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APPLICATION FOR AUTHORISATION: DNEL SETTING FOR REPROTOXIC PROPERTIES OF DIGLYME

Background

At the 22nd meeting of the Committee for Risk Assessment (RAC) in September 2012, the ECHA Secretariat presented a proposal to set DNELs/DMELs and dose response relationships for substances prior to receiving applications for authorisation (AfAs). This was initially approved by RAC as a trial exercise. However, in early 2015, ECHA agreed to continue supporting the practise for Annex XIV substances, recognising its value to the Authorisation process and its efficiency[1].

The DNEL and dose response relationships so derived serve as non-legally binding 'reference values'. They provide applicants with a clear signal as to how RAC is likely to evaluate these important elements of the risk assessment of AfA.

Reference values in the form of DNEL's for threshold substances and/or dose response relationships for non-threshold (mainly) carcinogens are published in advance of applications, for authorisation, so providing greater consistency and better use of the legally defined periods of opinion-development in the Committee for Risk Assessment (RAC).

Annex 1: DNEL setting for the reprotoxic properties of Diglyme

[1] At the Conference on "Lessons learnt on Applications for Authorisation" co-organised by ECHA and the European Commission that took place on 10-11 February 2015.

Annex 1 DNEL setting for the reprotoxic properties of Diglyme

The reference DNELs for all routes of exposure of diglyme as agreed by the RAC are given below.

Table 1. Overview of derivation of reference DNELs for workers and general population (adults and children) exposed to Diglyme by the inhalation, oral and dermal route

Point of departure for DNEL derivation by all routes for Diglyme (DuPont, 1989)		
Rat 2-week Inhalation NOAEC in mg/m^3 (testicular toxicity)	**167**	
Dosing regime	6 h/d, 5 d/wk, 2 wk	
Inhalation absorption percentage	100 %	
Derivation of Reference DNELs		
	WORKERS	GENERAL POPULATION
Assessment Factors		
Interspecies, Allometric scaling	-	-
Interspecies, remaining differences	2.5	2.5
Intraspecies	5	10
Subacute to chronic	4	4
Hours/day	8	24
Days/week	5	7
INHALATION		
Absorption percentage	100%	100%
Correction for exposure regime	6/8	6/24 x 5/7
Breathing rate for workers light activity vs rest	6.7/10	
NOAEC (corrected)	83.9	29.8
Reference DNEL INHALATION in mg/m³	**1.68**	**0.30**
DERMAL		
Absorption percentage	100%	100%
Correction for exposure regime	6/8	6/24 x 5/7
Standard respiratory volume in m^3/kg bw/day	0.384	1.15
NOAEL (corrected)	48.1	34.4
Reference DNEL DERMAL in mg/kg/day	**0.24**	**0.09**
ORAL		
Absorption percentage	100%	100%
Correction for exposure regime	6/8	6/24 x 5/7
Standard respiratory volume in m^3/kg bw/day	0.384	1.15
NOAEL (corrected)	48.1	34.4
Reference DNEL ORAL in mg/kg/day	**0.24**	**0.09**

SUBSTANCE NAME	EC NUMBER	CAS NUMBER
Bis(2-methoxyethyl) ether (Diglyme)	203-924-4	111-96-6

Relevance of endpoints

For applicants applying for authorisation under Article 60(2) (adequate control route), in order to conclude whether the adequate control is demonstrated, only endpoints (i.e. properties of concern) for which the substance is included in Annex XIV need to be addressed in the hazard assessment[2]. However, information on other endpoints might be necessary for comparing the risks with the alternatives.

For applicants aiming at authorisation based on Article 60(4) (socio-economic analysis route) Article 62(4)(d) also applies and the socio-economic analysis (SEA) route will as a consequence focus on the risks that are related to the intrinsic properties specified in Annex XIV. The SEA should in turn consider the impacts related to such risks. In practice the applicant is expected to provide this information in their (Chemical Safety Report) CSR for which an update may be advisable. However, for an authorisation to be granted, the applicant should also demonstrate that there are no suitable alternatives. In this latter analysis it may be the case that other endpoints than those for which the substance was listed in 'Annex XIV' become relevant in order to demonstrate that no suitable alternative is available.

Diglyme is included on Annex XIV due to its reprotoxic properties (Repr. 1B – H360FD). The DNELs relationships proposed in the present document are only based on reprotoxic properties arising from diglyme exposure[3].

Reproductive and developmental toxicity

Tables 2 and 3 below provide an overview of the studies on the reproductive and developmental toxicity of diglyme:

[2] Article 60(2) states "…an authorisation shall be granted if the risk to human health or the environment from the use of the substance arising from **intrinsic properties specified in Annex XIV** is adequately controlled."

[3] Endpoints relevant to the authorisation are also discussed in section 5 of the document: "How RAC and SEAC intend to evaluate the applications" (common approach of RAC and SEAC in opinion development on applications for authorisation, agreed RAC-20/SEAC14, 24/03/2012). Link: http://echa.europa.eu/web/guest/applying-for-authorisation/additional-information

Table 2. Reproductive toxicity study summary

Species	Route of exposure	Dose/concentration	Observations	NOAEL	Reference	Reliability
Rat (Crl:CD) male 20/group	Inhalation 6 h/day 5 days/week for 2 weeks 84 days post exposure	0, 110, 370, 1100 ppm (approximately 0, 614, 2064, 6137 mg/m³)	370 and 1100 ppm: decrease in absolute weight of testis, epididymides, seminal vesicles and prostate. 1100 ppm: Decreased relative weight of testis. Testicular atrophy. Effects reversible at 84 days except 1100 ppm 110 ppm: spermatocytes in pachytene and meiotic division at spermatogenic stages XII-XIV were mainly affected.	LOAEC 110 ppm (approx. 614 mg/m³)	DuPont (1988b), Valentine (1999)	1
Rat (Crl:CD) male 20/group	Inhalation 6h/day 5 days/week for 2 weeks 14 days post exposure	0, 3, 10, 30, 100 ppm (approximately 0, 17, 56, 167, 558 mg/m³)	Minimal to mild lesions below 100 ppm (degenerative germ cells in epididymal tubules, spermatic granuloma in epididymis, prostatitis). Not clear if lesions occurred in same or different animals. 100 ppm: decreased mean bodyweight, mild testicular atrophy. The NOAEL is that stated by the authors taking into consideration historical data (not shown) and repeated in the CICAD (WHO, 2002).	30 ppm (approx. 167 mg/m³)	DuPont (1989)	2

Species	Route of exposure	Dose/concentration	Observations	NOAEL	Reference	Reliability
Rat (CD) male 10/group	Inhalation 7h/day 5 days	0, 250, 1000 ppm (approximately 0, 1395, 5579 mg/m³)	1000 ppm: Reduced bodyweight in males. Decreased pregnancy frequency. Preimplantation losses. Recovery complete in week 10.	NOAEC of 250 ppm (1395 mg/m³)	McGregor (1983)	3
Mice (B6C3F1)	Inhalation 7h/day 4 days	0, 250, 1000 ppm (approximately 0, 1395, 5579 mg/m³)	Reduced bodyweight gain in both groups. 4 mice at top dose died on day 4. 1000 ppm: morphologically altered sperm.	LOAEC of 250 ppm (1395 mg/m³)	McGregor (1981)	3
Rats (Sprague-Dawley) Male 5/group	Oral 20 days	684 mg/kg bw/day 8 week recovery	Primary and secondary spermatocyte degeneration, spermatidic giant cells, reduced testis to bodyweight ration from day 12 until the end of study, testicular LDH-X activity decreased by day 18.	Effects at 684 mg/kg bw	Cheever (1985, 1989)	3

The conversion of air concentration (ppm) to doses in mg/m³ is done using a conversion factor of 5.579 (ECETOC, 2005).

Table 3. Developmental toxicity study summary

Species	Route of exposure	Dose/concentration	Observations	Maternal NOAEL	Foetal NOAEL	Reference	Reliability
Rabbits (New Zealand) Female 15-25/group	Gavage Day 6-19	0, 25, 50, 100, 175 mg/kg bw/day	50 mg/kg bw/day: dams: decreased weight gain, increased adversely affected implants per litter. 100 mg/kg bw/day: decreased gravid uterine weight, increased prenatal mortality (resorptions), increased malformations. 175 mg/kg bw/day: Decreased faecal output, increased mortality. Maternal toxicity only.	100 mg/kg bw/day 25 mg/kg bw/day	25 mg/kg bw/day 50 mg/kg bw/day	NTP (1987), WHO (2002) Schwertz *et al.*(1992)	2
Rats (CD) female 25-26/group	Inhalation 6h/day days 7-16	0, 25, 100, 400 ppm (approximately 0, 139, 558, 2232 mg/m³)	25 ppm: decreased foetal weight, variations 100 ppm: dams: increased relative liver weight, Foetus: structural malformations 400 ppm: dams: decreased food consumption, decreased bodyweight gain, total resorption.	25 ppm (approx. 139 mg/m³)	LOAEC 25 ppm (approx. 139 mg/m³)	DuPont (1988a) Driscoll (1998)	1

Species	Route of exposure	Dose/concentration	Observations	Maternal NOAEL	Foetal NOAEL	Reference	Reliability
Mice (CD-1) 20-24 /group	Gavage day 6-15	0, 62.5, 125, 250, 500 mg/kg bw/day	125 mg/kg bw/day: decreased foetal weight. 250 mg/kg bw/day: dams: decreased weight gain, increased late foetal death, increased malformations. 500 mg/kg bw/day: dams: decreased bodyweight gain, increased resorptions.	500 mg/kg bw/day	62.5 mg/kg bw/day	NTP (1985), Price (1987)	1
Mice (CD-1) Not provided	Gavage day 11	0, 537 mg/kg bw	Only examination for gross external malformations and foetal bodyweight. 537 mg/kg bw/day: increased malformations.	Effects at 537 mg/kg bw	Effects at 537 mg/kg bw	Hardin (1986, 1987)	3
Mice (CD-1) 49/group	Gavage day 6-13	0, 3000 mg/kg bw/day	Reproductive screening according to Chernoff and Kavlock, no systematic examination for malformations. 3000 mg/kg bw/day. Dams: increased mortality, no viable Litters.	Effects at lowest dose	Effects at lowest dose	Schuler (1984), Plasterer (1985), Hardin (1987)	3

The conversion of air concentration (ppm) to doses in mg/m³ is done using a conversion factor of 5.579 (ECETOC, 2005).

Critical studies

Multiple studies have been conducted via both the inhalation and oral routes to determine the reproductive toxicity of diglyme. The fertility studies focused on testicular toxicity, while foetal malformations were identified in the developmental studies. An oral fertility study was carried out in male rats, three inhalation studies were carried out in rats, and another in mice. One developmental toxicity study was carried out in rabbits and three in mice, all via gavage, while one study was carried out in rats via inhalation. The studies are summarised in Tables 2 and 3 above and the key points for their use in the setting of DNEL are outlined below.

DuPont/Valentine (DuPont, 1988b; Valentine 1999) exposed rats via inhalation for 6 hours/day, 5 days/week for only 2 weeks at concentrations of 0, 110, 370 or 1100 ppm (0, 614, 2064 and 6137 mg/m³). A decrease in the absolute weight of the testis, epididymides, seminal vesicles and prostate occurred at the mid and top dose; while decreased relative weight of the testis and testicular atrophy were observed at the top dose. At the lowest dose, spermatocytes in pachytene and meiotic division at spermatogenic stages XII-XIV were mainly affected. Only a LOAEC of 110 ppm (approximately 614 mg/m³) was derived from this study, and the duration of exposure was extremely short.

A rat inhalation study was conducted with concentrations of 0, 3, 10, 30, 100 ppm (approximately 0, 17, 56, 167, 558 mg/m³) where minimal to mild lesions (degenerative germ cells in epididymal tubules, spermatic granuloma in epididymis, prostatitis) were described below 100 ppm (DuPont, 1989). It is not clear whether these slight lesions occurred in the same or different animals. A NOAEL of 30 ppm (approx. 167 mg/m³) was stated by the authors taking into consideration historical data (not shown) and this conclusion is repeated in the CICAD document (WHO, 2002).

WHO (2002) and the ECHA Annex XV dossier (2011) have evaluated diglyme and identified an NTP oral gavage study in rabbits administered 0, 25, 50, 100, 175 mg/kg bw/day as the key developmental toxicity study (NTP, 1987). This study was well reported and conducted to OECD standards and under GLP. However, different interpretations of the maternal and foetal NOAELs exist for this study. A paper by Schwertz *et al*. (1992) identifies 50 mg/kg bw/day as the foetal NOAEL; however, a significant decrease in the number of implants per litter occurred at this dose, corresponding to the NOAEL identified by the NTP of 25 mg/kg bw/day.

A rat developmental toxicity study investigated effects via inhalation of 0, 25, 100, 400 ppm (0, 139, 558, 2232 mg/m³) (DuPont 1988a, Driscoll 1998). This study did not identify a NOAEC for foetal effects, as a decrease in foetal weight and an increase in variations were observed at the lowest concentration tested. Converting the LOAEC identified in this study of 25 ppm (139 mg/m³) into an internal dose results in a LOAEL of approximately 48 mg/kg bw/day (based on a rat breathing rate 0.24 l/minute and rat bodyweight 0.25 kg).

Mice were gavaged on days 6-15 of gestation at doses of 0, 62.5, 125, 250 or 500 mg/kg bw/day in a study by NTP (1985). Decreased foetal weight was observed at 125 mg/kg bw/day. Dams displayed decreased weight gain at 250 mg/kg bw/day and there was increased late foetal death and increased malformation. At the top dose there was decreased bodyweight gain in dams and increased resorptions. A foetal NOAEL of 62.5 mg/kg bw/day was identified from this study.

No data from dermal studies are available.

Bioavailability

Toxicokinetics

Diglyme is rapidly and completely absorbed in the rat and mouse following oral administration. Within 96 hours, approximately 86-90 % of administered dose is excreted (GBK, 2010). It is also absorbed through the skin and by inhalation.

Glycol ethers are readily distributed throughout the body and eliminated via urine. Significant accumulation does not occur (ECHA, 2011).

Two initial metabolic oxidations occur during the metabolism of diglyme. Both involve cytochrome P450. The first pathway metabolises diglyme via oxidative dealkylation of an interior ether bond to formally provide two molecules of 2-methoxyethanol. 2-Methoxyethanol is converted via oxidation, by way of the aldehyde, to 2-methoxyacetic acid. 2-Methoxyacetic acid has been associated with testicular toxicity in male experimental animals and development of the conceptus in pregnant female animals. In rats, most 2-methoxyacetic acid is excreted via the urine; however, some is conjugated with glycine to produce N-methoxyacetyl glycine.

The second pathway involves oxidative demethylation of diglyme, by unspecified cytochrome P450 isozymes to give 2-(2-methoxyethoxy)ethanol which is converted by oxidation of the aldehyde to 2-(2-methoxyethoxy)acetic acid. This molecule can be further metabolised via oxidative demethylation to give the alcohol, 2-hydroxyethoxyacetic acid. This will then be oxidised to diglycolic acid and excreted.

The human pathway for metabolism is similar to that in experimental animals, with human and rat microsomal preparations producing qualitatively and quantitatively similar oxidative metabolic products. Human liver microsomes may be more efficient than rat liver microsomes at cleaving diglyme into 2-methoxyethanol. The pathway of diglyme metabolism is dependent on where the oxidative attack occurs on the diglyme molecule, which is dependent on the relative quantities of cytochrome P450 isozymes that are present. The pathways of metabolism do not cross over. The metabolite, 2-methoxyacetic acid may accumulate in animals and humans, with a human half-life of 77.1 hours.

Following oral exposure, diglyme is excreted via the urine, and is almost complete within 96 hours of dosing (GBK, 2010). No further information is available on excretion though other routes of exposure.

Summary

Orally, diglyme is rapidly and completely absorbed and 100 % bioavailability will be taken for this route of exposure. Diglyme is also absorbed by inhalation (as demonstrated in several inhalation toxicity studies showing systemic effects) and via the dermal route, although there are no quantitative data available. In the absence of specific data, 100 % absorption via the inhalation and dermal route will be assumed. There are no data to differentiate toxicokinetics in humans and animals, therefore bioavailability for humans via the three routes of absorption is assumed to be the same as for animals.

Reproductive and developmental risk assessment

DNELs for exposure routes

DNEL and exposure estimates as presented in REACH registration dossiers are summarised in Table 4.

Table 4. DNELs and exposure estimates in registration dossiers

Long term systemic	DNELs Annex XV	DNELs registration	Guidance values (WHO 2002)	Exposure estimates (WHO 2002)	Exposure (registration dossier)
Worker dermal	0.8 mg/kg bw/day	2.08 mg/kg bw/day	-	-	*
Worker inhalation	11.16 mg/m³	26.8 mg/m³	0.6 mg/m³	36 mg/m³ Production 3 mg/m³ Semiconductor industry 31 mg/m³ Painting op	*
Worker oral	-	-	0.25 mg/kg bw/day	-	-
General population dermal	0.4 mg/kg bw/day	1.04 mg/kg bw/day	-	-	-
General population inhalation	2.8 mg/m³	6.7 mg/m³	0.6 mg/m³	-	-
General population oral		1.04 mg/kg bw/day	0.25 mg/kg bw/day	-	-

*Confidential

Important exposure routes

For completeness, DNELs have been derived for all routes of exposure for both workers and the general population. It is considered that dermal and inhalation are the most important routes for workers, while use by consumers is advised against, so any exposure should be oral or inhalation in the environment (GBK, 2010).

Derived No Effect Levels

For the inhalation route, DNELs have therefore been calculated based on the DuPont 1988a/Driscoll 1998 study (inhalation rat, developmental effects) and on the DuPont 1989 study (inhalation rat, testicular effects).

For the oral route, DNELs have been calculated based on the NTP 1987 and 1985 studies (oral rabbit and mouse, respectively, developmental effects).

The United Kingdom Interdepartmental Group on Health Risks from Chemicals document entitled '*Guidelines on route-to-route extrapolation of toxicity data when assessing health risks of chemicals*' (IGHRC, 2006) states that oral to dermal extrapolation is common for industrial chemical and pesticide exposure. This document assumes that dermal bioavailability is less than oral (i.e. less substance will be absorbed via the skin due to its barrier properties), therefore, using the oral data is precautionary, providing that the skin is not compromised by the substance being a severe irritant and causing increased absorption through a more permeable barrier. Diglyme is not considered to be irritant, therefore, equivalent bioavailability can be assumed for oral and dermal exposure to provide a precautionary DNEL. The approach used in the IGHRC document is that used in the ECHA REACH Guidance and is widely referenced.

For the purposes of comparison, extrapolation was also made from the inhalation study of DuPont (1989) for both oral and dermal exposure using 100 % bioavailability for both.

In the absence of substance-specific information, default assessment (uncertainty) factors (for inter- and intraspecies variation, exposure duration extrapolation etc.) as prescribed in the ECHA guidance (ECHA, 2012) are used.

RAC agreed that an assessment factor of 4 for testicular effects would be applied for extrapolation from sub-acute testicular toxicity studies to chronic effects. RAC considered that the assessment factor of 6 stated in the REACH Guidance was not appropriate due to two factors: firstly, the relatively short duration of the spermatogenesis process, and secondly, that bioaccumulation of diglyme had not been reported. This assessment factor was not required for developmental studies.

Inhalation exposure

Workers/General population

DuPont 1989 study

- Rat
- End-point: testicular toxicity
- Exposure regime: 6 h/day; 5 days/week; 2 weeks
- NOAEC = 167 mg/m^3
- Assuming 100 % bioavailability

NOAEC CORRECTION		
	Workers	General population
Exposure regime	6/8	(6/24) X (5/7)
Breathing rate	6.7/10	-
CORRECTED NOAEC (mg/m^3)	83.9	29.8

ASSESSMENT FACTORS		
	Workers	General population
Interspecies allometric scaling	-	-
Interspecies, remaining differences	2.5	2.5
Intraspecies	5	10
Subacute to chronic	4	4

DNEL workers = 1.68 mg/m^3
DNEL general population = 0.30 mg/m^3

DuPont 1988a study

- Rat
- End-point: development
- Exposure regime: 6 h/day; 10 days
- LOAEC = 139 mg/m^3
- Assuming 100 % bioavailability

LOAEC CORRECTION		
	Workers	General population
Exposure regime	(6/8) x (7/5)	6/24
Breathing rate	6.7/10	-
CORRECTED LOAEC (mg/m^3)	97.8	34.8

ASSESSMENT FACTORS		
	Workers	General population
Interspecies allometric scaling	-	-
Interspecies, remaining differences	2.5	2.5
LOAEC to NOAEC	3	3
Intraspecies	5	10
Subacute to chronic	-	-

DNEL workers = 2.61 mg/m^3
DNEL general population = 0.46 mg/m^3

DuPont 1988b study

- Rat
- End-point: testicular toxicity
- Exposure regime: 6 h/day; 5 days/week, 2 weeks
- LOAEC = 614 mg/m^3
- Assuming 100 % bioavailability

LOAEC CORRECTION		
	Workers	General population
Exposure regime	6/8	(6/24) X (5/7)
Breathing rate	6.7/10	-
CORRECTED LOAEC (mg/m^3)	308	110

ASSESSMENT FACTORS		
	Workers	General population
Interspecies allometric scaling	-	-
Interspecies, remaining differences	2.5	2.5
LOAEC to NOAEC	3	3
Intraspecies	5	10
Subacute to chronic	4	4

DNEL workers = 2.1 mg/m^3
DNEL general population = 0.37 mg/m^3

The DNELs derived from the all three inhalation studies (two fertility and 1 developmental) are similar, suggesting that in the rat the DNELs for fertility and development are comparable.

Oral exposure

Workers/General population

NTP 1985

- Mice
- End-point: development
- Exposure regime: 10 days
- NOAEL = 62.5 mg/kg bw/day
- Assuming 100 % bioavailability

LOAEC CORRECTION		
	Workers	General population
Exposure regime	7/5	-
CORRECTED NOAEL (mg/kg bw/day)	87.5	62.5

ASSESSMENT FACTORS		
	Workers	General population
Interspecies allometric scaling	7	7
Interspecies, remaining differences	2.5	2.5
Intra-species	5	10

DNEL workers = 1.0 mg/kg bw/day DNEL general population = 0.36 mg/kg bw/day

NTP 1987

- Rabbit
- End-point: development
- Exposure regime: 14 days
- NOAEL = 25 mg/kg bw/day
- Assuming 100 % bioavailability

LOAEC CORRECTION		
	Workers	General population
Exposure regime	7/5	-
CORRECTED NOAEL (mg/kg bw/day)	35	25

ASSESSMENT FACTORS		
	Workers	General population
Interspecies allometric scaling	2.4	2.4
Interspecies, remaining differences	2.5	2.5
Intraspecies	5	10

DNEL workers = 1.2 mg/kg bw/day DNEL general population = 0.42 mg/kg bw/day

By using an additional correction factor of 70 kg bw/person/20 m^3/day (for the general population) and 70 kg bw/person/10 m^3/working day, these same assessment and correction factors can be used for deriving inhalation DNELs from these two oral studies. The results are shown below:

	DNEL (mg/m^3)	
	Workers	**General population**
NTP 1985	7.0	1.3
NTP 1987	8.2	1.5

It is noteworthy that these DNELs are around 4 times higher than the corresponding values derived using inhalation studies, which suggests that either mice and rabbit species might be more resistant to diglyme or that bioavailability for the oral route is lower than for the inhalation route.

Therefore, and in absence of additional evidence, RAC agreed that all route-specific DNELs (oral, dermal and inhalation) would be based on the most sensitive rat inhalation study (DuPont 1989).

Thus, the derivation for **oral DNEL** is as follows:

DuPont 1989 study

- Rat
- End-point: testicular toxicity
- Exposure regime: 6 h/day; 5 days/week; 2 weeks
- NOAEC = 167 mg/m^3
- Assuming 100 % bioavailability

- Assuming respiratory rate of 0.8 l/min/kg

Corrected NOAEC for workers = 167 mg/m^3 x 6 hours x 60 min/hour x 0.0008 m^3/min/kg = 48 mg/kg bw/day

(NB = 167 x 0.384 x 6/8)

An additional factor of 5/7 is needed for correct NOAEC in general population:

Corrected NOAEC for general population = 167 mg/m^3 x 6 hours x 60 min/hour x 0.0008 m^3/min/kg x 5/7= 34.2 mg/kg bw/day

(NB = 167 x 1.15 x 6/24 x 5/7)

ASSESSMENT FACTORS		
	Workers	General population
Interspecies allometric scaling	4	4
Interspecies, remaining differences	2.5	2.5
Intraspecies	5	10
Subacute to chronic	4	4

DNEL workers = 0.24 mg/kg bw/day
DNEL general population = 0.09 mg/kg bw/day

Dermal exposure

Workers/General population

Assuming again 100 % dermal bioavailability the DNELs derived for the dermal route would be the same as those derived for the oral route: DNEL workers, 0.24 mg/kg bw/day; DNEL general population, 0.09 mg/kg bw/day.

Summary

In summary, the RAC agreed that the critical study for setting DNELs for inhalation, oral and dermal routes of diglyme is that of DuPont, 1989. The final DNELs set are shown in Table 5.

Table 5. Derived DNELs for Diglyme

Derived DNELs		
	General population	Workers
Inhalation (mg/m^3)	0.30	1.68
Oral (mg/kg bw/day)	0.09	0.24
Dermal (mg/kg bw/day)	0.09	0.24

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