MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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TO: File for Dipropylene Glycol n-Butyl Ether (CAS# 29911-28-2)

FROM: Keisha Williams, Air Quality Division (AQD) Toxics Unit

DATE: October 10, 2017

SUBJECT: Screening Level Update

The initial threshold screening level (ITSL) for dipropylene glycol n-butyl ether (DPnB) is 800 µg/m^3 (24-hour averaging time) based on the Michigan Department of Environmental Quality (MDEQ), Air Quality Division (AQD) Rule 336.1233 (1)[1] .

The chronic initial threshold screening level (ITSL) for exposure to dipropylene glycol n-butyl ether (DPnB) was previously 11 µg/m^3 (annual averaging time) based on the Michigan Department of Environmental Quality (MDEQ), Air Quality Division (AQD) Rule 336.1232 (1) (d). This ITSL was established on July 13, 1999 (MDEQ, 1999).

The following references and databases were searched to identify data for screening level derivation: United States Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS), the Registry of Toxic Effects of Chemical Substances, 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, MDEQ Library, International Agency for Research on Cancer Monographs, National Library of Medicine, Health Effects Assessment Summary Tables (HEAST), National Toxicology Program (NTP) Status Report, EPA Toxic Substances Control Act Test Submissions database, EPA Superfund Provisional Peer Reviewed Toxicity Values, EPA Acute Exposure Guideline Levels for Airborne Chemicals, EPA High Production Volume Database, United States Department of Labor Occupational Safety and Health Administration Permissible Exposure Limits, Spacecraft Maximum Allowable Concentrations, Agency for Toxic Substances and Disease Registry's (ATSDR's) Toxicological Profiles, California Office of Environmental Health Hazard Assessment's Reference Exposure Levels, Texas Commission on Environmental Quality Effects Screening Levels, Maximum Workplace Concentrations (Maximale Arbeitsplatzkonzentrationen) for Germany, EPA School Air Toxics Benchmarks, EPA National Air Toxics Assessment Benchmarks, World Health Organization Air Quality Guidelines, and European Chemicals Agency Registered Substances Dossiers.

Background Information

DPnB (Figure 1) is used as a solvent, and in coatings and cleaning products (Dow, 2012). Chemical properties are listed in Table 1.

[1] 336.1232. Air Pollution Control Rules in Michigan Administrative Code promulgated pursuant to Article II Pollution Control, Part 55 (Sections 324.5501-324.5542), Air Pollution Control, of the Natural Resources and Environmental Protection Act, 1994. PA 451, as amended (NREPA).

Figure 1. Chemical structure for DPnB

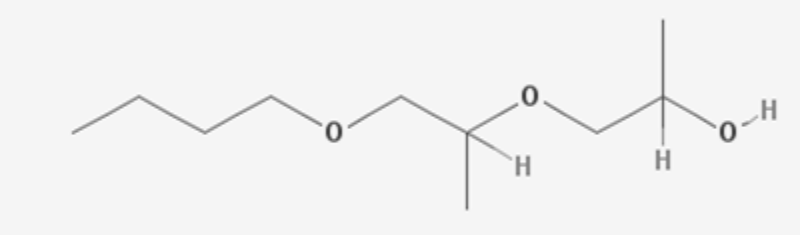


Table 1. Chemical and physical properties of DPnB

Molecular weight: 190.283 grams/mole
Boiling point: 417.2-422.6 °F
Vapor pressure: 0.06 mm Hg at 25°C (ECHA, 2017)
Physical state: liquid
Color: colorless

Reference: National Center for Biotechnology Information, https://pubchem.ncbi.nlm.nih.gov/compound/24752

DPnB has been shown to be a portal of entry irritant; and it is a possible nephrotoxicant (ECETOC, 2005; ECHA, 2017). Changes in liver weights have been noted in two inhalation studies; however, they were classified as adaptive changes and not adverse effects in both studies (MDEQ, 1999; ECHA, 2017). No long-term studies have been performed to evaluate the carcinogenicity of DPnB, and the weight of the evidence from genotoxicity studies suggest that DPnB is not genotoxic (ECETOC, 2005). As a result, DPnB is not classifiable as a carcinogen.

Only a couple of inhalation studies have been identified on which to derive ITSLs. The study published by Lomax et al. (1987) has previously been described and used to derive a chronic ITSL (MDEQ, 1999). With this updated review, the Cieszlak et al. (1991) study was identified.

The original (unpublished) report for the Cieszlak et al (1991) study has not yet been obtained from the source, but it has been requested. However, there is a sufficiently detailed summary from ECHA (2017) on which an ITSL can be derived. In this study, male and female Fischer 344 rats were exposed nose only to 0, 200, 810 or 2010 mg/m^3 DPnB (N=5 for each gender for each group) for “6 hours/day, 5 days week over a 2 week period for a total of 9 exposures” (ECHA, 2017). Mortality and morbidity were evaluated after each exposure. Body weights were collected approximately every 2-3 days, ophthalmic examinations were done at the start of the study and before necropsy. Hematology, clinical chemistry, and urinalyses were done before necropsy. Organs were weighed and processed for histological examination. “Organ weights (absolute and relative except testes), terminal body weights, hematologies, clinical chemistries and urinalysis (specific gravity) were evaluated using a 2-way (ANOVA) with the factors of sex and dose” (ECHA, 2017). Organ weight changes were noted for several organs, but were determined to be “secondary to the stress related influence from confinement in the polycarbonate exposure tubes. This conclusion was supported by a lack of accompanying histopathology or correlating clinical toxicity in most of these organs.” A similar conclusion was ascertained from the “slight to moderate lymphoid depletion in the thymus and spleen…in some rats (primarily males) in the mid and high exposure groups. [Since] no evidence was present for a hemolytic effect in these or other organs/tissues and the lymphoid effect was considered secondary to weight loss in the two highest exposure groups.”

Similar to the Lomax et al. (1987) study, absolute and relative liver weight changes were observed and attributed to adaptive changes. However, there was some inconsistency in results seen between the Cieszlak et al. (1991) study and the Lomax et al. (1987) study. Specifically, it was noted in the Cieszlak et al. (1991) study that, "relative kidney weights were increased in high dose males, which the authors conjectured might reflect lower body weights. No differential response existed between control and high exposure male kidney histopathology." Given that the mid exposure group and high exposure group from the Cieszlak et al. study are approximately two and six times, respectively, the high exposure group from the Lomax et al. (1987) study, significant relative body weight changes would have been expected for both the mid and high exposure groups in the Cieszlak et al. study. However, it was noted from the summary of the Cieszlak et al. study that, "urea nitrogen was statistically increased in high exposure males and total protein was statistically decreased in both sexes from all DPnB exposure groups." There was not enough information to evaluate whether an ITSL should be derived from the change in total protein. However, the ECHA summary of the study did not note kidney effects among the potential critical effects. Altogether, these results cast doubt on DPnB-induced nephrotoxicity as a critical effect. As a result, the chronic ITSL of 11 ug/m^3 (annual averaging time) is being rescinded.

Derivation of Acute ITSL

The Cieszlak et al. study did show portal of entry effects to be critical effects with DPnB inhalation exposure, where, "in the anterior nasal cavity, rats from the mid and high-exposure groups exhibited 1) multifocal epithelial hyperplasia (1 female at the mid-dose; 4 males and 3 females at the high dose) and 2) squamous metaplasia (1 male and 4 females at the mid-dose; 5 males and females at the high dose). Nasal effects were considered a direct response to irritation from DPnB typical for mucosal tissue and were sometimes accompanied by suppurative inflammation or degeneration of the olfactory epithelium."

Using Benchmark Dose Modeling (BMD version 2.6.0.1) program (U.S. EPA, 2015), the point of departure (POD) was obtained for DPnB-induced nasal lesions in female and/or male rats (See Table 2). Models suitable for dichotomous data were run (Appendix A). A benchmark response (BMR) of 10% extra risk was selected as the response level. The 95% lower confidence limit on the dose associated with this response level (BMDL) was used as the point of departure (POD). Since several models fit the data, the model that gave the lowest BMDL for each adverse effect within the context of different gender scenarios was considered (Appendix A).

Table 2. BMDL estimates from short-term exposure to DPnB

Endpoint within Context of Different Gender Groups	NOAEL (mg/m^3)	LOAEL (mg/m^3)	Model	Goodness of Fit (p-value/AIC)	BMR (%)	BMD (mg/m^3)	BMDL (mg/m^3)
Female Rats							
Multifocal epithelial hyperplasia	200	810	Log Probit	0.987/15.778	10	601	77
Squamous metaplasia	**200**	**810**	**Quantal-Linear**	**0.527/10.747**	**10**	**68**	**35.8**
Male Rats							
Multifocal epithelial hyperplasia	810	2010	n/a	n/a	n/a	n/a	n/a
Squamous metaplasia	200	810	Quantal-Linear	0.323/12.419	10	149	76.5
Male and Female Rats							
Multifocal epithelial hyperplasia	200	810	Quantal-Linear	0.343/25.068	10	288	167
Squamous metaplasia	200	810	Quantal-Linear	0.272/22.855	10	103	64.8

Bold font indicates the adverse effect and BMDL selected for the POD.

Equation 1 shows the derivation of the human equivalent concentration (HEC) and Equation 2 shows the subsequent potential ITSL derivation.

Equation 1.

$$POD_{HEC} = POD_A \, x \, DAF = POD_A \, x \, RDDR$$

Where:

-DAF = dosimetric adjustment factor

-RDDR = regional deposited dose ratio, where RDD at 35.8 mg/m^3 for nasal-breathing human is 0.63 and RDD for the obligate, nasal-breathing rat is 0.95 based on modeling of a surrogate chemical's particle characteristics in the Multiple path particle dosimetry model (MPPD v2.1) (RIVM, 2002) (Appendix B)

$$POD_{HEC} = 35.8 \frac{mg}{m^3} x \frac{0.63}{0.95} = 23.74 \frac{mg}{m^3}$$

Equation 2. Based on AQD Rule 233 (1)(b)

$$Acute\ ITSL = \frac{POD_{HEC}}{UF_H x\ UF_A x\ UF_L} x\ \frac{hours\ exposed}{AT}$$

Where:
-POD_{HEC} is 23.74 mg/m^3

-The combined uncertainty factor for human variability (UF_H) and extrapolation from an animal study(UF_A) is 30: UF_H is 10 and UF_A is ≈ 3 since dosimetric adjustment was used to determine the POD_{HEC}, and UF_L is 1 for LOAEL to NOAEL extrapolation

-hours exposed/averaging time was set equal to 1, since these irritancy effects are expected to be concentration-dependent and not duration-dependent

$$Acute\ ITSL = \frac{23.74\ mg/m^3}{30} x\ 1\ x \frac{10^3 \mu g}{mg} = 791.37\ \frac{\mu g}{m^3} \approx 800 \frac{\mu g}{m^3}, 24 - hour\ averaging\ time$$

Although this is a repeated exposure study, the averaging time is being set at 24 hours, since irritancy effects are expected to occur acutely as well.

References

Cieszlak, F.S., Stebbins, K.E., Verschuuren, H.G., 1991. Dowanol DPnB: two-week aerosol toxicity study in Fischer 344 rats. Unpublished report, study K-005474-010. Toxicology Research Laboratory, Health and Environmental Sciences, Dow Chemical, Midland, Michigan, USA (as cited in ECETOC, 2005; ECHA, 2017).

Dow. 2012. Technical Data Sheet. Form No. 110-00620-0812. The Dow Chemical Company.

ECETOC. 2005. The toxicology of glycol ethers and its relevance to man. Tech Rep 95.

ECHA. 2017. Registration dossier: 1-(2-butoxy-1-methylethoxy)propan-2-ol. https://echa.europa.eu/registration-dossier/-/registered-dossier/14152/1 (Accessed October 1, 2017).

Lomax, L.G., Gushow, T.S., Hopkins, P.J. 1987. Dipropylene glycol normal butyl ether: 2-week nose-only vapor inhalation study with Fischer 344 rats. Unpublished report. The Dow Chemical Company.

MDEQ. 1999. Memo from Marco Bianchi to File for Dipropylene Glycol N-Butyl Ether (29911-28-2). Subject: Initial Threshold Screening Level. July 13, 1999.

National Center for Biotechnology Information. PubChem Compound Database; CID=24752, https://pubchem.ncbi.nlm.nih.gov/compound/24752 (Accessed October 1, 2017).

RIVM. 2002. The Dutch National Institute for Public Health and the Environment (RIVM). Multiple Path Particle Dosimetry Model (MPPD v 1.0): A Model for Human and Rat Airway Particle Dosimetry. Bilthoven, The Netherlands. RIVA Report 650010030.

U.S. EPA (Environmental Protection Agency), 2015. Benchmark Dose Software (BMDS) Version 2.6.0.1 (Build 88, 6/25/2015). National Center for Environmental Assessment. Available from: http://bmds.epa.gov (Accessed October 1, 2017).

Appendix A. Summary Reports from Benchmark Dose Modeling

Table A1. Summary of BMD Modeling Results for Multifocal Epithelial Hyperplasia in Female Rats

Model[a]	Goodness of fit		BMD (mg/m3)	BMDL (mg/m3)
	p-value	AIC		
Gamma	0.959	15.862	608	158
Dichotomous-Hill	1.000	17.734	751	547
Logistic	0.714	16.624	837	436
LogLogistic	0.964	15.854	603	123
Probit	0.766	16.420	781	412
LogProbit	0.987	15.778	601	77.0
Weibull	0.944	15.920	599	157
Multistage 4°	error	error	error[b]	error[b]
Multistage 3°[c]	0.982	13.946	655	156
Multistage 2°[d]	0.982	13.946	655	156
Quantal-Linear	0.897	14.677	298	142

[a] No model was selected as a best-fitting model.
[b] BMD or BMDL computation failed for this model.
[c] The Multistage 3° model may appear equivalent to the Multistage 2° model, however differences exist in digits not displayed in the table.
[d] The Multistage 2° model may appear equivalent to the Multistage 3° model, however differences exist in digits not displayed in the table.

Table A2. Summary of BMD Modeling Results for Squamous Metaplasia in Female Rats

Model[a]	Goodness of fit		BMD (mg/m3)	BMDL (mg/m3)
	p-value	AIC		
Gamma	1.000	7.0041	484	104
Dichotomous-Hill	1.000	7.0040	664	538
Logistic	1.000	9.0040	703	180
LogLogistic	1.000	7.0040	664	130
Probit	1.000	9.0040	614	166
LogProbit	1.000	9.0040	547	131
Weibull	1.000	9.0041	608	97.3
Multistage 4°	error	error	error[b]	error[b]
Multistage 3°	0.989	7.2419	330	73.0
Multistage 2°	0.918	7.9205	222	61.2
Quantal-Linear	0.527	10.747	68.9	35.8

[a] No model was selected as a best-fitting model.

[b] BMD or BMDL computation failed for this model.

Table A3. Summary of BMD Modeling Results for Squamous Metaplasia in Male Rats

Model[a]	Goodness of fit		BMD (mg/m3)	BMDL (mg/m3)
	p-value	AIC		
Gamma	1.000	7.0081	722	313
Dichotomous-Hill LogLogistic	1.000	7.0040	774	373
Logistic	1.000	9.0040	782	365
Probit	1.000	9.0040	756	331
LogProbit	1.000	9.0040	762	368
Weibull	1.000	9.0040	746	281
Multistage 4°	error	error	error[b]	error[b]
Multistage 3°	0.986	7.2409	583	182
Multistage 2°	0.802	8.5386	403	157
Quantal-Linear	0.323	12.419	149	76.5

[a] No model was selected as a best-fitting model.
[b] BMD or BMDL computation failed for this model.

Table A4. Summary of BMD Modeling Results for Multifocal Epithelial Hyperplasia in Female and Male Rats

Model[a]	Goodness of fit		BMD (mg/m3)	BMDL (mg/m3)
	p-value	AIC		
Gamma	0.998	22.728	815	375
Dichotomous-Hill	1.000	24.719	810	395
Logistic	0.841	23.245	970	596
LogLogistic	0.995	22.739	816	393
Probit	0.912	23.001	906	554
LogProbit	1.000	22.719	810	400
Weibull	0.988	22.765	827	365
Multistage 4°	error	error	error[b]	error[b]
Multistage 3°	0.982	22.782	838	326
Multistage 2°	0.929	21.312	633	307
Quantal-Linear	0.343	25.068	288	167

[a] No model was selected as a best-fitting model.
[b] BMD or BMDL computation failed for this model.

Table A5. Summary of BMD Modeling Results for Squamous Metaplasia in Female and Male Rats

Model[a]	Goodness of fit		BMD (mg/m3)	BMDL (mg/m3)
	p-value	AIC		
Gamma	1.000	15.863	588	230
Dichotomous-Hill	1.000	15.863	717	581
Logistic	1.000	17.863	739	319
LogLogistic	1.000	15.863	717	280
Probit	1.000	17.863	673	286
LogProbit	1.000	17.863	660	263
Weibull	1.000	17.863	660	212
Multistage 4°	error	error	error[b]	error[b]
Multistage 3°	0.991	16.070	435	157
Multistage 2°	0.903	16.986	312	148
Quantal-Linear	0.272	22.855	103	64.8

[a] No model was selected as a best-fitting model.
[b] BMD or BMDL computation failed for this model.

Appendix B. Multiple-Path Particle Dosimetry Model Results

Particle characteristics of tripropylene glycol monomethyl ether (CAS# 25498-49-1) were used as a surrogate for DPnB. These particle characteristics, specifically mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) were taken from averages of the reported MMADs and GSDs from the following study:

Miller, R.R., Lomax, L.G., Calhoun, L.L. 1985. Tripropylene glycol monomethyl ether (TPGME): 2-week Aerosol Inhalation Toxicity Study in Rats and Mice. Unpublished Report-The Dow Chemical Company.

Figure B1.Output file of the modeled regional dose depositions for rat model

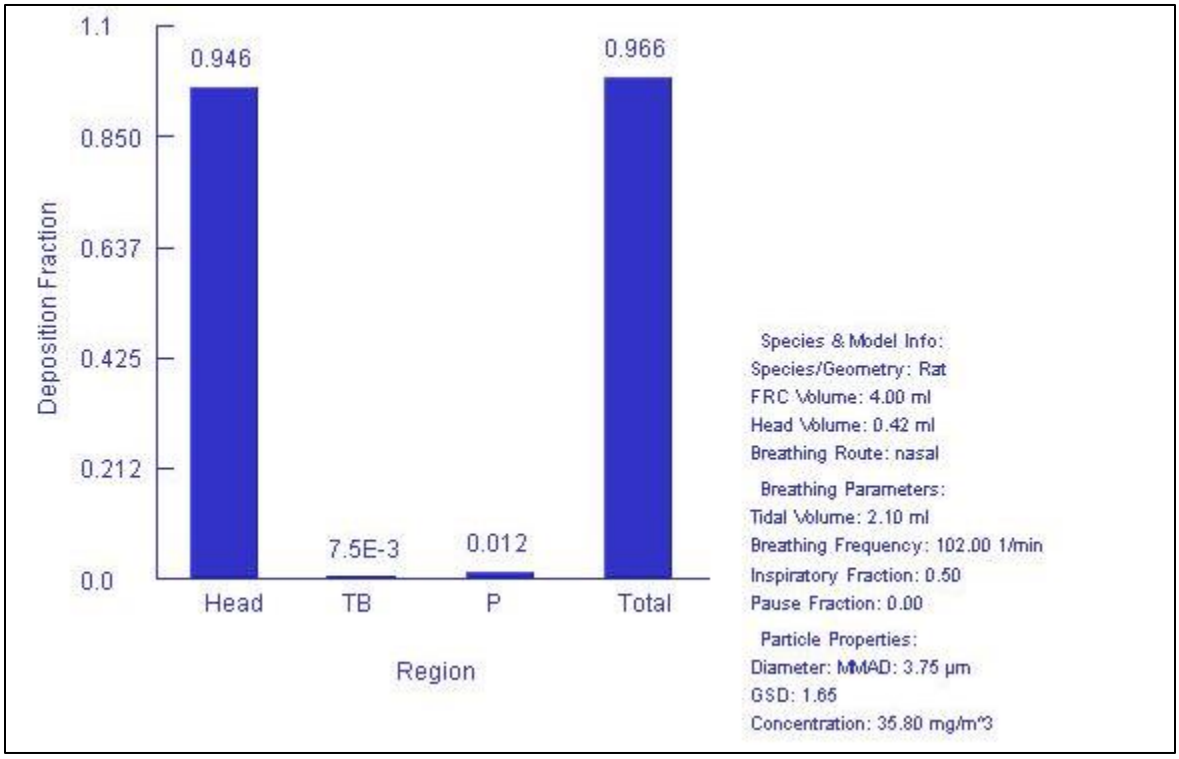
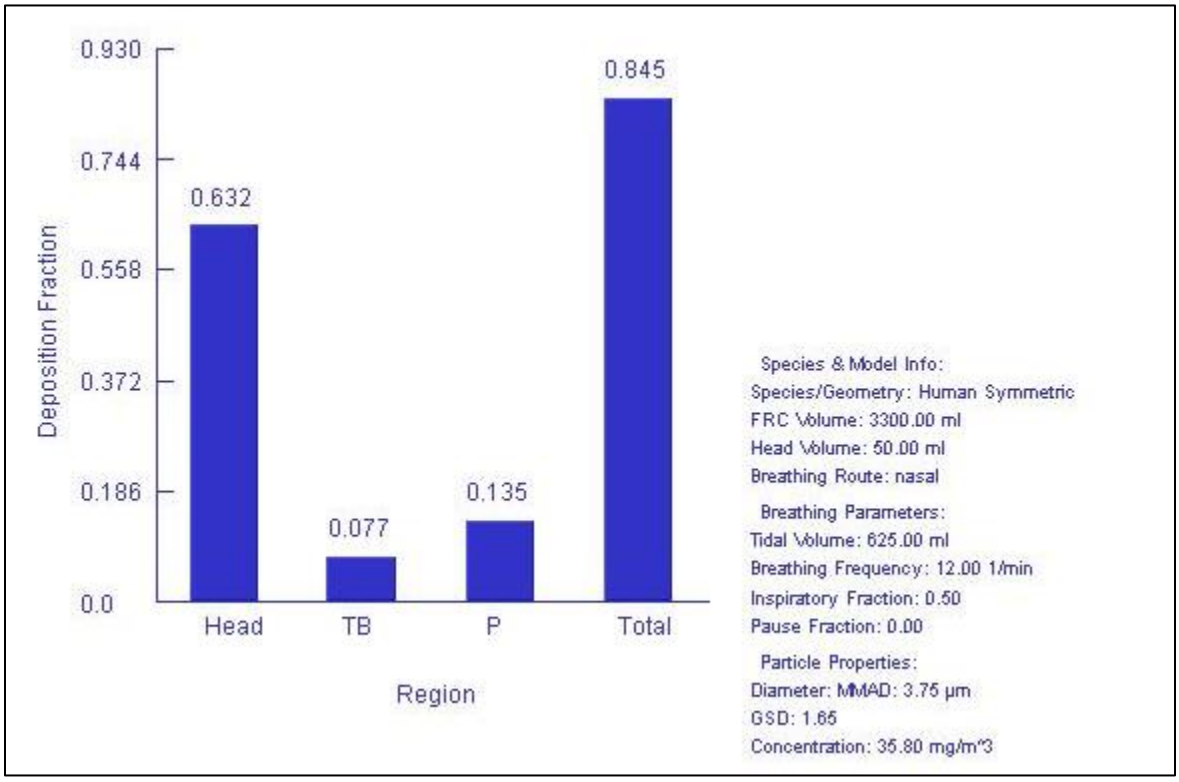


Figure B2. Output file for the modeled regional dose deposition in human model



MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

July 13, 1999

TO: File for Dipropylene Glycol N-Butyl Ether (29911-28-2)

FROM: Marco Bianchi

SUBJECT: Initial Threshold Screening Level

The initial threshold screening level (ITSL) for dipropylene glycol n-butyl ether (DPnB) is 11 ug/m^3 based on an annual averaging time. This compound was initially evaluated by Air Quality Division (AQD) staff in 1994, but no data was available other than an LD_{50} which was used to set an ITSL at 5 ug/m^3, annual averaging time. Recently, Dow Chemical Company has submitted an unpublished 9-day rat inhalation study for AQD's re-evaluation of the ITSL.

Included in the 9-day inhalation study submitted by Dow was a toxicological summary of an acute 4-hour vapor inhalation study. This study used the maximally attainable concentration of 42 ppm (322 mg/m^3) on Fischer 344 rats. There were no mortalities or clinical signs during the exposure period or 14-day post-exposure period. No gross pathologic changes were observed at necropsy. However, the observation of wet-coats during exposure and a four-fold difference between the nominal chamber concentration (169 ppm) and the analytical concentration (42 ppm) suggested that test material was being deposited on the haircoats of exposed animals. Therefore, the nose-only method was selected to provide the best defined inhalation exposure environment for the 9-day study.

In the 9-day inhalation study, groups of five Fischer 344 rats/sex/group were exposed to 0, 20, or 40 ppm (0, 160, and 320 mg/m^3), 6 hours/day for 9 days. Parameters that were evaluated included general appearance and demeanor, functional observational battery, body weights, feed and water consumption, hematology, clinical chemistry, urinalysis, organ weights, gross pathology, and histopathology. Test animals were sacrificed the day after the last exposure.

According to the study results, all rats survived until the scheduled necropsy with no apparent indication of clinical signs as a result of exposure to the test material. Some animals in all exposure groups including the controls had porphyrin-staining around the external nares and/or slight perineal soiling. These clinical observations were considered indicative of the stress of confinement in the nose-only exposure system. There were no statistically identified differences in mean body weights or mean body

weight gains for the control and DPnB-exposed animals at any time during the course of the study. All other apparent changes observed on various study parameters (e.g., clinical chemistry and hematological effects), were considered of no toxicological significance as they were within normal physiologic limits or within historical control values, and were not associated with histopathologic alterations. There were, however, statistical changes in organ weights for both males and females. Low dose males had a statistical decrease in absolute brain weight, while females had a statistical increase in relative kidney weight for the high dose group, and a statistical increase in liver weight for both dose groups (see table below).

Dipropylene Glycol N-butyl Ether (Rats)
Exposure Group Brain (mg/m3)

Male		Mean (g)	%Change		Relative (g/100)	% Change
0		1.763			0.918	
160		1.718	*-2.6		0.904	-1.5
320		1.73	-1.9		0.904	-1.5

Dipropylene Glycol N-butyl Ether (Rats)
Exposure Group Kidneys (mg/m3)

Female		Mean (g)	%Change		Relative (g/100)	% Change
0		0.945			0.737	
160		1.011	7.0		0.804	9.1
320		1.024	8.4		0.809	*9.8

Dipropylene Glycol N-butyl Ether (Rats)
Exposure Group Liver (mg/m3)

Female		Mean (g)	%Change		Relative (g/100)	% Change
0		3.566			2.78	
160		3.823	7.2		3.042	*9.4
320		3.796	6.4		2.995	*7.7

*Statistical change from control mean by Dunnett's test, alpha=0.05

From these study results, Dow interpreted changes in liver, kidney, and brain weights as not toxicologically significant because these organs lacked histopathologic effects. The liver weight increases, and the brain weight decrease did not follow a clear dose-response relationship, nor did any of these organs have morphologic changes indicative of a toxic effect. Dow considered 320 mg/m^3 a no-observable-adverse-effect-level (NOAEL).

Although there is scientific debate on interpretation of organ weight changes, statistically significant weight changes in organs that follow a dose-response relationship strongly suggests a potential for future toxic effects to exposed animals. Presently, uncertainty exists in the scientific community as to whether a change in liver weight is a clear indication of potential adverse effects if there are no other morphologic changes indicating toxicity. This is because the liver is a major site of chemical metabolism, and a temporary increase in liver size and weight may occur from a chemical exposure due to an increase in liver function. This condition may return to normal after the chemical has been metabolized. Several experts from EPA (Annie Jarabek, Henry Spencer, and Gary Foureman - personal communication) were contacted on this subject. In their professional judgement, they generally consider compound related changes in liver weights, but not other organ weights, as adaptive in nature provided no other adverse effects have been observed. In making such a determination, however, they also consider other relevant studies and structure activity relationships. For example, necrogenic or frank liver effects found in an acute study for a compound may be suggestive that liver weight effects only seen in a subacute or chronic study could progress to more significant effects.

Considering all available information, the weight-of-evidence suggests changes in brain and liver weights seen in this 9-day study are not adverse effects. This includes the lack of a dose-response relationship and/or morphologic changes. Although there was a statistical decrease in absolute brain weight for low dose male rats, the high dose group exhibited a smaller non-statistical decrease. In a similar fashion, there was a statistical increase in relative liver weight for low dose females, but a smaller statistical increase in the high dose group. From these non-dose-response related effects, it is uncertain whether they would lead to toxic endpoints. In contrast, the weight-of-evidence for changes in kidney weight supports consideration of this as an adverse effect. There was a 9.1% increase in kidney weight in the low dose, and a statistically significant 9.8% increase in the high dose exposure group compared to controls. Although there were no morphologic changes observed in the kidney, the organ weight increases followed a dose-response relationship and represented a statistical change for the 320 mg/m^3 dose group. Therefore, the LOAEL for this study is 320 mg/m^3, while the NOAEL is 160 mg/m^3. The NOAEL will be used to determine an ITSL by Rule 231(1)(d).

The ITSL was determined as follows:

NOAEL = 160 mg/m^3.

$$ITSL = \frac{NOAEL}{35 \times 100} \times \frac{\text{hours exposed/day}}{24 \text{ hours /day}}$$

$$ITSL = \frac{160 \text{ mg/kg/day}}{35 \times 100} \times \frac{6 \text{ hrs/day}}{24 \text{ hours/day}} = 0.011 \text{ mg/m}^3$$

Conversion of mg/m^3 to ug/m^3

0.011 mg/m^3 x 1000 = 11.0 ug/m^3

The ITSL for dipropylene glycol n-butyl ether = 11 $\mu g/m^3$ based on an annual averaging.

References:

1. Lomax LG, et al., 1985. Dipropylene glycol normal butyl ether: 2-week nose-only vapor inhalation study with Fischer 344 rats. Unpublished Report - The Dow Chemical Company.

2. Annie Jarabek. Personal communication. September 12, 1997.

3. Henry Spencer. Personal communication. September 15, 1997.

4. Gary Foureman. Personal communication. September 24, 1997.