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

Stofdocument deel A

CAS-nr: 329-99-7 **Cyclosarin** **$C_7H_{14}FO_2P$** **VN-nr: n.v.t.**
GEVI: geen

Synoniemen: Agent GF; O-cyclohexylmethyl-fluorofosfonaat (Engels: Cyclosarin)

Interventiewaarden		10 min.	30 min.	1 uur	2 uur	4 uur	8 uur
Voorlichtingsrichtwaarden	**VRW (mg/m^3)**	0,0034	0,0020	0,0010	0,00071	0,00060	0,00042
Alarmeringsgrenswaarden	**AGW (mg/m^3)**	0,043	0,025	0,018	0,013	0,0088	0,0063
Levensbedreigende waarden	**LBW (mg/m^3)**	0,38	0,19	0,13	0,094	0,070	0,051

Datum vaststelling: November 2015

1 mg/m^3 = 0,133 ppm; 1 ppm = 7,50 mg/m^3

Explosiegrens: Geen data

Geur: zwakke fruitige of kruidige geur

LOA: niet afgeleid

Fysisch-chemische eigenschappen

Uiterlijk: visceuze, kleurloze, vluchtige vloeistof
Brand: Geen data

Relatieve dichtheid van verzadigd damp-lucht mengsel: 6,2

Molecuulmassa:	180,2 g/mol
Zuurgraad:	Geen data
LogKow:	1,67
Wateroplosbaarheid:	3.7 mg/l (bij 20 °C, slecht)
Verzadigde dampdruk:	0,044 (mmHg, 25°C)

Overige informatie

Publieke grenswaarde: Niet afgeleid
MAK: Niet afgeleid
TLV-TWA: Niet afgeleid

Toxicologische eigenschappen

Effecten bij inhalatoire blootstelling

Onder VRW:	hoofdpijn
VRW → AGW:	pupilvernauwing, misselijkheid, braken
AGW → LBW:	speekselvloed, zweten, tranenvloed, moeizaam ademen, zwaktegevoel, buikkrampen, spierkrampen, kleine spiertrekkingen, verlammingsverschijnselen, bewustzijnsdaling
Boven LBW:	convulsies, coma, verlamming, ademstilstand, sterfte

Toxiciteit bij eenmalige, inhalatoire blootstelling

- Cyclosarin is een zeer potente irreversibele cholinesterase remmer. Hierdoor wordt de afbraak van de neurotransmitter acetylcholine geremd en de zenuwimpuls bij de motorische eindplaat verstoord.
- Doelorganen zijn het centrale, het perifere en het autonome zenuwstelsel. De meeste effecten treden zeer snel op, echter neuropathologische effecten zoals verlamming kunnen vertraagd optreden en langdurig van aard zijn.
- Kinderen zijn gevoeliger voor de effecten van de stof dan volwassenen. Ook kan het klinische beeld bij kinderen anders zijn dan bij volwassenen.
- Mogelijk zijn vrouwen gevoeliger voor de effecten van de stof dan mannen.

Effecten bij blootstelling aan vloeistof

Huidcontact: roodheid, (lokale) spiertrekkingen, verder zie: 'Effecten bij inhalatoire blootstelling'

Oogcontact: roodheid en (hevige) pijn, nauwe pupillen, visusklachten, tranenvloed, verder zie: 'Effecten bij inhalatoire blootstelling'

Carcinogeniteit

IARC classificatie: Niet geclassificeerd
CRP: Niet afgeleid

Beknopte medische informatie

Ontsmetting damp

algemeen: frisse lucht, rust, halfzittende houding, specifieke behandeling en direct spoedeisende medische hulp inzetten.

Ontsmetting vloeistof

huid: verontreinigde kleding uittrekken, spoelen en wassen met water en zeep, specifieke behandeling en direct spoedeisende medische hulp inzetten.

ogen: minimaal 15 min. spoelen met water (evt. contactlenzen verwijderen), dan naar oogarts brengen, blijven spoelen tijdens vervoer.

inslikken: mond laten spoelen (uitspugen!) , specifieke behandeling en direct spoedeisende medische hulp inzetten.

Specifieke behandeling en materialen*: CAVE hulpverleners: draag persoonlijke bescherming!* Bij vergiftiging is specifieke eerste hulp noodzakelijk; 100% zuurstof en het specifieke antidotum atropine) moet met gebruiksaanwijzing ter plekke beschikbaar zijn. Toediening van andere middelen (zoals oximen) kan bij de spoedeisende hulpverlening (in het ziekenhuis) overwogen worden.

Neem contact op met het NVIC (tel: +31 (0)30 –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: 329-99-7 **Cyclosarin** **$C_7H_{14}FO_2P$** **UN-nr: -**

Basis for the Dutch Intervention Values

VRW: AEGL value is adopted, 2h value added

AGW: AEGL value is adopted, 2h value added

LBW: AEGL value is adopted, 2h value added

Date: November 2015 | AEGL document: Final, 2003

Dutch Intervention Values (mg/m^3)

	10 min	30 min	1 h	2 h	4 h	8 h	End point
VRW	0.0034	0.0020	0.0010	0.00071	0.00060	0.00042	0.5 times the VRW values for Agent GB. End point for agent GB: EC_{50} for miosis in rats.
AGW	0.043	0.025	0.018	0.013	0.0088	0.0063	0.5 times the AGW values for Agent GB. End point for agent GB: miosis, dyspnea, RBC-ChE inhibition, single fibre electro-myography (SFEMG) changes in human volunteers.
LBW	0.38	0.19	0.13	0.094	0.070	0.051	LBW values for agent GB were adopted. End point for agent GB: lethality in rats (LC_{01}).

Derivation of the Dutch Intervention Values

Because of the sparse human and animal toxicity dataset for cyclosarin (agent GF) all Dutch Intervention Values for this nerve agent are based on the values for nerve agent GB (Sarin) by applying a relative potency method.This approach is justified given: 1) the reasonably complete dataset for the nerve agents as a group, and 2) the same mode of action for agent GB and agent GF.

VRW:

The VRW values for agent GF were based on a well-conducted whole body inhalation study in adult female rats exposed to a range of GB vapor concentrations (0.01 to 0.48 mg/m^3) over three time durations (10 min, 60 min, or 240 min). Female rats are reported to be more sensitive to GB vapor toxicity than males. Analysis of rat pupil diameters assessed pre- and postexposure allowed determination of EC_{50} values for miosis (which is defined as a postexposure pupil diameter of 50% or less of the preexposure diameter in 50% of the exposed population). Although the EC_{50} for miosis is not considered an adverse effect in humans, miosis is regarded the first measurable change in the continuum of effects caused by inhibition of acetylcholinesterase. As miosis is transient and reversible, this effect is thought to be the most relevant endpoint for VRW-levels. The selection of miosis induction as the basis for the VRW is supported by the observation that cholinesterase activity depression is too variable for application as critical effects. Human data are also available and showing rhinorrhea, headache, tightness in chest, cramps nausea, and miosis (mean maximal decrease in pupil diameter) in human volunteers exposed to GB at 0.05 mg/m^3 for 20 min. These human data are considered secondary and supportive, leading to almost the same values.
The 10-min, 60-min and 240-min rat EC_{50} values for miosis of 0.068, 0.020 and 0.012 mg/m^3 respectively were used as point of departure for determining VRW-levels. Time scaling was performed for the remaining 30-min, 2-h and 8-h values using the $C^n \times t = k$ equation, where n = 2 based on regression analysis of miosis and lethality data in rats. An interspecies uncertainty factor of 1 and an intraspecies uncertainty factor of 10 were used, resulting in a total uncertainty factor of 10. For miosis as a critical effect, comparison of the EC_{50} values for miosis in the eye of the rabbit indicated that agent GF is approximately twice as potent as agent GB. The VRW-values for agent GF are therefore set equal to 0.5 times the VRW-values derived for agent GB (correction applied to mg/m^3 values).

AGW: The AGW values for agent GF were based on a study in which miosis, dyspnea, photophobia, inhibition of red blood cell cholinesterase (RBC-ChE), and changes in single fibre electromyography

(SFEMG) were observed in human volunteers following a 30-min exposure at 0.5 mg agent GB/m^3. The SFEMG changes noted in the study were not clinically significant and were not detectable after 15-30 months. Although the observed SFEMG changes were reversible and subclinical, these effects are considered an early indicator of exposures that potentially could result in more significant effects. Selection of this effect as a protective definition of an AGW level is considered appropriate given the steep dose-response toxicity curve of nerve agents. Time scaling was performed by using the C^n x t = k equation, where n = 2 based on regression analysis of miosis and lethality data in female rats. An interspecies uncertainty factor of 1 and an intraspecies uncertainty factor of 10 were used, resulting in a total uncertainty factor of 10. For miosis as a critical effect, comparison of the EC_{50} values for miosis in the eye of the rabbit indicated that agent GF is approximately twice as potent as agent GB. The AGW-values for agent GF are therefore set equal to 0.5 times the values derived for agent GB (correction applied to mg/m^3 values).

LBW: LBW values for agent GF were derived from recent whole-body inhalation studies in which the lethality of GB vapor in female rats was evaluated after various exposure periods. Female rats are reported to be more sensitive to GB vapor toxicity than males. Using probit analysis, the estimated LC_{01} values for female rats were as follows: 11.537 mg/m^3 for 10 min, 5.836 mg/m^3 for 30 min, 4.006 mg/m^3 for 60 min, 2.087 mg/m^3 for 4 h, and 1.761 mg/m^3 for 6 h. Time scaling was performed to derive the 2-h and 8-h value using the C^n x t = k equation, where n = 2 based on regression analysis of miosis and lethality data in female rats. An interspecies uncertainty factor of 3 and an intraspecies uncertainty factor of 10 were used, resulting in a total uncertainty factor of 30. For LBW effects agent GF and agent GB are considered equipotent based on lethality data in rats. The LBW-values for agent GF are therefore set equal to the values derived for agent GB.

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

Nerve agents exert toxic effects on the central and peripheral nervous system indirectly through acetylcholinesterase inhibition, nerve agents may also affect nerve impulse transmission by additional mechanisms at neuromuscular junctions and at neurotransmitter receptor sites in the CNS. The first symptoms are related to the nerve conduction inhibition by the substance and consist of: pupil constriction (miosis), headache, shortness of breath, tightness of the chest. A runny nose and lacrimation can also be observed. At increasing exposure levels or prolonged exposures sweating, diarrhea, bradycardia, tremors, overall weakness, paralysis, unconsciousness, convulsions, suppression of respiration and death can occur. The dose-response relation is considered very steep and effects may occur rapidly. However, delayed neuropathological effects (such as paralysis) may occur.

The inhibited acetylcholinesterase can be reactivated by the process of dephosphorylation, but this is not possible once the nerve agent-cholinesterase complex undergoes “aging,” which is thought to happen because of a loss of an alkyl or alkoxy group. No information is found on the velocity of aging of agent GF.

No information found on human reproductive toxicity. Animal data from vapor and oral exposure studies for agent GB suggest that agent GB does not induce reproductive or developmental effects in mammals.

No harmonized hazard sentences were found.

Carcinogenicity and derivation of the CRP value

IARC classification: Not classified.

No carcinogenic risk potency (CRP) was derived

Odour and derivation of the LOA value

Odour: Sweet or musty odour of peaches

Odour thresholds of 10.4-14.8 mg/m^3 are reported, but no OT50 was derived.

No LOA was derived

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

VRW level	*AEGL-1*	*ERPG-1*		*IDLH: Not Derived*
0.0010	0.0010	NA		
AGW level	*AEGL-2*	*ERPG-2*		
0.018	0.018	NA		

LBW level	*AEGL-3*	*ERPG-3*		
0.13	0.13	NA		