	0.192751
Power	18	1.35287

Analysis of Deviance Table

Model	Log (likelihood)	# Param's	Deviance	Test d.f.	p-value
Full model	-9.75249	4			
Fitted model	-9.75249	2	0.0000104539	2	1
Reduced model	-27.6759	1	35.8468	3	<.0001

AIC: = 23.505

Goodness of Fit Table

Dose	Est. Prob.	Expected	Observed	Size	Scaled Resid
0	0.1	1	1	10	0
1.25	0.1	1	1	10	0
7.5	0.9	9	9	10	0
15	1	10	10	10	0.002

Chi^2 = 0 d.f = 2 P-value = 1

References:

U. S. EPA (Environmental Protection Agency), 2013. Benchmark Dose Software (BMDS) Version 2.4 R70 [Build: 04/01/2013]. National Center for Environmental Assessment. Available from: http://www.epa.gov/NCEA/bmds/index.html

Hazleton Laboratories. 1984. Subacute inhalation toxicity study in rats. o-Nitrophenol. Submitted to U.S. EPA under TSCA Section 8ECP. EPA Document No. 88-920007617.

Appendix B
Additional Toxicological Information from EPA (PPRTV)

Animal Studies
Oral Exposure.
Available repeated-dose oral studies consist of two limited 28-day gavage studies (Andrae et al., 1981; Koerdel et al., 1981; both in German) performed to evaluate OECD guideline 407 and a range-finding developmental toxicity study (IRDC, 1990).
Andrae et al. (1981) administered 2-nitrophenol to groups of Sprague-Dawley rats (10/sex/dose) at gavage doses of 0, 70, 210 or 630 mg/kg-day for 28 days. Because the original German report of this study was not available, information from the CICAD for mononitrophenols (WHO, 2000) was used to summarize the findings. Mid- and high-dose animals exhibited what was described by the WHO (2000) as locomotor inhibition for approximately 2 hours postdosing. Mortality rates were 1/10 in mid-dose males and 4/10 and 6/10 in high-dose males and females, respectively. Gross and histopathological examinations revealed pale liver in 7/20 low-dose rats (not reported by sex), hydropic liver cell swelling in 4/10 and 0/10 high-dose males and females, respectively, and vascular congestion of the liver in all high-dose male and female rats that died prior to terminal sacrifice. Fatty degeneration of the liver was noted in 6/20 control animals, 14/20 low-dose and 13/20 mid-dose rats, but not in high-dose rats. Other treatment-related effects, noted only at the highest dose level, included significantly increased alanine aminotransferase activity in males (data not reported), increased nephrosis in 2 and 5 males and females, respectively, testicular atrophy (1 male) and decreased spermatogenesis (2 males), and follicular atresia (4 females). This report did not contain information on hematological effects. WHO (2000) concluded that a NOAEL could not be determined for this study due to "unclear effects in the liver."

Koerdel et al. (1981) administered 2-nitrophenol to groups of rats (5/sex/dose) at gavage doses of 0, 22, 67 or 200 mg/kg-day for 28 days. The summary from WHO (2000) was used as the source of study details because the original study was not available. Reported treatment-related effects included decreased food intake in high-dose males and mid- and high-dose females, non-significantly depressed final body weight in all dosed animals, decreased absolute liver and kidney weights in mid-dose groups, increased relative testes weight in low- and mid-dose males (decreased in high-dose males) and increased absolute and relative adrenal weight in all dosed groups. Hematology, clinical chemistry and histopathological examinations gave no indication of treatment-related effects. The study did not show a clear dose-response relationship for any of the endpoints examined.

In a range-finding developmental toxicity study, groups of Charles River COBS CD rats (5 dams/group) were administered 2-nitrophenol (in corn oil) at gavage doses of 0, 50, 125, 250, 500, or 1000 mg/kg-day on days 6-15 of gestation (IRDC, 1990). Body weights were determined during the treatment period and clinical signs were noted. Uterine examinations were performed on gestation day 20. A single high-dose dam died, but cause of death was not determined. Excessive salivation was observed in two high-dose dams. Mean maternal body weight gains in the 0, 50, 125, 250, 500 and 1000 mg/kg-day dose groups were 8, 7, 5, 6, 1 and -8 grams, respectively, for the initial 4 days of treatment (gestation days 6-9) and 52, 56, 54, 55, 45 and 39 grams, respectively, for the entire treatment period (gestation days 6-15). The appearance and behavior of the 50 mg/kg-day group of dams were comparable to the control group. Dose-related increases in the incidence of yellow staining around the nose, mouth and anogenital area were observed at doses ≥125 mg/kg-day. Dose-related increases in the incidence of darkly colored urine (probably due to the

presence of the test chemical) occurred at doses ≥250 mg/kg-day. An increase in the number of early resorptions was observed in the highest dose group (2.3 versus 1.2 in controls), resulting in mean postimplantation loss of 13.8% compared to 8.2% in controls (statistical significance not reported). Among dams surviving until necropsy, no biologically significant treatment-related effects were seen. There were no biologically significant treatment-related effects on mean number of viable fetuses, implantations or corpora lutea. No data on hematological parameters were included in this study. This study assessed a limited number of potential adverse endpoints and is therefore of limited usefulness for risk assessment.

Other Studies

Limited genotoxicity data are available for 2-nitrophenol. The chemical produced negative results in the Ames test with Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 both in the presence and absence of rat liver S9 metabolic activation (Chiu et al., 1978; Dellarco and Prival, 1989; Haworth et al., 1983; Kawai et al., 1987; Koerdel et al., 1981; Massey et al., 1994; Shimizu and Yano, 1986; Suzuki et al., 1983). 2-Nitrophenol did not induce DNA breakage in λ phage DNA (Yamada et al., 1987) or increase reversions from streptomycin dependence to independence in Escherichia coli strain Sd-4-73 (Szybalski, 1958). Negative results were reported for mutagenic activity in post-meiotic and meiotic germ cells of male Drosophila melanogaster exposed to 2-nitrophenol via feeding (400-500 ppm) or injection (2500 or 5000 ppm) (Foureman et al., 1994).

2-Nitrophenol did not exhibit skin tumor-promoting action in mice receiving dermal applications of a 20% solution twice weekly for 12 weeks (Boutwell and Bosch, 1959).