Arbeidstilsynet

Grunnlag for fastsettelse av grenseverdi

Grunnlagsdokument for amitrol ($C_2H_4N_4$)

Kommisjonsdirektiv 2017/164/EU

Tittel: Grunnlag for fastsettelse av grenseverdi. Grunnlagsdokument for amitrol ($C_2H_4N_4$).

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Denne rapporten omhandler det toksikologiske grunnlaget og vurderinger, samt tekniske og økonomiske hensyn for fastsettelse av grenseverdi for amitrol ($C_2H_4N_4$).

Innhold

Forord

Grunnlagsdokumenter for fastsettelse av grenseverdier utarbeides av Arbeidstilsynet i samarbeid med Statens arbeidsmiljøinstitutt (STAMI) og partene i arbeidslivet (Næringslivets hovedorganisasjon/Norsk Industri og Landsorganisasjonen i Norge) i henhold til *Strategi for utarbeidelse og fastsettelse av grenseverdier for forurensninger i arbeidsatmosfæren*. Dette dokumentet er utarbeidet ved implementering av kommisjonsdirektiv 2017/164/EU fastsatt 31. januar 2017.

EU-rådets direktiv 98/24/EC (Vern av helse og sikkerhet til arbeidstakere mot risiko i forbindelse med kjemiske agenser på arbeidsplassen) av 7. april 1998 stiller krav om at EU- kommisjonen skal legge frem forslag til indikative grenseverdier for eksponering av visse kjemikalier som medlemslandene må innføre på nasjonalt nivå. De nasjonale grenseverdiene kan være høyere enn de som står oppført i direktivet, dersom et medlemsland mener at det er nødvendig av tekniske og/eller økonomiske hensyn, men landene bør nærme seg den indikative grenseverdien. Direktivet stiller krav om at indikative grenseverdier vedtas gjennom kommisjonsdirektiv.

I Norge ble de indikative grenseverdiene innført som veiledende administrative normer. Da nye Arbeidsmiljøforskrifter trådte i kraft 1.1.2013 ble de veiledende administrative normene forskriftsfestet i forskrift om tiltaks- og grenseverdier og fikk betegnelsen tiltaksverdier. I 2015 ble begrepet «grenseverdi» for kjemikalier presisert og begrepet «tiltaksverdi» for kjemikalier ble opphevet i forskrift om tiltaks- og grenseverdier. I vedlegg 1 til forskriften ble det innført en tydeliggjøring av anmerkningene.

Arbeidstilsynet har ansvaret for revisjonsprosessen og utarbeidelse av grunnlagsdokumenter for stoffene som blir vurdert. Det toksikologiske grunnlaget for stoffene i denne revisjonen baserer seg i hovedsak på kriteriedokumenter fra EUs vitenskapskomité for fastsettelse av grenseverdier, Scientific Committee for Occupational Exposure Limits (SCOEL). SCOEL utarbeider de vitenskapelige vurderingene som danner grunnlaget for anbefalinger til helsebaserte grenseverdier, og disse legges fram for kommisjonen.

Statens arbeidsmiljøinstitutt (STAMI) ved Toksikologisk ekspertgruppe for administrative normer (TEAN) bidrar med faglige vurderinger i dette arbeidet. TEAN vurderer og evaluerer de aktuelle SCOEL dokumentene, presiserer kritiske effekter og vurderer behov for korttidsverdier ut i fra den foreliggende dokumentasjonen. Videre søker og evaluerer TEAN nyere litteratur etter utgivelsen av dokumentet. TEAN bruker kriteriene gitt i SCOEL's metodedokument, "Methodology for the derivation of occupational exposure limits: Key documentation (version 7, June 2013)". Dette er inkludert i TEANs Metodedokument del B (Prosedyre for utarbeidelse av toksikologiske vurderinger for stoffer som skal implementeres i det norske regelverket for grenseverdier etter direktiv fra EU-kommisjonen) utarbeidet for denne revisjonen.

Informasjon om bruk og eksponering i Norge innhentes fra Produktregisteret, EXPO databasen ved STAMI og eventuelle tilgjengelige måledata fra virksomheter/næringer.
Beslutningsprosessen skjer gjennom drøftingsmøter der Arbeidstilsynet, Næringslivets hovedorganisasjon/Norsk Industri og Landsorganisasjonen i Norge deltar, samt orienteringsmøter og offentlig høring. Konklusjonene fra høringen med forskriftsendringer og nye grenseverdier forelegges Arbeids- og sosialdepartementet som tar den endelige beslutningen.

Innledning

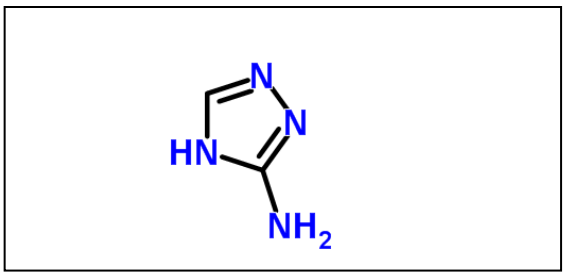
Dette grunnlagsdokumentet omhandler vurderingsgrunnlaget for fastsettelse av grenseverdi for amitrol. Innholdet bygger på anbefalinger fra Scientific Committee on Occupational Exposure Limits (SCOEL) i EU for amitrol (vedlegg 1), samt vurderinger og kommentarer fra Toksikologisk Ekspertgruppe for Administrative Normer (TEAN).

1. Stoffets identitet

Amitrol ($C_2H_4N_4$) og stoffets molekylformel, synonymer av stoffets navn, stoffets identifikasjonsnummer i Chemical Abstract Service (CAS-nr.), European Inventory of Existing Commercial Chemical Substances (EINECS-nr. og/eller EC-nr.) og Indeks-nr. der disse er kjent er gitt i tabell 1. Strukturformel av amitrol er vist i figur 1.

Tabell 1. Stoffets navn og identitet.

Navn **Mokelylformel**	**Amitrol** **$C_2H_4N_4$**
Synonymer	2-amino-1,3,4-triazol, 3-amino-1H-1,2,4-triazol, 3-Amino-s-triazol, 1,2,4-triazol-3-amin
CAS-nr.	61-82-5
EC-nr.	200-521-5
Indeks-nr.	613-011-00-6



Figur 1. Strukturformel av amitrol.

2. Fysikalske og kjemiske data

Amitrol er et krystallinsk og fargeløst stoff som blir brukt som ugressmiddel og for å regulere vekst hos planter.

Det vises til tabell 2 for fysikalske og kjemiske data for amitrol.

Tabell 2. Fysikalske og kjemiske data for amitrol ($C_2H_4N_4$).

Molekylvekt (g/mol)	84,080
Fysisk tilstand	Fargeløst, krystallinsk pulver
Smeltepunkt (°C)	157 - 159
Løselighet i vann (20 - 25 °C) (g/l) **Løselighet i eter og alkohol (20 °C)**	280 - 335
Damptrykk ved 20 °C (10^{-7} hPa)	5,79
Tetthet (20 °C) (g/cm^3)	0,6 - 0,85
Omregningsfaktor (20 °C, 101 kPa)	1 ppm = 3,50 mg/m^3 1 mg/m^3 = 0,286 ppm

2.1. Forekomst og bruk

Amitrol har vært forbudt i Norge siden 1979 grunnet kreftfremkallende potensiale. Amitrol fikk avslag på regodkjenning som aktivt stoff som kan inngå i plantevernmiddel etter Europaparlaments- og rådsforordning (EF) nr. 1107/2009 om markedsføring av plantevernmidler. Bakgrunnen for avslaget var blant annet helsevurderingene og at amitrol er klassifisert som reprotoksisk kategori 2. Fra 2016 er amitrol forbudt å omsette i EU-land, Norge inkludert.

3. Grenseverdier

3.1 Nåværende grenseverdi

Det er ikke fastsatt en grenseverdi for amitrol i Norge.

3.2. Grenseverdi fra EU

Den europeiske vitenskapskomiteen, SCOEL foreslår for amitrol i sitt kriteriedokument fra 2009:

IOELV (Indicative Occupational Exposure Limit Value) (8 timer): 0,2 mg/m^3

SCOEL vurderer amitrol i karsinogen gruppe D, ikke gentoksisk.

3.3. Grenseverdier fra andre land og organisasjoner

Tabell 3. Grenseverdier for amitrol fra andre land og organisasjoner. Land og organisasjoner som ikke har grenseverdier eller korttidsverdier for amitrol er markert med -.

Land Organisasjon	Grenseverdi (8 timer)	Korttidsverdi (15 min)	Anmerkning Kommentar
Sverige[1]	-	-	-
Danmark[2]	0,2 mg/m³	-	K – stoffet er oppført i listen over stoffer som ansees for å være kreftfremkallende.
Finland[3]	-	-	-
Storbritannia[4]	-	-	-
Nederland[5]	0,2 mg/m³	-	-
ACGIH, USA[6]	0,2 mg/m³	-	-
NIOSH, USA[6]	0,2 mg/m³	-	-
Tyskland, MAK[6]	0,2 mg/m³	-	Skin; hudopptak C – Takverdi, Overskridelsesfaktor for takverdi - II (8) TWA: 0,2 I - Overskridelsesfaktor
Tyskland, Myndighetene[7]	0,2 mg/m³, E	-	8 (II) - Overskridelsesfaktor H - hudopptak Y - ikke fare for skade på foster dersom grenseverdien overholdes

[1] Arbetsmiljöverkets Hygieniska gränsvärden AFS 2015:7, https://www.av.se/globalassets/filer/publikationer/foreskrifter/hygieniska-gransvarden-afs-2015-7.pdf.
[2] At-vejledning, stoffer og materialer - C.0.1, 2007, https://arbejdstilsynet.dk/da/regler/at-vejledninger/g/c-0-1-graensevaerdi-for-stoffer-og-mat.
[3] Social og hälsovårdsministeriet, HTP-värden, Koncentrationer som befunnits skadliga, Helsingfors, 2016, http://julkaisut.valtioneuvosto.fi/bitstream/handle/10024/79110/STM_9_2016_HTP-varden_2016_Ruotsi_22122016_NETTI.pdf .
[4] EH40 andre utgave, 2013, http://www.hse.gov.uk/pubns/priced/eh40.pdf
[5] http://www.ser.nl/en/oel_database.aspx; http://www.ser.nl/en/grenswaarden/2%20butyne%201%204%20diol.aspx
[6] Guide to occupational exposure values compiled by ACGIH, 2017.
[7] Baua, TRGS 900, oppdatert 2016, https://www.baua.de/DE/Angebote/Rechtstexte-und-Technische-Regeln/Regelwerk/TRGS/pdf/TRGS-900.pdf;jsessionid=439FFF321DF2323E60F868CD08E9CD3A.s1t2?__blob=publicationFile&v=2

3.4. Stoffets klassifisering

Amitrol er i henhold til CLP Annex VI (Forordning EC No 1272/2008)[1], tabell 3.1 (Liste over harmonisert klassifisering og merking av farlige kjemikalier). klassifisert og merket i ulike fareklasser, med faresetninger og koder, som gitt i tabell 4 nedenfor.

Tabell 4. Fareklasser, farekategori med forkortelse, merkekoder og faresetninger for amitrol[1]

Fareklasse **Farekategori** **Forkortelse**	**Merkekode**	**Faresetning**
Spesifikk målorgantoksisitet – gjentatt eksponering Kategori 2 STOT RE 2	H373	Kan forårsake organskader ved langvarig eller gjentatt eksponering
Farlig for vannmiljøet Kronisk kategori 2 Aquatic Chronic 2	H411	Giftig, med langtidsvirkning, for liv i vann
Reproduksjonstoksisitet Kategori 2 Repr. 2	H361d	Mistenkes for å kunne gi fosterskader.

[1] CLP ((Forordning (EC) Nr. 1272/2008), http://www.miljodirektoratet.no/Documents/publikasjoner/M259/M259.pdf https://echa.europa.eu/information-on-chemicals/cl-inventory-database

3.5 Biologisk overvåking

For å vurdere grad av eksponering for forurensning i luften på arbeidsplassen kan man anvende konsentrasjonen av forurensningen i arbeidstakerens urin, blod eller utåndingsluft, eller annen respons på eksponeringen i kroppen. EU har satt verdier for dette kalt biologisk grenseverdi (BLV).

SCOEL fremmer ikke et forslag til biologisk grenseverdi for amitrol.

4. Toksikologiske data og helseeffekter

4.1. Kommentarer fra TEAN

Amitrol er et herbicid som det fra 2016 er forbudt å omsette i EU-land, Norge inkludert. Begrunnelsen for forbudet fra EU-kommisjonen er fare for forurensning av grunnvann samt at stoffet er mistenkt for å ha hormonforstyrrende effekter. Det pågår for tiden diskusjoner i fagmiljøer om hvordan slike stoffer skal testes toksikologisk og hvordan de skal risikovurderes, spesielt med hensyn til terskelverdier.

SCOEL har, basert på rotteforsøk, satt opptak av jod og andre effekter på tyroidea-kjertelen som kritisk effekt.

SCOEL har i sitt dokument fra 2009 ikke vurdert helseskadelige konsekvenser knyttet til mulige hormonforstyrrende mekanismer. For amitrol er kunnskapene om dette fremdeles mangelfulle, men stoffet er satt opp på EUs liste over stoffer som er sterkt mistenkt for å ha slike effekter og derfor er høyt prioritert for utredning.

Basert på at Amitrol nå ikke tillates omsatt i Norge har TEAN ingen ytterligere kommentarer om stoffet.

5. Bruk og eksponering

5.1. Opplysning fra Produktregistret

Amitrol inngår ikke i produkter som er registreringspliktige i Produktregisteret (oktober 2016). Det foreligger derfor ingen opplysninger om hvilke typer produkter stoffet inngår i og ingen opplysninger om bransjeanvendelse fra registeret.

5.2. Eksponering og måledokumentasjon

Det foreligger ingen måledokumentasjon for amitrol i STAMIs eksponeringsdatabase EXPO (2016).

5.2.1. Prøvetakings- og analysemetode

I tabell 5 er anbefalte metoder for prøvetaking og analyser av amitrol presentert.

Tabell 5. Anbefalte metoder for prøvetaking og analyse av amitrol.

Prøvetakingsmetode	Analysemetode	Referanse
Impinger m/H_2O	HPLC/UV[1]	OSHA-metode PV 2006[2]

[1] Væskekromatografikromatografi med standard ultrafiolett (UV) detektor for høy oppløselighet.
[2] https://www.osha.gov/dts/sltc/methods/partial/pv2006/2006.html

6. Vurdering

SCOEL har i sitt kriteriedokument satt opptak av jod og andre effekter på skjoldbruskkjertelen som kritisk effekt for eksponering av amitrol.

De har vurdert at det ikke er tilstrekkelige humane data til å etablere en NOAEL/LOAEL som en indikativ grenseverdi for yrkeseksponering av amitrol kan baseres på. SCOELs foreslår derfor en verdi basert på dyrestudier som de mener vil beskytte skjoldbruskkjertelen.

Ingen ytterligere vurderinger er gjort for amitrol da dette vurderes som lite relevant siden stoffet er forbudt å omsette.

7. Konklusjon med forslag til ny grenseverdi

Med bakgrunn i at amitrol er forbudt å omsettes i EU og Norge samt at Norge er forpliktet til å innføre en grenseverdi for amitrol, foreslår Arbeidstilsynet at den indikative grenseverdien kommisjonen har foreslått i direktiv 2017/164/EU innføres i Norge og at anmerkning E (EU har fastsatt grenseverdi for stoffet) innføres.

Forslag til ny grenseverdi og anmerkning for amitrol:

Grenseverdi (8-timers TWA): 0,2 mg/m^3

Anmerkning: E (EU har fastsatt grenseverdi for stoffet)

8. Ny grenseverdi

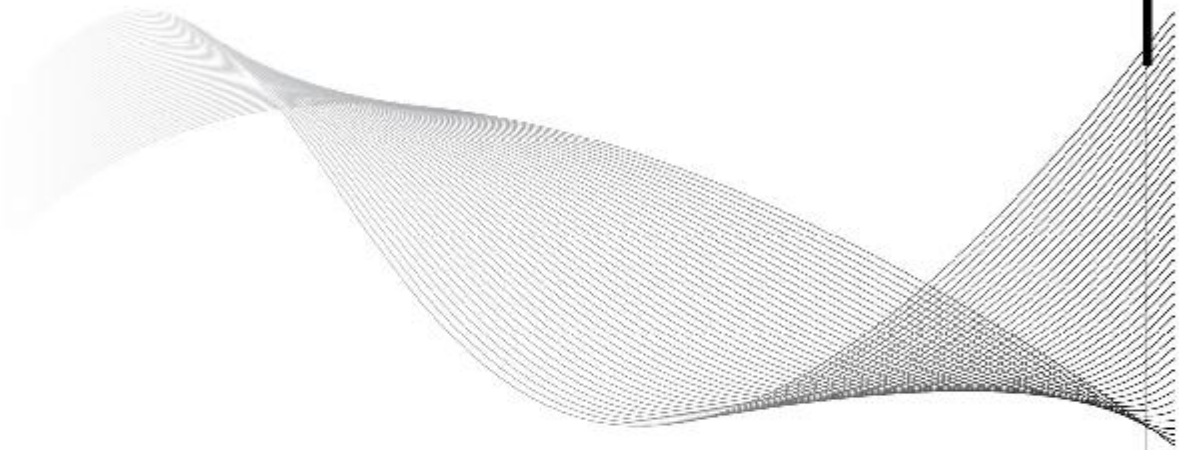
På grunnlag av drøftinger med partene og høringsuttalelser ble ny grenseverdi for amitrol fastsatt til:

Grenseverdi (8-timers TWA): 0,2 mg/m^3

Anmerkning: E (EU har fastsatt grenseverdi for stoffet)

Vedlegg: SCOEL/SUM/157

Social Europe



Recommendation from the Scientific Committee on Occupational Exposure Limits for amitrole

SCOEL/SUM/157
February 2009

European Commission

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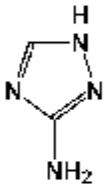
Recommendation from the Scientific Committee on Occupational Exposure Limits for amitrole

Eight-hour TWA:	0.2 mg/m³
STEL (15 minutes): –	
Notation: –	
Biological Limit Value (BLV):	
SCOEL carcinogenic group:	D ("non-genotoxic carcinogen")

Substance identification

Amitrole:



Synonyms: 1*H*-1,2,4-Triazol-3-amine; delta2-1,2,4-Triazoline 5-imino-; s-Triazole, 3-amino-; 3-Amino-1,2,4-triazole
EC No.: 200-521-5
Annex I Index No.: 613-011-00-6
EU Classification: Repr.Cat.3; R63 - Xn; R48/22 - N; R51-53
CAS No.: 61-82-5
MWt: 84.080
Conversion factor (20 °C, 101 kPa): 1 ppm = 3.50 mg/m³; 1 mg/m³ = 0.286 ppm
This evaluation is based on ACGIH (2001), ECB (2000), Greim (1998, 1999, 2002), Henschler (1983), IARC (2001), WHO (1993, 1994a,b), FAO (1997) and the references cited in these reviews.

Physico-chemical properties

Amitrole is a crystalline, colourless solid. The melting point of the substance is 157 -159 °C and the vapour pressure is 5.79 • 10^{-7} hPa at 20 °C. The water solubility of amitrole is 280 - 335 g/l at 20 - 25 °C and the log P_{OW} is -0.969. The substance has a density of 0.6 - 0.85 g/cm³ at 20 °C (ECB, 2000).

1. Occurrence/use and occupational exposure

Amitrole is used as a herbicide and as a growth regulator for plants (ACGIH, 2001; IARC, 2001).

2. Health significance

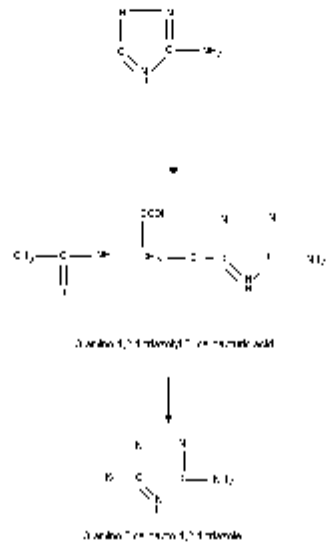
2.1 Toxicokinetics

2.1.1 Human data

After intentional ingestion of approximately 20 mg/kg amitrole, a female subject excreted the unchanged compound at a concentration of about 1 g/l in urine (Geldmacher-von Mallingkrodt and Schmidt, 1970).

2.1.2. Animal data

The fraction of amitrole absorbed by the rat lung was 50% (ECB, 2000). The fraction of oral absorption in rats was 70 - 95% (Fang et al., 1964, 1966; WHO, 1993; FAO, 1997; IARC, 2001). After dermal exposure of rabbits for 24 h, 70% remained at the application site and about 30% was absorbed (WHO, 1993). However, EC (2001) reported a dermal absorption rate of only 1% (no further details). After oral or intravenous administration to mice, amitrole was found first in the bone marrow, spleen, thymus and gastrointestinal tract. After 3 days, amitrole was identified only in the livers of rats and mice (less than 3% of the administered dose). Little metabolic transformation of amitrole occurs in mammals. The two main urinary metabolites in rats (3-amino-5-mercapto-1,2,4-triazole and 3-amino-1,2,4-triazolyl-(5)-mercapturic acid) represented less than 10% of the administered dose. When rats were exposed by inhalation to aqueous aerosols of amitrole (25.8 or 49.2 mg/m^3, 1 h), urine was the major excretion route. About 75% of the eliminated material was found in the urine within 12 h. After oral administration, most of the compound was eliminated unchanged in urine within 24 h. Minor amounts were found in faeces and expired air. Following dermal exposure, rabbits excreted amitrole in urine and faeces in similar amounts (WHO, 1993; FAO 1997; IARC, 2001).



2.1.3. Biological monitoring

There are no data available.

2.2. Acute toxicity

2.2.1. Human data

A single case report described the development of a severe alveolar damage after a single 2 h exposure to a spray containing 19% amitrole, 17% ammonium thiocyanate, less than 1% sodium diethylsulfosuccinate and less than 1% ethylene oxide (Balkisson et al., 1992).

No toxic symptoms appeared following the intentional ingestion of 20 mg/kg amitrole by a female subject (Geldmacher-von Mallingkrodt and Schmidt, 1970).

Astwood (1960) reported that a single oral dose of 100 mg amitrole inhibited radioiodine uptake by the thyroid for 24 hours in both normal subjects and subjects with hyperthyroidism. A dose of 10 mg (0.15 - 0.2 mg/kg, Henschler, 1983) had only a slight effect on iodine uptake.

2.2.2. Animal data

The 4 h-inhalation LC_{50} in rats was > 439 mg/m³. The oral LD_{50} was > 4000 - 25000 mg/kg in rats and 11000 - 14700 mg/kg in mice. The dermal LD_{50} values in rats and rabbits were > 2500 mg/kg and > 10000 mg/kg, respectively (Henschler, 1983; WHO, 1993, 1994b).

Signs of toxicity at high doses included depression, dyspnoea, diarrhoea, ataxia, convulsions, coma and death. Macroscopic findings were irritation and haemorrhage of the gastrointestinal tract (WHO, 1993). The presence of sodium carbonate, sodium bicarbonate and wetting agents considerably increased the toxicity of amitrole (WHO, 1993).

2.3. Irritation and corrosivity

2.3.1. Human data

Amitrole was not irritating in a patch test with a human volunteer exposed for 4 or 8 hours. A slight irritating effect was observed in 3 out of 6 subjects after 24 hours of exposure (Hecht, 1954).

Amitrole-exposed workers in different plants occasionally developed mild dermatitis, which was interpreted as a primary irritant effect (WHO, 1993).

2.3.2. Animal data

Skin

Dermal exposure of rabbits to 10000 mg/kg amitrole or rats to 2500 mg/kg produced mild and reversible erythema (Elsea, 1954; IPCS, 1994).

Eyes

A single 4 h exposure by inhalation to 439 mg/m³ did not produce eye irritation in rats (ACGIH, 2001). The application of 3 mg into the conjunctival sac of rabbits caused mild eye irritation (Elsea, 1954; IPCS, 1994).

Respiratory tract

A single 4 h exposure by inhalation to 439 mg/m³ did not irritate the respiratory tract of rats (ACGIH, 2001).

2.4. Sensitisation

2.4.1. Human data

A case study of a weed control operator with contact dermatitis was reported. Patch testing with 1% amitrole resulted in a strong positive vesicular reaction on days 2 and 4, indicating an allergic contact dermatitis (English et al., 1986).

2.4.2. Animal data

A Magnusson-Kligman maximisation test with Freund's adjuvant on guinea pigs yielded positive results after intradermal induction with 2.5% amitrole, dermal induction with 25% and 2 challenges with 12% (Bayer AG, 1984). No sensitisation was observed in a Klecak open epicutaneous test on guinea pigs, exposed 20-times dermally to 3 - 30% amitrole and challenged twice with 1 - 30% amitrole (Bayer AG, 1985).

2.5. Repeated dose toxicity

2.5.1. Human data

No medical findings except skin irritation were reported in workers in different plants with chronic amitrole exposure (Greim, 2001; WHO, 1994a). No effects on thyroid function (up to 14 days after the end of exposure) were observed in men who had sprayed amitrole for 10 days. Their exposure was estimated to about 340 mg/d (5 mg/kg • d) (Baughter et al., 1982). In a study by Bayer AG (1983), thyroid function was examined in 5 employees exposed to unknown level of amitrole who had worked for prolonged periods in the production and packaging of the substance. There were no indications of thyroid dysfunction.

2.5.2. Animal data

Rodents, especially rats, are more prone to thyroid effects than dogs or humans (see section "recommendations"). These effects are reversible after cessation of exposure (Greim, 1983).

Inhalation

No published studies are available.
In an unpublished study by Cox and Re (1978), F-344 rats (15 per sex and dose) were exposed to amitrole aerosols at concentrations of 0, 100, 320, 990 and 4050 mg/m³ on 5 h/d, 5 d/w for 4 weeks. At 320 mg/m³ and above, hyperplasia of the thyroid was evident and triiodothyronine (T_3) levels were significantly depressed. Thyroxine (T_4) levels were significantly depressed at 990 and 4050 mg/m³. The NOAEC of this study was 100 mg/m³.
Fischer rats (75 per sex and dose) were exposed by inhalation to 0, 15.8 - 32.2 and 97.9 - 376.4 mg/m³ (ranges for the two dose groups) on 5 h/d, 5 d/w on study weeks 1 - 13, 40 - 52 and 78 - 90, interrupted by recovery periods (Becci, 1983 cited in WHO). The exposure of the high-dose animals was terminated early at week 51 (high mortality due to technical problems, but not substance-related). The most prominent findings of exposure were alterations of the thyroid in both dose groups, including reduced T_3 and T_4 levels, increased organ weights and follicular hyperplasia. At the terminal sacrifice (after 24 months) there was also an increased incidence of thyroid tumours.
ECB (2000) refers to a rat inhalation study with duration of 2 years, in which the animals were exposed once a week (duration not stated) to 2000 mg/m³ amitrole aerosol. There were no effects on mortality, body weights and tumour incidences. No histological alterations in liver and thyroid were observed (no further details).

Oral

Numerous studies examined the effects of short-term and long-term oral exposure to rats and mice (overviews in ECB, 2000; Greim, 1983; IARC, 2001; WHO, 1993, 1994a). Only the most relevant studies concerning the effects on the thyroid are described here.

Fregly (1968) performed a study on rats (Blue Spruce Farm strain, 10 males per dose) in order to establish the minimum dose affecting thyroid activity. Amitrole was administered in the diet at concentrations of 0, 0.25, 0.5, 2, 10 or 50 mg/kg for 11 - 13 weeks. At 2 mg/kg feed (0.1 mg/kg/d) and above, the uptake of iodine by the thyroid was reduced in a dose-related manner. A decrease in the serum protein-bound iodine level was also observed, but was not dose-related. Histological changes in the thyroid were noted at 10 and 50 mg/kg feed. The NOAEL of this study is 0.5 mg/kg feed (0.025 mg/kg/d).

This above NOAEL was corroborated by an unpublished rat study, which revealed a NOAEL of 0.5 mg/kg feed (0.025 mg/kg • d) and a threshold of 1 mg/kg feed (0.05 mg/kg/d) for decreased iodine uptake, reduced levels of T_3 and T_4 and increased thyroid weight (Henschler, 1983). Further studies have confirmed the antithyroid effect of amitrole at higher doses. EC (2001) reported a NOAEL of 0.1 mg/kg/d for thyroid effects in a 90-day rat study, but no further details are given.

Thyroid effects were also seen in rat studies on reproduction, but at higher doses (see section "reproductive toxicity").

Beagle dogs (4 per sex and group) were exposed for one year to amitrole in the diet at concentrations of 0, 10, 500 and 1500 mg/kg (corresponding to doses of 0.3, 13 and 32 mg/kg/d) (Bayer AG, 1994). The predominant finding was an effect on the thyroid starting at 500 mg/kg feed (enlargement, ectopic tissue, slight hypertrophy, follicular hyperplasia, decreased levels of T_3 and T_4). Thrombosis, pigmentation, and haemorrhage were observed in the thyroids at the highest dose. Haematological alterations typical of hyperthyroidism included lower erythrocyte, haemoglobin and haematocrit counts as well as slightly lower mean cell volume and mean cell haemoglobin. Pituitary hyperplasia (in males at 1500 mg/kg) and hypertrophy (in males at 500 mg/kg feed and in both sexes at 1500 mg/kg feed) were also evident. Males at the high dose group showed a slight decrease in food consumption and body weight as well as an increase in cholesterol levels and platelet counts. No effects were observed at 10 mg/kg feed (0.3 mg/kg/d).

Rabbits developed cataracts after oral exposure to amitrole (0.2% in the diet or 0.2% in drinking water) for up to 25 weeks (Bhuyan et al., 1973).

The thyroid effects in subchronic rat studies were reversible within 2-4 weeks after cessation of exposure (Greim, 1981).

Dermal

Toxicity after dermal exposure was only observed at high doses.

No systemic toxicity was observed after dermal exposure of rats to 2.39 mg/kg/d once a week for 23 months (ECB, 2000).

No local or systemic effects were observed following dermal exposure of rabbits to doses of 0, 25 or 100 mg/kg/d for 6 h/d for 15 days (six animals per group, three animals per group tested with abraded skin (Mihail and Schilde, 1984).

EC (2001) reported a NOAEL of 100 mg/kg/d for a 28-day dermal exposure study in rats, but further details are not given.

Local effects and systemic maternal toxicity was observed in a dermal teratogenicity study on rabbits. The LOAEL was 2000 mg/kg/d in rabbits, the NOAEL 1500 mg/kg/d (see section "reproductive toxicology").

2.6. Genotoxicity

2.6.1. In vitro

Most of the *in vitro* tests on the genotoxicity of amitrole – either with and without metabolic activation – yielded negative results, including tests in bacteria (*Salmonella typhimurium* of different strain, *Bacillus subtilis*, *E. coli*), yeasts and fungi (Greim, 1998; IARC, 2001; WHO, 1994a). Tests with positive responses were criticised due to the use of inappropriate methods (use of S9 from fish or mussels) or lack of documentation. However, it was stated that *in vitro* tests may be insensitive because an *in vivo* activation could occur by peroxidases, which are not present *in vitro* (Greim, 1998). No gene mutations were induced in L5187Y mouse lymphoma cells or human fibroblasts but in Syrian hamster embryo cells *in vitro* (HPRT- and Na/K ATPase locus). These cells are also sensitive to morphological transformation by amitrole. The prostaglandin-H-synthetase activity, present in Syrian hamster embryo cells, is suggested to be responsible for the sensitivity of these cells. No chromosomal aberrations were observed in Chinese hamster lung cells or human lymphocytes. One test on the induction of sister chromatid exchange in Chinese hamster lung cells yielded a positive response; but without a dose-response-relationship (Greim, 1998; IARC, 2001; WHO, 1994a).

2.6.2. In vivo – Human data

Human data on the genotoxic effects *in vivo* are not available.

2.6.3. In vivo – Animal data

In a host-mediated assay with *Salmonella typhimurium* TA1530 in mice, a positive, but not dose-related effect was observed. Amitrole did not induce dominant lethal mutations or micronuclei in the bone marrow of mice (oral or intraperitoneal exposure). Unscheduled DNA synthesis was not observed in rat hepatocytes *in vivo* (Greim, 1998; IARC, 2001; WHO, 1994a). It did not induce mutations in *Drosophila* after oral exposure (Pontecorvo and Fantaccione, 2005).

2.7. Carcinogenicity

2.7.1. Human data

Axelson and Sundell (1974) and Axelson et al. (1980) performed a cohort study on 348 railroad workers with exposure to amitrole, other herbicides and chemicals. In a sub-cohort exposed to amitrole in combination with chlorophenoxy herbicides and other chemicals, there was a significant increase in cancer deaths. However, in a sub-cohort mainly exposed to amitrole alone, no significant increase in tumours was reported.

2.7.2. Animal data

In most of the available long-term inhalation and oral studies on mice and rats, amitrole induced tumours of the thyroid (follicular-cell adenomas and carcinomas) at doses of about 2.5 mg/kg/d and above. This effect was attributed to a specific sensitivity of rodents (see "recommendations") (Greim, 1998; IARC, 2001; WHO, 1993, 1994a).
Other target organs were the liver and pituitary. In the study by Napalkov (1962), Albino rats were exposed for their whole life to amitrole via drinking water (resulting in a dose of 20 - 25 mg/animal per day) or feed (doses of 250 and 500 mg/animal per day). The incidence of liver tumours in surviving animals at the time of appearance of the first tumour were 6/8 (drinking water study), 8/10 and 10/11 (250 and 500 mg group in the feed study, respectively), for thyroid tumours 3/8, 2/10 and 5/11. This study lacked control groups.
Steinhoff et al. (1983) fed Wistar rats, NMRI mice and Golden hamsters with a diet containing 0, 1, 10 and 100 mg/kg feed for their whole lifespan. They were estimated induction of tumors and thyroid function test (in 5 animals for each species): thyroid

weights, percentage of accumulation of radioiodine and protein-bound radioiodine. Increased incidences of malignant thyroid tumors and adenomas of the pituitary were observed in female rats of the high dose group (36/41 vs. 14/59 in controls). No carcinogenic effects were seen in mice or hamsters, but the administered doses were low. The dose below which there was neither long-lasting interference with thyroid function nor induction of tumors (NOAEL) for female rats was 10 mg/kg feed equivalent to 1.5 mg/kg bw/day.

Table 1. Numbers of animals with tumor and distribution of tumors observed in liver, pituitary, and thyroid gland (Steinhoff et al., 1983)

Species	ntration mg/kg	Sex	Animals with tumor	Animals with malignant tumor	Primary tumors of					
					Liver cells		Pituitary		Thyroid	
					Benign	Malig-nant	Benign	Malig-nant	Benign	Malig-nant
Hamster (76/sex/ group)	0	M	20	7	-	-	1	-	2	-
		F	13	1	1	-	-	-	1	-
	1	M	11	2	-	-	-	-	2	-
		F	10	2	1	-	-	-	2	-
	10	M	13	5	-	-	-	-	-	-
		F	12	3	-	-	-	1	-	-
	100	M	11	2	-	-	-	-	1	-
		F	11	3	-	-	-	-	-	-
Mouse (75/sex/group)	0	M	52	27	4	1	1	-	-	-
		F	60	46	-	-	10	-	-	-
	1	M	56	38	2	-	-	-	-	-
		F	48	26	-	-	4	-	-	-
	10	M	47	26	3	1	2	-	-	-
		F	59	46	-	-	6	-	-	-
	100	M	46	32	2	1	-	-	-	-
		F	55	38	-	-	10	-	-	-
Rat (75/sex/group)	0	M	36	19	-	-	4	-	5	3
		F	59	20	-	-	14	1	7	-
	1	M	41	20	-	-	9	1	9	-
		F	67	34	-	-	20	2	12	1
	10	M	44	23	-	1	10	-	4	3
		F	60	29	-	-	15	4	8	4
	100	M	53	23	-	-	10	3	45	18
		F	71	45	-	-	36	5	44	28

B6C3F1 mice were exposed by Vesselinovitch (1983) to amitrole in the diet at concentrations of 500 mg/kg feed from weaning for 90 weeks. The tumour incidences in the liver were significantly increased. There was one hepatocellular adenoma in 98 control males, 9 adenomas and 11 carcinomas in 55 exposed males as well as 5 adenomas and 4

carcinomas in 49 exposed females. Other studies on mice confirmed these findings, but the mechanism of the formation of liver tumours is non-genotoxic (Greim, 1998; IARC, 2001).
No increased tumour incidences were observed after dermal exposure of rats to low doses of 2.39 mg/kg/d once a week for 23 months (ECB, 2000).

The International Agency for Research on Cancer (IARC) in 1987 classified amitrole as Group 2B (*possibly carcinogenic to humans*). The Working Group reported that amitrole had been tested for carcinogenicity in mice by oral administration, skin application and transplacental exposure, in rats by oral and subcutaneous administration and in hamsters by oral administration. After oral administration, it produced thyroid tumors and benign and malignant liver tumors in mice of each sex, benign and malignant thyroid tumors in male and female rats and benign pituitary tumors in female rats. There was *sufficient evidence* in experimental animals for the carcinogenicity of amitrole. No data were available on the genetic and related effects of amitrole in humans.

The IARC Working Group in 2001 changed the classification and concluded that amitrole is *not classifiable as to its carcinogenicity to humans* (Group 3). In making its evaluation, the Working Group concluded that amitrole produces thyroid tumors in mice and rats by a non-genotoxic mechanism, which involves interference with the functioning of thyroid peroxidase, resulting in a reduction in circulating thyroid hormone concentrations and increased secretion of thyroid-stimulating hormone. Consequently, amitrole would not be expected to produce thyroid cancer in humans exposed to concentrations that do not alter thyroid hormone homeostasis. An additional consideration of the Working Group, based on the lack of genotoxicity of amitrole, was that the liver tumors in mice and benign pituitary tumors in rats were also produced by a non-genotoxic mechanism. Epidemiological studies and toxicological studies in experimental animals provide compelling evidence that rodents are substantially more sensitive than humans to the development of thyroid tumors in response to thyroid hormone imbalance.

2.8. Reproductive toxicity

2.8.1. Human data

Human data on reproductive or developmental effects are not available.

2.8.2. Animal data

Fertility

Rats (Sherman strain) were exposed to amitrole in a one-generation study by Gaines et al. (1973) at concentrations of 0, 500 and 1000 mg/kg feed (for F_0 females: 31 - 43 mg/kg/d and 68 - 86 mg/kg/d; for F_0 males: 28 - 42 mg/kg/d and 60 - 87 mg/kg/d) from 55 days before mating until weaning of the F_1 generation. There was no effect on fertility, but the body weights of the exposed F_0 and F_1 animals were reduced and spleen and thymus were atrophic. A marked increase in offspring mortality was observed within the first week after weaning.
Gaines et al. (1973) performed a subsequent two-generation study with 0, 25 and 100 mg/kg feed (for F_0 females: 1.3 - 2.5 mg/kg/d and 4.8 - 9.6 mg/kg/d; for F_0 males: 1.1 - 2.5 mg/kg/d and 4.2 - 9.5 mg/kg/d). There were no effects on reproduction or development, but hyperplasia of the thyroid was observed in all treated groups of both studies.
More recent studies on reproductive toxicity by Savary (1994) and Richard (1995) are available (unpublished, but extensively documented in FAO, 1997).
In a one-generation study by Savary (1994), Sprague-Dawley rats were exposed to amitrole in the diet at levels of 0, 2, 10, 40 or 160 mg/kg (F_0 females: 0.29, 1.4, 5.3 and 28 mg/kg/d; F_0 males: 0.19, 0.94, 3.7 and 12 mg/kg/d) for 29 days before mating until

weaning of the F_1 pups. At the highest dose, clinical signs of maternal toxicity were evident and the mortality of F_1 pups was increased in this group. Decreased body weights and decreased feed consumption were seen at 160 mg/kg in F_0 and F_1 animals as well as in F_1 males at 40 mg/kg. Females at the highest dose had a lower implantation rate (12.1 implantation sites) than controls (16.6 sites), which was reflected in significantly lower birth rates and litter sizes. The viability indices were not affected by the treatment. The number of females with a normal oestrus cycle was decreased in a dose-related fashion in animals at 40 or 160 mg/kg. At doses of ≥ 10 mg/kg in males and at ≥ 40 mg/kg in females, the thyroid glands of F_0 animals showed a dose-related increase in size and reddish colouration. All animals exposed to 160 mg/kg also revealed other organ lesions (reddened pituitary glands, greyish-white foci on the lungs, reduced adrenal glands and spleen sizes). No treatment-related histopathological lesions were seen in pups killed on day 14 post partum. Male and female F_1 adults (40 mg/kg or above) had enlarged, reddened thyroid glands and reddened pituitary glands. Histopathological examination showed dose-related effects in the liver and pituitary gland in F_0 and F_1 animals, namely decreased colloid content in females of both generations at 10 mg/kg and above, vascular ectasia in all animals of both generations treated with 40 or 160 mg/kg, and periadenitis in a small number of F_0 males at 160 mg/kg.

In a subsequent two-generation study (Richard, 1995), groups of 30 male and 30 female Sprague-Dawley rats were fed diets containing amitrole at levels of 0, 0.5, 2, 15 or 110 mg/kg (F_0 females: 0.04, 0.16, 1.2 and 7.8 mg/kg/d; F_0 males: 0.03, 0.12, 0.9 and 5.9 mg/kg/d) from 72 days before mating throughout gestation and lactation for two generations (Richard, 1995). Increased mortality and/or clinical signs of toxicity were observed in F_1 males and females of the highest dose group. Both F_0 and F_1 parental animals at this dose had relevant decreases in feed consumption and body weight throughout the study, the F1 generation being more affected. Animals of the 110 mg/kg group showed widespread systemic toxicity in the form of increased weights and histological alterations of the thyroid, pituitary and spleen, increased weights of testes, epididymis, seminal vesicles (both generations), prostate and uterus (only F_1) and decreased relative ovarian weights (F_0). Histopathological effects were also seen in reproductive organs (testis and epididymis of F_1 animals and in the ovaries, uterus, and vagina in both generations). Many of the histopathological effects on the reproductive tissues were considered to be related to immaturity of the animals at this dose. Other affected organs in animals of the highest dose groups were the adrenals (decreased weight, histopathological alterations), kidneys (increased weight, renal lesions) and liver (hepatocellular hypertrophy). Owing to a low survival rate of F_2 pups in this group, treatment-related organ changes could not be identified. Significantly decreased mating indices and decreased fertility indices were evident among F_1 males and females, as well as increased length of gestation in F_1 females and a low implantation rate in F_0 and F_1 females of the highest dose. In the offspring there was a low prenatal survival in the F_2 generation, significantly decreased mean litter size at day 1 (F_1 and F_2) and day 4 or 21 (F_2 only) post partum, very low viability indices for the F_2 generation and decreased F_1 and F_2 pup body weights during lactation. In the F2 generation at 110 mg/kg, there was a high postnatal mortality. There appeared to be no effects on the development of the F_1 pups and the F_2 generation could not be examined due to poor survival. At 15 mg/kg, the only effect observed was a slight increase in the severity of some histopathological changes in the thyroid. The NOAEL was 2 mg/kg (0.12 mg/kg/d) on the basis of thyroid effects. The NOAEL for reproductive toxicity was 15 mg/kg feed (0.9 mg/kg/d).

Both studies showed similar effects. The pup survival was markedly reduced in the F_2 generation of the two-generation study. The cause for the discrepancy with regard to liver and pituitary effects at lower doses in the one-generation study than in the two-generation study is unknown.

Developmental toxicity

Tyl (1986a) exposed Sprague-Dawley rats to amitrole in doses of 0, 100, 500 or 1000 mg/kg/d by gavage on days 6 - 15 of gestation. Foetuses were examined on day 21 of gestation. Furthermore, 14 females per dose level were allowed to litter and wean, and were maintained until day 21 post partum. Food consumption and body weight gain of dams were reduced at the two higher doses, and maternal thyroid weights were increased at these dose levels. At the highest dose, foetotoxicity was observed, including reduced foetal body weight per litter, increased incidences of foetuses with unossified or poorly ossified bones and an increased number of foetuses with enlarged and/or dark thyroid. These latter findings in the thyroid were also observed in the 500 mg/kg/d dose group. No teratogenicity was observed. The postnatal evaluations indicated no other effects of the treatment. The NOAEL for maternal toxicity and developmental effects was 100 mg/kg/d (Tyl, 1986a).

In another developmental studies on rats (Long-Evans) with a similar design, a NOAEL of 1000 mg/kg/d was obtained (Bayer, 1977). The discrepancies in the NOAEL values may be due to the use of different rat strains.

Tjälve (1974) exposed NMRI mice on gestation days 6 - 18 to amitrole in drinking water (0, 500, 1000, 2500 and 5000 mg/l). At 1000 mg/l (140 mg/kg/d), maternal body weight gain and foetal weights were decreased and skeletal development was retarded. The highest dose produced an increased rate of resorptions. No teratogenic effects were observed. The NOAEL for maternal toxicity and developmental effects was 500 mg/l drinking water (70 mg/kg/d). Another study on mice reported a decrease of maternal and foetal body weights and an increased foetal mortality after oral administration of 215 mg/kg/d from days 6 - 14 of gestation (Bionetics Research Laboratories, 1968).

New Zealand white rabbits were exposed to amitrole by gavage at doses of 0, 4, 40, and 400 mg/kg/d on days 6 - 18 of gestation (Tyl, 1986b). The two higher doses caused a reduced maternal body weight gain. At 400 mg/kg/d, there were also increased liver weights. A dose-related increase in the number of abortions was observed (0, 1, 3 and 5 for controls, the 4, 40 and 400 mg/kg/d dose groups, respectively). The number of non-viable implants per litter was increased and the percentage of live foetuses per litter as well as the foetal weights per litter were decreased at 40 and 400 mg/kg/d (all statistically significant only at the highest dose). At 40 and 400 mg/kg/d, there were significant and dose-related increases in the incidence of malformations, especially of the head and limbs, as well as visceral and skeletal variations. Effects on the foetal thyroid (enlargement, discolouration) were also evident at these doses. The NOAEL for maternal and developmental toxicity was 4 mg/kg/d (Tyl, 1986b).

Kolb (1994) exposed Russian rabbits to amitrole in doses of 0, 5, 20 or 80 mg/kg/d by gavage on days 6 - 18 of gestation. Adverse effects were evident in the highest dose group, consisting of reduced maternal feed consumption and body weight gain as well as decreased foetal body weights and litter weights. There was no evidence of teratogenicity. The NOAEL for maternal and foetal toxicity was 20 mg/kg/d. The discrepancies between the rabbit studies may be due to the use of different strains and the higher doses used in the study by Tyl (1986b).

Subcutaneous exposure of C57/BL6 mice to 0, 215 and 464 mg/kg/d from days 6 -14 of gestation resulted in a decrease of maternal body weight and an increased foetal mortality at the higher dose (Bionetics Research Laboratories, 1968).

Dermal exposure of rabbits to 0, 1000, 1500 or 2000 mg/kg/d amitrole on days 7 to 19 of gestation (6 h/d) produced dose-related dermal irritation of the treated skin. Anorexia, decreased feed intake and decreased body weight gain as well as slightly reduced uterine weights at term were observed at 2000 mg/kg/d. At this dose, there were also effects on the offspring, consisting of reduced foetal weights, increased incidence of total resorptions (mainly early resorptions) and malformations. The NOAEL for maternal and developmental toxicity was 1500 mg/kg/d (Henwood, 1988).

Recommendations

There is no sufficient human data to establish NOAEL/LOAEL or on which IOELV could be based for occupational exposure for amitrole. This value will protect about disturbance of thyroid.

In a patch test conducted with a human volunteer, amitrole exerted no primary dermal irritant effect. Patch testing with 1% amitrole on a weed control operator showed a strong positive vesicular reaction at 2 and 4 days, indicative of allergic contact dermatitis. Single oral dose of 100 mg amitrole inhibited radioiodine uptake by the thyroid of both normal and thyrotoxic subjects for 24 hours. A dose of 10 mg (0.15 - 0.2 mg/kg corresponding to about 1 mg/m³, Henschler, 1983) had a slight effect on iodine uptake. An epidemiological study was conducted on Swedish railway workers exposed to various herbicides. A statistically significant increase in the incidence of total tumors and lung tumors was found among workers exposed to amitrole and combinations of other herbicides (Axelson et al. 1974). However, in a follow-up study which combined data from the earlier study, results did not show a statistically significant increase in cancer incidence among those workers exposed to amitrole alone (Axelson et al. 1980). The thyroid function of 5 employees exposed to unknown level of amitrole between 3 and 16 years did not change (Bayer 1983). However, no data for repeated human exposure are available.

Amitrole has a low acute toxicity when tested in a several species by various routes of administration. The substance is rapidly absorbed from the gastrointestinal tract and lung. It is rapidly distributed throughout most body tissues, but with a slight accumulation in those tissues with a rapid cell turnover (bone marrow, spleen, thymus, gastrointestinal tract). Amitrole passes through the placenta into the fetuses with the same distribution pattern as in the mothers. Excretion is rapid after oral exposure. Within 24 hours, 70-95% of the administered radioactivitley-labelled compound is excreted via the urine, mainly as the parent compound. Based on experiences in animal studies, amitrole does not demonstrate irritating properties (ACGIH, 2001). Evidence of a moderate sensitizing potential was observed in a Magnusson-Kligman test but not in a Klecak open epicutaneous test. Therefore the data is to weak for sensitization assessment. Also, no reports on respiratory sensitization are available.

Exposure to amitrole leads to effects on the thyroid, which is also responsible for the induction of thyroid cancers and for reproductive toxicity in animals. The mechanism of this action is non-genotoxic.

Rodents, especially rats, are generally considered to be an especially sensitive species as Henschler (1983) showed a slight effect at 0.15 – 0.2 mg/m³. Rats are more prone to disturbances of the thyroid hormone balance than humans or dogs due to the lack of specific binding proteins in serum. Thyroid effects were reversible in the rat after cessation of exposure (Greim, 1998; Henschler, 1983; IARC, 2001; WHO, 1994a,b).

Several rat studies, highlighted in Table 2, showed that the uptake of iodine in the thyroid gland and other thyroid gland effects appeared to be the critical effect with a NOAEL around 0.1 mg/kg/d.

If we take the lowest NOAEL (0.025 mg/kg) and directly make a route-to route extrapolation (0.025 x 70/10) the OEL should be 0.2 mg/m³. As the lowest NOAEL is used and rats are assumed to be the most sensitive species, no assessment factor is needed.

If departure from the dog study with a NOAEL of 0.3 mg/kg/d for the route-to-route extrapolation and accepting an assessment factor of 10 as dog are not considered an especially sensitive species, the occupational exposure limit estimate is also estimated to be 0.2 mg/m³. This value will protect against the disturbance of thyroid function in human, where a slight effect occurred at ≥ 0.15 mg/kg, which corresponds to about 1 mg/m³ from a route-to-route extrapolation assuming a 70 kg person inhaling 10 m³ per day.

With respect to the greater sensitivity of rodents to thyroid effects, amitrole would not be expected to produce thyroid cancer in humans exposed to concentrations that do not alter thyroid homeostasis (IARC, 2001). On the basis of the lack of genotoxicity, the benign

pituitary tumours in rats and liver tumours in mice may be considered to be of non-genotoxic origin (IARC, 2001).

A "skin" notation is not proposed. Although one study reported a relevant dermal absorption of 30% in rabbits after exposure for 24 h (WHO, 1993), EC (2001) documented a dermal absorption of only 1%. No indication exists for a relevant skin sensitising potency of amitrole.
There are no data available for biological monitoring.
At the recommended IOELV, no analytical difficulties are expected.

Table 2. Summary of lowest-observed-adverse-effects levels (LOAELs) and no-observed-adverse-efefct levels (NOAELs) for amitrole.

Species	Type of study	Effects	Reference
Humans	Uptake of iodine in the thyroid gland	Slight effect: 0.15-0.2 mg/kg	Henschler, 1983
Rats	Exposures were through weeks: 1-13, 40-52 and 78-90 for 5h/d, 5d/w.	At about 25 mg/m^3: decreased T_3 and T_4, increased thyroid weight and follicular hyperplasia.	Becci, 1983
Rats	Amitrole in the diet for about three months. Uptake of iodine in the thyroid gland.	Reduced iodine uptake at 0.1 mg/kg/d (LOAEL). NOAEL: 0.025 mg/kg/d Another study: NOAEL: 0.1 mg/kg/d	Fregly, 1968 Unpublished study
Rats	Life-long amitrol in the diet. Tumours and thyroid function.	NOAEL: 1.5 mg/kg/d	Steinhoff et al. , 1983
Rats	Amitrole in the diet. Two-generation study.	About 2 mg/kg/d were without effect on reproduction and development, but thyroid gland hypertrophy appeared, i.e. LOAEL.	Gaines et al., 1973
Rats	One-generation study	About 1 mg/kg/d showed dose-related effects in the liver and pituitary gland in F_0 and F_1 animals with decreased colloid content in females of both generations, i.e. LOAEL.	Savary, 1994
Rats	Two generation study	About 7 mg/kg/d caused increased death (F_1 and F_2) and multiple organ effects. The NOAEL was 0.12 mg/kg/d on the thyroid effect and the NOAEL for reproductive toxicity was 0.9 mg/kg/d.	Richard, 1995
Beagle dogs	Amitrole in the diet for 1 year.	Thyroid gland effects (T_3 and T_4, hypertrophy, follicular hyperplasia) LOAEL: 13 mg/kg/d NOAEL: 0.3 mg/kg/d	Bayer, 1994

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