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

Stofdocument deel A

CAS-nr: 107-13-1 **Acrylnitril** **CH_2=CH-CN** **VN-nr: 1093**
GEVI: 336

Synoniemen: acrylonitril, 2-propeennitril, vinylcyanide (Engels: acrylonitrile)

Interventiewaarden		10 min.	30 min.	1 uur	2 uur	4 uur	8 uur
Voorlichtingsrichtwaarden	**VRW (mg/m^3)**	3,3	3,3	3,3	3,3	3,3	3,3
Alarmeringsgrenswaarden	**AGW (mg/m^3)**	650	240	130	67	36	19
Levensbedreigende waarden	**LBW (mg/m^3)**	1300	440	220	110	58	30
Datum vaststelling: November 2015				1 mg/m^3 = 0,453 ppm; 1 ppm = 2,21 mg/m^3			

Explosiegrens: LEL = 2,8 vol% ≈ 62.000 mg/m^3

Geur: scherp, ui- en knoflookachtig
LOA: 323 mg/m^3

Fysisch-chemische eigenschappen

Uiterlijk: kleurloze tot lichtgele vloeistof
Brand: zeer brandgevaarlijk

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

Molecuulmassa:	53,1 g/mol
Zuurgraad:	Geen data
LogKow:	-0,9
Wateroplosbaarheid:	7,3 g/100 ml (matig)
Verzadigde dampdruk:	124 mbar

Overige informatie

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

Toxicologische eigenschappen

Effecten bij inhalatoire blootstelling

Onder VRW: geen klachten

VRW → AGW: rode en geïrriteerde brandende ogen, lichte tranenvloed, pijn in keel en neus, niezen, hoesten, hoofdpijn

AGW → LBW: pijn op de borst en pijn bij (door)ademen, piepende ademhaling, benauwdheid, misselijkheid, braken, duizeligheid, krachtsverlies, verwardheid

Boven LBW: convulsies, ademnood, ademstilstand, coma, overlijden

Toxiciteit bij eenmalige, inhalatoire blootstelling

- Acrylnitril wordt omgezet tot o.a. cyanide en 2-cyano-ethyleenoxide.
- Cyanide blokkeert de ademhalingsketen in de cel. Hierdoor wordt de energiehuishouding verstoord en kan lactaatacidose ontstaan.
- Acrylnitril werkt irriterend op de luchtwegen; mogelijk veroorzaakt door cyanide.
- Primaire systemische doelorganen zijn het centrale zenuwstelsel en het cardiovasculaire systeem.
- Acrylnitril kan hematologische effecten veroorzaken, mogelijk veroorzaakt door adduct-vorming van acrylnitril of 2-cyano-ethyleenoxide met hemoglobine. Methemoglobinevorming en hemolyse zijn een mogelijk gevolg hiervan.

Effecten bij blootstelling aan vloeistof

Huidcontact: roodheid, pijn, blaren, brandwonden. De stof wordt door de huid opgenomen!

Oogcontact: bijtend, roodheid, pijn, ernstige brandwonden

Carcinogeniteit

IARC classificatie: 2B
CRP: 329 mg/m^3

Beknopte medische informatie

Ontsmetting damp

algemeen: DIRECT 100% ZUURSTOF TOEDIENEN!, specifieke behandeling en direct spoedeisende medische hulp inzetten.

Ontsmetting vloeistof

huid: PAS OP: HUIDOPNAME! DIRECT 100% ZUURSTOF TOEDIENEN! (GEEN mond-op-mondbeademing), specifieke behandeling en direct spoedeisende medische hulp inzetten, ondertussen verontreinigde kleding uittrekken, minimaal 20 min. spoelen met veel water of douchen.

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

inslikken: DIRECT 100% ZUURSTOF TOEDIENEN!, mond laten spoelen (uitspugen!), GEEN braken opwekken, specifieke behandeling en direct spoedeisende medische hulp inzetten.

Specifieke behandeling en materialen:

De benodigde middelen (specifieke antidota zoals 100% zuurstof en o.a. N-acetylcysteïne, hydroxocobalamine en natriumthiosulfaat) moeten met gebruiksaanwijzing ter plekke beschikbaar zijn.

Voor aanwijzingen over verdere behandeling zo nodig het NVIC (tel: +31 (0)30 –274 8888) bellen.

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

Stofdocument deel B

CAS-nr: 107-13-1 **Acrylonitrile** **CH_2=CH-CN** **UN-nr: 1093**

Basis for the Dutch Intervention Values

VRW: AEGL endpoint is adopted but used for all timepoints, 2h value added

AGW: Different point of departure than AEGL values, 2h value added

LBW: Different point of departure than AEGL, 2h value added

Date: November 2015 | AEGL document: Final, 2014

Dutch Intervention Values (mg/m^3)

	10 min	30 min	1 h	2 h	4 h	8 h	End point
VRW	3.3	3.3	3.3	3.3	3.3	3.3	No effect level in human volunteers
AGW	650	240	130	67	36	19	Slight ocular and nasal irritation in rats
LBW	1300	440	220	110	58	30	Lethality threshold in rats

Derivation of the Dutch Intervention Values

VRW: The VRW values are developed based upon results from a controlled experiment with 6 male human volunteers exposed by inhalation to 2.3 ppm (5 mg/m^3) and 4.6 ppm (10 mg/m^3) acrylonitrile for 8 hours. Exposure to the highest concentration (4.6 ppm/10 mg/m^3) for 8 hours did not result in any symptoms of exposure. This finding is consistent with a report stating that workers routinely exposed to approximately 5 ppm (11 mg/m^3) acrylonitrile experienced mild effects (initial conjunctival irritation) to which some degree of accommodation occurred. Data indicate that at higher concentrations during occupational exposure (16 to 100 ppm (35-221 mg/m^3) for 20-45 minutes) more severe effects like nasal and ocular irritation, discomfort of the chest, nervousness, irritability and headaches were reported. A 3-fold reduction (an appropriate adjustment for mild irritation effects) of the lower limit of this range is equivalent to the 4.6 ppm (10 mg/m^3) which is in line with the no-effect concentration of the study in human volunteers. Therefore, the point of departure for the derivation of the VRW is the 8 hour exposure to 4.6 ppm (10 mg/m^3) acrylonitrile, based on data from healthy volunteers and workers. As the data are partly obtained in workers and because some accommodation occurred an intraspecies uncertainty factor of 3 was applied. The VRW values are not time scaled, because the effect is ocular irritation for which it is not to be expected that effects vary over time. This is supported by data in humans. The VRW values where held constant at 1.5 ppm (3.3 mg/m^3) for all timepoints.
This approach deviates from the AEGL-1 derivation, where values above 30 minutes were not recommended, because these would result in levels higher than the AEGL-2.

AGW: The AGW values are based upon data from rats (16/group) showing slight transient effects (ocular and nasal irritation) following a 2-hour exposure by inhalation to 305 ppm (674 mg/m^3) acrylonitrile. At the next highest concentration (595 ppm, 1300 mg/m^3) effects were indicated as marked. All effects resolved within 12 hours post exposure. Point of departure was 305 ppm (674 mg/m^3) exposure for 2 hours. An interspecies uncertainty factor of 3 and an intraspecies uncertainty factor of 3 was applied because the effects associated with acute irritation effects are not likely to vary greatly among individuals and because metabolism may be of limited relevance regarding such effects. An overall uncertainty factor of 10 was applied. Application of higher or additional uncertainty factors would also result in AGW values unacceptably similar to VRW values that were based upon human exposure data. Time scaling was performed using the equation $C^n \times t = k$ with n = 1.1 based on ten Berge (1986). This approach deviates from the AEGL which uses reprotoxic effects (decreases in fetal body weight) for derivation of AEGL-2 levels. Fetal body weight effects are not considered relevant for AGW.
This approach deviates from the AEGL-2 derivation, where the AEGL-2 levels were calculated using the change in fetal body weight in a developmental study as point of departure.

LBW: In contrast to the AEGK-3, the LBW values were derived from a rat lethality study (Dudley and Neal, 1942) from which 30 minute, 1-, 2-, 4-, and 8-hour LC_{01} values (12660, 4370, 2233, 1141, 583, 298 mg/m^3) were calculated. Although the dog appears to be the most sensitive species, the overall

database for rats is more robust thereby justifying use of the rat data. The LC_{01} values were points of departure for derivation of LBW-values. An interspecies factor of 3 was considered sufficient to account for possible toxicodynamic/metabolism differences, because PBPK models demonstrated that predicted concentrations of acrylonitrile and the metabolite 2-cyanoethylene oxide in blood and brain were similar in rats and humans exposed by inhalation. For effects resulting from a single acute exposure, an intraspecies uncertainty factor of 3 would seem sufficient for accounting for variability in metabolism-mediated effects. Additional uncertainty factor application would result in incompatible LBW and AGW values. The 30-minute, 1-hour, 2-hour and 8-hour LBW values were derived based upon their respective LC_{01} values.

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

Generally, the toxic effects following acute inhalation exposure to acrylonitrile appear to be irritation of the respiratory tract and toxic effects which appear to be related to the metabolism of acrylonitrile to cyanide. Acrylonitrile-induced neurological effects in laboratory animals appear to involve the parent compound and the cyanide metabolite. The pivotal role of cyanide has been clearly demonstrated. Acrylonitrile-induced convulsions are likely the result of cyanide resulting from acrylonitrile metabolism, although recent work suggests that only the early seizures are cyanide-mediated and that severe clonic convulsions preceding death may be due to parent compound. The mechanism by which acrylonitrile causes irritation is unknown. Nasal tissue damage in rats may be related to metabolism of acrylonitrile by this tissue. Hematologic effects may be due to acrylonitrile hemoglobin adducts and 2-cyanoethylene oxide hemoglobin adducts, while GSH depletion in red blood cells may result in the oxidation of hemoglobin to methemoglobin.

Acrylonitrile toxicity appears to be directly related to its metabolism. Two major metabolism pathways have been described; conjugation with glutathione and epoxidation by microsomal cytochrome P4502E1 which forms 2-cyanoethylene oxide. Metabolites from both pathways are subject to additional biotransformation. The glutathione conjugate may form a mercapturic acid which is excreted in urine. 2-Cyanoethylene oxide is further metabolized via conjugation with glutathione (catalysis with cytosolic GST or nonenzymatically) resulting in additional conjugates and via hydrolysis by microsomal epoxide hydrolase (EH). The secondary metabolites of 2-cyanoethylene oxide may also be further metabolized. Cyanide may be generated via the EH pathway and by one of the GSH conjugation products. Cyanide, in turn, is detoxified to thiocyanate via rhodanese mediated reactions with thiosulfate.

A developmental inhalation toxicity study in rats showed a statistically increased incidence of malformations (short tail, short trunk, missing ribs, delayed ossification of skull bones, omphalocele and hemivertebrae) in rats exposed to 80 ppm (180 mg/m^3) acrylonitrile for 6 hrs/day on gestation days 6 through 15. There was no evidence of teratogenicity or embryotoxicity in rats exposed to 40 ppm (90 mg/m^3). In another developmental inhalation toxicity study in rats evaluation of external, visceral and skeletal variation in the fetuses revealed no acrylonitrile related effects at exposures up to 100 ppm (220 mg/m^3) for 6 hrs/day on gestation days 6 to 20. Another study found nonlethal effect on fetal development that included decreases in fetal body weight without fetal malformations (25-100 ppm; 55-221 mg/m^3) and nonlethal fetal malformations (40 and 80 ppm; 88 and 176 mg/m^3). A two generation reproductive toxicity study revealed weight decreases in the F_1 offspring of the 90-ppm (198 mg/m^3) group.

H350: May cause cancer, H301: Toxic if swallowed, H331: Toxic by inhalation, H318: Causes serious eye damage, H335: May cause respiratory irritation, H315: Causes skin irritation, H317: May cause allergic skin reaction

Carcinogenicity and derivation of the CRP value

IARC classification: 2B (possibly carcinogenic to humans)

IARC downgraded acrylonitrile from a category 2A to a category 2B (1999). This status change was based upon the lack of carcinogenic evidence from the more recent epidemiological studies. The data regarding potential carcinogenicity in humans is considered to be inadequate and no evidence of a causal association exists. This decision supports the conclusion that acrylonitrile is probably not carcinogenic to man.

Odour and derivation of the LOA value

Odour: Sharp, onion-garlic

OT_{50}: 20.5 mg/m^3 [Nagata, 2003; corrected value derived from 9.3 ppm]

$LOA = 11.8 * OT_{50} * 1.33 = 323\ mg/m^3$

(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)

Note, the AEGL document states a LOA of 145 ppm (320

Derivation of the carcinogenic risk potency (CRP): 10^{-4} risk level after inhalation: $1,5*10^{-3}$ mg/m^3 [EPA, 1984] CRP = ($1,5*10^{-3}$ mg/m^3 * 613,200) /2.8 = 329 mg/m^3 The CRP values lie above the AGW, VRW and LBW values.	mg/m3) The LOA lies above the AGW, VRW and LBW values.

***Other standards and guidelines** (1h values in mg/m^3, unless otherwise indicated)*				
VRW level **3.3**	*AEGL-1* NR	*ERPG-1* 22		*IDLH:* 188 (30 minutes)
AGW level **130**	*AEGL-2* 3.8	*ERPG-2* 77		
LBW level **220**	*AEGL-3* 62	*ERPG-3* 166		