Rijksinstituut voor Volksgezondheid en Milieu
Ministerie van Volksgezondheid, Welzijn en Sport

Stofdocument deel A

CAS-nr: 123-91-1

1,4-Dioxaan

$C_4H_8O_2$, cyclisch

VN-nr: 1165
GEVI: 33

Synoniemen: diethyleendioxide, diethyleenether, p-dioxaan (Engels: 1,4-dioxane)

Interventiewaarden		10 min.	30 min.	1 uur	2 uur	4 uur	8 uur
Voorlichtingsrichtwaarden	**VRW (mg/m^3)**	180	180	180	180	180	180
Alarmeringsgrenswaarden	**AGW (mg/m^3)**	2100	1500	1200	920	730	370
Levensbedreigende waarden	**LBW (mg/m^3)**	5000	3500	2800	2200	1700	870

Datum vaststelling: 28-11-2008

1 mg/m^3 = 0,273 ppm; 1 ppm = 3,67 mg/m^3

Explosiegrens: LEL = 1,9 vol% ≈ 70.000 mg/m^3

Geur: sterke etherachtige geur

LOA: 6,3 mg/m^3

Fysisch-chemische eigenschappen

Uiterlijk: kleurloze vloeistof
Brand: zeer brandgevaarlijk

Relatieve dichtheid van verzadigd damp-lucht mengsel: 1,08

Molecuulmassa: 88,1 g/mol
Zuurgraad: geen data
LogKow: -0,4
Wateroplosbaarheid: volledig
Verzadigde dampdruk: 41 mbar

Overige informatie

Publieke grenswaarde:
20 mg/m^3 (8 uur)
MAK: 73 mg/m^3
TLV-TWA: 92 mg/m^3

Toxicologische eigenschappen

Effecten bij inhalatoire blootstelling

Onder VRW geen effecten

VRW → AGW: oog-, keel- en neusirritatie, tranenvloed

AGW → LBW: bewustzijnsdaling, benauwdheid, longschade, nierschade, leverschade

Boven LBW: coma, sterfte

Toxiciteit bij eenmalige, inhalatoire blootstelling

- De stof werkt irriterend op de huid, ogen en luchtwegen
- 1,4-Dioxaan kan het centrale zenuwstelsel onderdrukken.
- Nierschade en leverschade kunnen optreden na blootstelling aan 1,4-dioxaan.

Effecten bij blootstelling aan vloeistof

Huidcontact: roodheid, ruwe huid

Oogcontact: roodheid, pijn

Carcinogeniteit

IARC classificatie: 2B
CRP: 31.000 mg/m^3

Beknopte medische informatie

Ontsmetting damp
algemeen: frisse lucht, rust en arts raadplegen

Ontsmetting vloeistof
huid: verontreinigde kleding uittrekken, afspoelen met water
ogen: spoelen met water (evt. contactlenzen verwijderen)
inslikken: mond laten spoelen (uitspugen!), GEEN braken opwekken en direct arts raadplegen

Specifieke behandeling en materialen: geen.

Neem contact op met het NVIC (Tel: 030 - 274 8888) voor informatie met betrekking tot medisch handelen

National Institute for Public Health and the Environment
Ministry of Health, Welfare and Sport

Stofdocument deel B

CAS-nr: 123-91-1 **1,4-Dioxane** **$C_4H_8O_2$, cyclic** **VN-nr: 1165**

Basis for the Dutch Intervention Values

VRW: Same point of departure as for AEGL-1, using different uncertainty factors, 2h value added

AGW: AEGL value is adopted, 2h value added

LBW: AEGL value is adopted except for the 10-min value, 2h value added

Date: 28-11-2008 | AEGL document: Interim, 2005

Dutch Intervention Values (mg/m^3)

	10 min	30 min	1 h	2 h	4 h	8 h	End point
VRW	180	180	180	180	180	180	Threshold of notable discomfort
AGW	2100	1500	1200	920	730	370	Threshold of irreversible liver toxicity
LBW	5000	3500	2800	2200	1700	870	Threshold of lethality in animals

Derivation of the Dutch Intervention Values

VRW: For the derivation of VRW values, eye irritation in human volunteers at 50 ppm (183 mg/m^3) throughout a 6-hour exposure period was used as point of departure. The severity level of the eye irritation was not defined but was considered to be below the notable discomfort level as described in the VRW definition. To derive VRW values the same exposure concentration was used for all time points. In contrast to AEGL-1, no uncertainty factor was applied to derive the VRW, as the point of departure is below the definition of VRW.
The derived VRW-values are supported by data from two different studies with human volunteers. Volunteers exposed for 15 minutes at 300 ppm (1100 mg/m^3) complained of irritation to eyes, nose and throat. At a similar concentration of 280 ppm (1026 mg/m^3), another study reported slight mucous membrane irritation in humans.

AGW: Exposure at 2000 ppm (7330 mg/m^3) for 4 hours was considered a threshold for irreversible liver toxicity in rats and was used as the basis for AGW derivation. A total uncertainty factor of 10 was used. An interspecies uncertainty factor of 3 and an intraspecies factor of 10 were applied. Time scaling using the equation $C^n \times t = k$ was carried out to derive exposure duration-specific values with the default values of n=3 and n=1 for extrapolation to shorter and longer exposure durations, respectively. Time extrapolation was continued to the 10-minute period because even at higher concentrations of 1600 ppm (5900 mg/m^3) for 10 minutes or 1400 ppm (5130 mg/m^3) for 5 minutes exposed subjects did not experience more severe effects than moderate eye, nose and throat irritation.

LBW: No acute inhalation toxicity study that followed today's standards and guidelines was available for dioxane. The derivation of the LBW values was based on a 4-hour LC_{50} of 14,300 ppm (52,400 mg/m^3) in rats. The LC_{50} reported in the key study is supported by other studies in rats. For extrapolation from the LC_{50} value to the threshold for lethality, a factor of 3 was used. This factor was considered adequate because available data indicate a very steep dose-response curve for lethality after inhalation exposure. A total uncertainty factor of 10 was used. An interspecies uncertainty factor of 3 and an intraspecies factor of 10 were applied. Time scaling using the equation $C^n \times t = k$ was carried out using the default values of n=3 and n=1 for extrapolation to shorter and longer exposure durations, respectively. Time extrapolation was continued to the 10-minute period because even at higher concentrations of 1600 ppm (5860 mg/m^3) for 10 minutes or 1400 ppm (5130 mg/m^3) for 5 minutes exposed subjects did not experience more severe effects than moderate eye, nose and throat irritation.

Additional toxicological information (including relevant results of a general literature search, if any)

Fatalities after repeated inhalation exposure to unknown concentrations of dioxane at the workplace are described. Exposure probably also comprised dermal contact. The men experienced nausea and vomiting, described as "stomach trouble", followed after 2-3 days by oliguria and anuria. About 3-7 days after the first symptoms, coma developed, followed by death. Microscopic examinations revealed centrilobular liver necrosis, almost symmetrical necrosis of the outer renal cortex and haemorrhages around the glomeruli.

Volunteers exposed for 15 minutes at 300 ppm (1100 mg/m^3) complained of irritation to eyes, nose and throat. At a similar concentration of 280 ppm (1026 mg/m^3), another study reported slight mucous membrane irritation in humans. More distinct irritation was observed at 1400-1600 ppm (5130-5860 mg/m^3) and severe irritation occurred at 2800-5500 ppm (10,260-20,160 mg/m^3). Three of the subjects exposed to 5500 ppm (20,160 mg/m^3) noticed a slight vertigo which disappeared quickly after leaving the exposure. The shallow increase of irritative effects with concentration also supports the interpretation that the effects found at 50 ppm (183 mg/m^3) can be considered as mild.

Acute toxic effects in animals are mainly central nervous system depression, kidney and liver damage, peripheral nervous system effects as well as irritative effects. At lethal concentrations, narcosis has been observed in rats and guinea pigs.

No relevant studies documenting developmental or reproductive effects of 1,4-dioxane in humans were identified.

H319: Causes serious eye irritation; H335: May cause respiratory irritation; H351: Suspected of causing cancer.

Carcinogenicity and derivation of the CRP value

IARC classification: 2B, possibly carcinogenic to humans

Derivation of the carcinogenic risk potency (CRP):

10^{-4} risk level after inhalation: 0.14 mg/m^3 [AEGL]

CRP = (10^{-4} risk level * average life span in hours)/DRCF

= (0.14 * 613,200) /2.8 = 31,000 mg/m^3

When administered orally, dioxane produced malignant tumours of the nasal cavity and liver in rats, liver tumours in mice, and tumours of the liver and gallbladder in guinea pigs. A lifetime bioassay exposing rats at 111 ppm (410 mg/m^3) for 7 hours/day, 5 days/week found no evidence for carcinogenic effects. Two epidemiological studies in humans found no higher incidence of cancer deaths in workers exposed to 1,4-dioxane.

Odour and derivation of the LOA value

Odour: strong ethereal odour that diminishes rapidly during exposure

OT_{50}: 0.11 ppm (0.40 mg/m^3) [AEGL (2005)]
LOA = 11.8 * OT_{50} * 1.33 = 6.3 mg/m^3

(The concentration Level leading to distinct Odour Awareness (I=3) is calculated using the formula: I = 2.33 * log (C/OT_{50}) + 0.5. A correction factor of 1.33 is applied to this value)

The LOA is far below the VRW values

Other standards and guidelines (1h values in mg/m^3, unless otherwise indicated)

VRW level **180**	*AEGL-1* 62	*ERPG-1* not derived	*IDLH:* 7330 *(30 minutes)*
AGW level **1200**	*AEGL-2* 1200	*AEGL-2* not derived	
LBW level **2800**	*AEGL-3* 2800	*AEGL-3* not derived	