EUROPEAN COMMISSION
DIRECTORATE-GENERAL
Joint Research Centre

Institute for Health and Consumer Protection
European Chemicals Bureau
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3,4-DICHLOROANILINE (3,4-DCA)

CAS No: 95-76-1

EINECS No: 202-448-4

Summary Risk Assessment Report

2006 **EUR 22234 EN**

The mission of the IHCP is to provide scientific support to the development and implementation of EU polices related to health and consumer protection. The IHCP carries out research to improve the understanding of potential health risks posed by chemical, physical and biological agents from various sources to which consumers are exposed.

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SUMMARY RISK ASSESSMENT REPORT

Final report, 2006

Germany

The risk assessment of 3,4-dichloroaniline (3,4-DCA) has been prepared by Germany on behalf of the European Union.

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PREFACE

This report provides a summary, with conclusions, of the risk assessment report of the substance 3,4-dichloroaniline (3,4-DCA), that has been prepared by Germany in the context of Council Regulation (EEC) No. 793/93 on the evaluation and control of existing substances.

For detailed information on the risk assessment principles and procedures followed, the underlying data and the literature references the reader is referred to the comprehensive Final Risk Assessment Report (Final RAR) that can be obtained from the European Chemicals Bureau[1]. The Final RAR should be used for citation purposes rather than this present Summary Report.

[1] European Chemicals Bureau – Existing Chemicals – http://ecb.jrc.it

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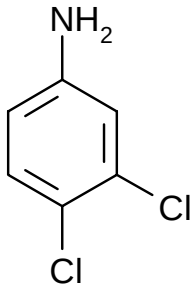
1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS No.: 95-76-1
EINECS No.: 202-448-4
IUPAC Name: 3,4-dichlorophenylamine
Synonyms: 3,4-dichloroaniline
3,4-dichlorobenzeneamine
3,4-DCA
Molecular weight: 162 g/mol
Empirical formula: $C_6 H_5 Cl_2 N$
Structural formula:



1.2 PURITY/IMPURITIES, ADDITIVES

Commercial 3,4-dichloroaniline has a purity of > 95%, typical concentration 99%. The impurities are Cyclohexylamine (< 2%), Chlorobenzene (1%), 1,2-dichlorobenzene (0.2%), Aniline (<1%), 2-chloroaniline (0.1%), 3,4-dichloronitrobenzene (< 0.7%), 4-chloroaniline (< 0.1%), 3-chloroaniline (< 0.1%), 2-chloro-4-aminotoluene (0.2%), 2,5-dichloroaniline (0.1%), 2,3-dichloroaniline (0.6%), water (< 0.1%), 3,3’,4,4’-tetrachloroazobenzene (< 0.01%), 3,3’,4,4’-tetrachloroazooxybenzene (approximately 15 ppm) and Morpholine (< 0.4%).

1.3 PHYSICO-CHEMICAL PROPERTIES

Table 1.1 Physico-chemical properties

Parameter	Value
Physical state	solid at 20°C
Melting point	72°C
Boiling point	272°C at 1,013 hPa
Density	1.57 g/cm3 at 20°C
Vapour pressure	0.184 Pa at 20°C
Surface tension	71.8 mN/m at 19.8°C (0.54 g/l solution in water)
Water solubility	580 mg/l at 20°C
Partition coefficient (log Pow)	2.7 (Shake Flask - method)
Flash point	not determined, solid
Auto flammability	no auto flammability up to the melting point at 72°C
Flammability	not highly flammable
Explosive properties	no explosive properties
Oxidising properties	no oxidising properties

1.4 CLASSIFICATION

Classification according to Annex I in 29th ATP[2]

Toxic	R 23/24/25	Toxic by inhalation, in contact with skin and if swallowed
Dangerous for the environment	R50/53	Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
Concentration limits	none	
Irritant	R 41	Risk of serious damage to eyes
Sensitising	R 43	May cause sensitisation by skin contact

[2] The classification of the substance is established by Commission Directive 2004/73/EC of 29 April 2004 (29th ATP) adapting to technical progress for the 29th time Council Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances, OJ. L 152 of 30/04/2004.

2 GENERAL INFORMATION ON EXPOSURE

In Western Europe, 12,000 tonnes of 3,4-DCA was produced in 1991. Presently there are two production sites in the European Union: Bayer AG, Leverkusen (GER), Tolochimi, Toulouse (F).

In the period 1996-1998, their total production volume was 13,500-15,500 tonnes/annum, from this 3,750-4,600 tonnes/annum were exported.

3,4-DCA is exclusively used as an intermediate in the chemical industry for the synthesis of 3,4-dichlorophenylisocyanate, the herbicide propanil and an azo dye for polyester fabrics. Actually, there are no direct uses of 3,4-DCA without chemical transformation.

3,4-dichlorophenylisocyanate is sold and further used for the production of phenylurea herbicides (diuron, linuron) and the bactericide trichlorocarbanilide by further sites.

The quantitative use pattern is (all figures related to 3,4-DCA [tonnes/annum]):

Table 2.1 **Use pattern of 3,4-DCA [tonnes/annum]**

Product	2nd Generation Products	Processing Volume	Export	Use in EU
3,4-Dichlorophenylisocyanate	Diuron Linuron	9,200-10,200	4,900-5,300	4,300-4,900
3,4-Dichlorophenylisocyanate	Trichlorocarbanilide	780	714	66*
Propanil	-	confidential (1 site)		
5-Amino-2,3-dimethylbenzenesulphethanolamide	Dyes	100	?	?

* Recent information from TCC producers in the EU indicate that the total amount of TCC used in the EU is only 30 tonnes/annum.

In the Danish Product Register, 2 products (not specified) with a 3,4-DCA content of < 0.1% are recorded with a total quantity of < 1 tonnes/annum. The substance is recorded neither in the Swedish nor in the Norwegian Product Register.

3,4-DCA is a biodegradation product of several phenylcarbamates, phenylurea and acylanilide herbicides.

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

During production DCA is released via waste water into the hydrosphere. Further releases into the hydrosphere are expected from processing of the isocyanate compound to the plant protection agents diuron, linuron, and propanil.

Releases into the environment occur during use of plant protection agents (linuron, diuron, propanil). 3,4-DCA is formed by biotransformation from certain crop protecting agents produced from 3,4-DCA. Additionally 3,4-DCA is released as it is an impurity of these agents. The major part is released in agricultural soils. When these agents are released into the hydrosphere, unknown amounts of 3,4-DCA will be formed as well.

Further releases during production and use of trichlorocarbanilide (TCC) are to be expected. TCC is produced either from 3,4-DCA and 4-chlorophenyl isocyanate, or from 4-chloroaniline and 3,4-dichlorophenyl isocyanate. It is used as a deodorant and soap bactericide in household products.

General characteristics of 3,4-DCA which are relevant for the exposure assessment are:

estimated atmospheric half-life of 9 hours,

no volatilisation because of the low Henry's law constant (0.05 $Pa \cdot m^3 \cdot mol^{-1}$),

no hydrolysis,

photolysis in surface waters (estimated half-lives of 18 days),

no significant biodegradation occurs in WWTPs and surface waters,

reaction with humic substances in soils and sediments. The reaction product accumulates due to the very low biodegradation (estimated half-life of 1,000 days),

low bioaccumulation in fish. Possibly accumulation of the reaction product with humic substances in sediment dwelling organisms.

For the environmental exposure assessment site-specific scenarios are used for calculating the PECs in surface waters and sediments. The scenarios are based on actual sewage monitoring data from industry. Local concentrations for production and processing are between 0.07 and 22 µg/l. For the manufacture of plant protection agents PEClocal between 0.0049 and 0.12 µg/l are calculated.

The releases from the use of plant protection agents and biocides into the hydrosphere were analysed by using the available monitoring data revealed that the non-agricultural use of diuron as total herbicide on sealed areas is the source of frequent DCA detection. Apparently at several sampling sites the measured concentrations are above the PNEC of 0.2 µg/l. For the interpretation of the positive detections, different life-cycle steps have to be considered.

For the maximum concentration measured at Meusse (Kreizersveer) of 0.68 µg/l, a sediment concentration of 0.15 mg/kg could be calculated

Because of the binding properties of 3,4-DCA onto organic matter, a high accumulation of the substance in sediments is expected. PEClocal for sediment could be calculated from the PEClocal for production of DCA and plant protection agents, for processing and use of TCC between 0.001 and 4.8 mg/kg.

Because no significant releases of 3,4-DCA into the atmosphere during production and processing are expected, a risk assessment for this compartment is not necessary.

No direct releases into soil were identified except of small amounts of 3,4-DCA contained as impurity in plant protection agents which are its subsequent products. However, additional 3,4-DCA is originated from these agents by microbial degradation.

For the calculation of a PEClocal for agricultural application of plant protection agents the sewage sludge model was used. For the use of diuron a PEClocal soil of 3.9 mg/kg dw with an application of 4.1 kg diuron/ha once a year was calculated. There is a good agreement between the calculated PEC and the reported concentration of 2 mg/kg (based on measurements, with an application of 1.76 kg diuron/ha).

When diuron is used as a total herbicide in non-agricultural areas, the application amounts are up 5.6 kg diuron/ha, and with this figure a PEClocal_soil of 5.3 mg/kg dw is calculated.

Presently, for linuron application rates of maximum 2.9 kg/ha are permitted, which leads to a PEClocal_soil of 2.6 mg/kg dw. According to the proposal of the EU review programme in the frame of Council Directive 91/414/EEC, the maximum proposed application rate is 0.95 kg/ha, which leads to a PEClocal_soil of 0.85 mg/kg.

For propanil, a PEClocal_soil of 4.4 mg/kg dw is calculated with a maximum application rate of 5 kg/ha.

Due to the high bioaccumulation and bioconcentration factors for sediment dwelling organisms biomagnification may occur for the route sediment - sediment dwelling organisms - worm-eating fish or bird. For an exposure scenario for the sediment food chain (sediment - worm - bird or mammal) for the different scenarios, the mean sediment concentrations are calculated, which are considered for exposure via the food chain. The $PECs_{oral,worm}$ are calculated from the mean aquatic concentration and a BAF for *Lumbriculus variegatus* of 570 l/kg. $PEC_{oral,worm}$ between 0.0026 and 6.3 mg/kg were calculated.

3.2 EFFECTS ASSESSMENT

For 3,4-DCA short- and long term tests with fish, daphnids and algae are available. Daphnids are the most sensitive species in short term tests. For *Daphnia magna* a 48-hour LC_{50} of 0.23 mg/l and a 96-hour LC_{50} of 0.16 mg/l could be found. The most sensitive species in long-term tests are *Brachydanio rerio* and *Poecilia reticulata* with 42-day NOECs of 2 µg/l. A PNEC of 0.2 µg/l was determined on the available data basis using an AF of 10.

When applied 3,4-DCA during a test in soil or sediment, the 3,4-DCA will be mobile only for a few hours. After one or two days the substance is almost quantitatively bound and the same DCA-humic acid-complexes will be formed as under environmental conditions. Effect tests in which the test substance is pre-incubated several weeks before starting the test would be more appropriate for the risk assessment. Therefore, long-term tests in which the test substance is pre-incubated in soil several weeks before starting the tests were performed.

A number of short-term tests with benthic invertebrates are available, but in these tests the organisms were exposed to 3,4-DCA in water and not to contaminated sediment. Only one acute 10 days growth test on *Chironomus riparius* with sediments spiked with 3,4-DCA is available. The test investigated survival and the sub-lethal endpoints length and dry weight. Due to the short time of test duration, the data refer only to a restricted period of larval development, the stage of emergence is not reached and more over no reproduction is investigated. As it is known

that 3,4-DCA influences the reproduction of different species and that the acute to chronic ration for 3,4-DCA is very high, the test cannot be used as a long-term test. Additionally two long-term tests with *Chironomus riparius* and one with *Lumbriculus variegatus* with sediments spiked with 3,4-DCA are available. The lowest endpoint available for *Chironomus riparius* with a LOEC of 0.064 mg/kg dw was questioned therefore the test was repeated. From the repeated test an EC_{10} of 104 mg/kg dw for developmental rate (female) was obtained. For *Lumbriculus variegatus* a NOEC of 5 mg/kg dw was found for the total number of worms. This can be seen as the endpoint relevant for the assessment. The assessment factor for two valid long-term tests is set to 50 according TGD and therefore a PNECsediment of 0.04 mg/kg ww (0.1 mg/kg dw) is calculated.

For the terrestrial compartment long-term data are available with pre-incubated 3,4-DCA for plants, micro-organisms and invertebrates. The most sensitive species appears to be the micro-organisms with a 28-day NOEC of 100 mg/kg for inhibition of nitrification. As long-term tests are available for species from three trophic levels an assessment factor of 10 can be used on the NOEC for the species showing the most sensitive endpoint, giving a PNECsoil of 10 mg/kg.

3,4-DCA is known to have endocrine effects on fish. It could be shown that 3,4-DCA causes lowered androgen synthesis at tested concentrations of 200 and 400 µg/l in breeding male Sticklebacks (*Gasterosteus aculeatus*). The changes in androgen metabolism are accompanied by changes in the secondary sex characters at concentration of 100, 200 und 400 µg/l. The splendid colour typical of breeding males become regressive and courtship behaviour occurs no longer.

The PNEC for microorganisms is extrapolated from a test with activated sludge (EC_{50} = 44 mg/l) using an assessment factor of 100. This leads to a PNEC of 0.44 mg/l.

3.3 RISK CHARACTERISATION

3.3.1 Aquatic Compartment

For the aquatic compartment, the risk characterisation based on site-specific information for 3,4-DCA production leads for one producer to a PEC/PNEC ratio > 1 which indicate a hazard for the aquatic environment including sediment. However, the production at this site was closed and therefore the risk identified for this site is no longer present. **Conclusion (ii)**.

For the manufacture of plant protection agents Diuron and Linuron the PEC/PNEC ratios are below one for waste water treatment plants, aquatic compartment and sediment compartment. Therefore, no risk is to be expected for the environment from this life-cycle step. **Conclusion (ii)**.

For the manufacture of Propanil the PEC/PNEC ratio are below one for waste water treatment plants, aquatic compartment and sediment compartment. **Conclusion (ii)**.

In a series of rivers the measured concentrations are above the PNEC. Therefore, for the use of plant protection agents the PEC/PNEC ratios for the aquatic are > 1. A risk to aquatic organisms has to be expected. **Conclusion (iii)**. For the maximum concentration measured at Meusse (Kreizersveer) of 0.68 µg/l with sediment concentration of 0.15 mg/kg ww a PECsed/PNECsed ratio of 3.75 could be calculated. Therefore a risk to sediment organisms has to be expected as well. The data basis for the sediment can be improved by performing long term tests with a third sediment organisms representing a further exposure pathway (*Hyalella azteca*). However, the requirement for further testing should await the outcome of the risk reduction strategy for the aquatic (surface water) compartment, since the sediment PECs will be directly affected by any

measures to reduce concentrations in water and the PEC/PNEC ratio for sediment is only slightly higher than for the aquatic compartment. **Conclusion (i)**.

The risk assessment for the releases during production of trichlorocarbanilid (TCC) does not indicate a risk for aquatic and sediment organisms and for water treatment plants. **Conclusion (ii)**.

For the use of TCC in house hold products, the assessment resulted in PEC/PNEC ratios below one for waste water treatment plants, aquatic compartment and sediment compartment. **Conclusion (ii)**.

It has to be considered that if the use of TCC as biocide in the EU will increase again a risk to the aquatic and sediment compartment cannot be excluded.

3.3.2 Atmosphere

Because a low volatility of 3,4-DCA is to be expected, no significant exposure of the atmosphere is assumed. **Conclusion (ii)**.

3.3.3 Terrestrial compartment

The risk assessment indicates that a risk to soil organisms due to 3,4-DCA is not to be expected. **Conclusion (ii)**.

3.3.4 Secondary poisoning

For the food chain sediment - worm - bird or mammals various $PECs_{oral,worm}$ were calculated. Comparison with the lowest determined PNECoral of 0.3 mg/kg results in PEC/PNEC ratios for DCA producer D. However, as the production of 3,4-DCA at this site has stopped, the risk identified for this site is no longer present. **Conclusion (ii)**.

4 HUMAN HEALTH

4.1 HUMAN EXPOSURE

4.1.1 Occupational exposure

3,4-DCA is employed exclusively as a chemical intermediate. The main quantity (99.8%) is used for the production of herbicides. The remaining 0.2% is used for the manufacture of an azo dispersive dye.

3,4-DCA may be formed by decomposition of diuron which is an antifouling agent used for coating ships. Based on the available information on half-lives of degradation under different conditions and on the high water solubility, exposure to 3,4-DCA during the application of antifouling formulations can be neglected.

Occupational exposure limit for 3,4-DCA are not established.

Dermal and inhalation exposures are estimated for one exposure scenario: production and further processing of the substance in the large-scale chemical industry. The exposure assessment is based on measured data, expert judgement and estimations according to the EASE model.

Since the substance is solid at ambient temperature, 3,4-DCA is transferred in a molten form at elevated temperatures (90°C). Because workers avoided contact with hot substances, dermal exposure regarding transfer activities (drumming, connecting/disconnecting transfer lines) is assessed as low. For handling the cooled, solidified substance, cleaning, maintenance and repair tasks are regarded to be the most probable activities with possible dermal exposure.

The results for this scenario are summarised in **Table 4.1**.

Table 4.1 Summary of exposure data

Exposure scenario	Duration and frequency	Inhalation exposure	Dermal exposure
		Shift average [mg/m³]	Shift average [mg/p/day]
Chemical industry			
Production and further processing as an chemical intermediate	shift length, daily 0.5 hours/day [2)]	< 0.07 [1)] 0.57 [1, 3)]	low 26 – 260 [4)]

1) Assessed on the basis of the submitted data
2) Activities like transfer, cleaning works
3) Short term value, workers wear respiratory equipment
4) Worst case estimate, the limited protection of gloves cannot be considered

4.1.2 Consumer exposure

Presumably, direct use of 3,4-dichloroaniline (3,4-DCA) by consumer does not exist. Thus, calculation of consumer exposure has not been carried out.

Possible release of 3,4-dichloroaniline from products used by consumers has to be considered additionally. The formation of 3,4-DCA is possible from the use of trichlorcarbanilide which is used as a deodorant and soap bactericide in household products (TCA content < 1%).

The herbicide diuron and paint formulations with this substance do not contain 3,4-dichloroaniline itself. However, 3,4-DCA is one of the metabolites which are formed *in vivo*

from diuron. According to the current use pattern diuron is used in anti-fouling products, as preservative in paints for facades and plasters and as an algicide. The possibility of an internal exposure to 3,4-DCA due to its formation from diuron containing products is considered to be negligible for the following reasons: low contents of diuron, short time of exposure, low dermal absorption, and only minor amounts of 3,4-DCA are metabolically formed in humans from diuron.

4.1.3 Indirect exposure via the environment

Man can be exposed indirectly via emissions into hydrosphere from industrial sites and via releases from plant protection products via the terrestrial compartment.

For the estimation of the total daily intake for humans, the different life-cycle steps of 3,4-DCA are considered. The total daily dose is estimated for the different production sites from $3.3 \cdot 10^{-7}$ to $1.7 \cdot 10^{-3}$ mg/kg bw/day for the emissions from industrial sources on a local scale. For the use of trichlorocarbanilide a total daily dose of $4 \cdot 10^{-6}$ mg/kg bw/day could be estimated. Concerning the intake of 3,4-DCA from plant protection agents, a daily dose of $2.3 \cdot 10^{-3}$ is calculated. The main contribution to the intake is to $DOSE_{stem}$ and the $DOSE_{root.}$ Additionally, DCA metabolites like 3,3',4,4'-tetrachloroazobenzene (TCAB), 3,3',4,4'-tetrachloroazoxybenzene (TCAOB) and related compounds were taken up. For an initial approach, for TCAB a PEC of 60 µg/kg was determined from a monitoring study.

4.2 EFFECTS ASSESSMENT

Data are available which show that 3,4-dichloroaniline is absorbed from the gastrointestinal tract, whereas absorption through skin and lungs has not investigated by kinetic studies. However, from the toxic effects which are observed it can be concluded that 3,4-dichloroaniline is also absorbed through skin and lungs. *In vivo* hydroxylation of 3,4-dichloroaniline leads to the formation of ortho- and para-hydroxylated compounds. N-hydroxylation was additionally observed *in vitro*. Rats completely excreted orally administered 3,4-dichloroaniline predominantly in the urine and to a lesser content in faeces. Thus, there seems to be no concern for bioaccumulation.

Data on acute toxic effects caused by exposure of humans to 3,4-dichloroaniline is not available. In animal experiments the acute toxicity of the substance was moderate in rats (oral and inhalation exposure) and more pronounced in rabbits (when applied dermally): Oral LD_{50} values of 570-880 mg/kg for male and of 530 mg/kg for female rats and an inhalation LC_{50} value (substance vapours) of 3.3 mg/l/4 hours for male rats were determined; the dermal LD_{50} for male rabbits was approximately 300 mg/kg. Clinical signs like diarrhoea, paralysis of the hind extremities, cyanosis, narcosis and reduced reflexes mostly appeared on the day of application of the substance. Methaemoglobin analysis in an acute inhalation toxicity study revealed that rats survived methaemoglobin contents of about 28% while deaths occurred at methaemoglobin contents of 47-62%. After 24 hours recovery, methaemoglobin levels were still highly elevated in the test animals; methaemoglobin increases had returned to base levels by approximately 9 days post exposure. Like other chloroaniline compounds, the primary toxic effect of 3,4-dichloroaniline is methaemoglobin formation. Taking into account that humans are much more sensitive to methaemoglobin-producing substances than rats and that results of studies with cats, better suited to judge the level of toxicity for humans, are not available, 3,4-dichloroaniline is classified as “T, Toxic” and labelled as “R 23/24/25, toxic by inhalation, in contact with skin and if swallowed”.

Studies in humans on local irritation/corrosion caused by 3,4-dichloroaniline are not available. Based on the studies in animals on Draize tests with rabbits, the substance is only slightly irritating to skin (no oedema, erythema grade 1 reversible within 2 days, but causes serious damage to eyes. The scores detected in a Draize eye test after 24/48/72 hours per animal were as follows: Redness of the conjunctivae 1.7/2/2; chemosis 0.7/0.7/1.3; iris 1/0.7/0.3 and cornea 1.3/1/0. Vascularisation of the cornea starting 7 days after treatment was observed but data on reversibility of that effect were not documented. Similar corneal vascularisation was detected in 2/3 rabbits in a further study where this effect was still present at day 14. Based on these data, 3,4-dichloroaniline is classified as "Xi, Irritating"and labelled with "R 41, Risk of serious damage to eyes".

Cases of chloracne recorded in previous years after exposure to industrial 3,4-dichloroaniline are attributed to the hyperkeratogenous and acnegenic effects of 3,3',4,4'-tetrachloro-azobenzene and 3,3',4,4'-tetrachloroazoxybenzene, impurities formerly present in industrial 3,4-dichloroaniline. No more cases of chloracne have been observed in Germany since 3,4-dichloroaniline was produced containing virtually none of these impurities.

Studies in humans on sensitisation by inhalation or skin contact are not available. In one Magnusson Kligman test up to 75% of the test animals demonstrated a positive reaction. Based on this result 3,4-dichloroaniline is labelled with "R 43, May cause sensitisation by skin contact".

Repeated dose studies on rats and rabbits indicated that 3,4-dichloroaniline has erythrotoxic properties, produces increased concentrations of methaemoglobin, enhances erythropoiesis, and as a sequence of erythrotoxicity induces persistent hemosiderosis. These effects were seen at concentrations of 10 mg/m³ (LOAEC) after 14-day inhalation exposure (6 hours/day, 5 days/week) and 60 mg/kg bw/day after daily application to the dorsal skin on 10 days. From another inhalation study there is some concern that 3,4-dichloroaniline may also affect the neurofunction. Altered enzyme activities on liver and kidney cells may give some indication on possible cytotoxic effects *in vitro*, but actually no support was obtained from *in vivo* studies. Studies from structurally related substances reveal consistent effects to those of 3,4-dichloroaniline. The reports from human exposure gave indications on methaemoglobinemia, cyanosis, eye and skin irritation after repeated exposure to 3,4-dichloroaniline, however data could not clearly be attributed to this substance mainly because of mixed chemical exposure.

In vitro genotoxicity tests were negative for gene and chromosome mutations. However, there is limited evidence for a mutagenic potential mainly due to a weakly positive SCE test *in vitro* and a positive test for induction of spindle damage *in vitro*. The clearly negative *in vivo* micronucleus tests indicate that this potential is unlikely to be expressed *in vivo*.

Related to carcinogenicity, there are no data available from long term studies on 3,4-dichloroaniline. *In vivo* genotoxicity data did not give concern on carcinogenic properties of 3,4-dichloroaniline itself. On the structurally related chloroaniline compounds 2,5-chloroaniline, 2-chloroaniline, and 3-chloroaniline carcinogenicity data are not available. On the other hand, 4-chloroaniline is carcinogenic in rats and mice. Thus, there might be some concern that 3,4-dichloroaniline may have carcinogenic properties, too. However, the available metabolic data give no evidence for an *in vivo* dehalogenation of 3,4-dichloroaniline to 4-chloroaniline thus this suspicion is considered to be negligible.

No fertility studies are available following treatment with 3,4-dichloroaniline. Likewise, data from adequate 90-day repeated dose toxicity studies are not available. Thus, information from studies in rats and dogs with the herbicide diuron from which 3,4-dichloroaniline is

metabolically formed *in vivo* is used to supplement the reproductive toxicity data. From a two-year feeding study on dogs with diuron no histopathological changes in gonads and uterus were reported at the highest dose of 1,250 mg/kg bw food (equivalent to 62.5 mg/kg bw/day diuron). This dose corresponds to an internal exposure to 3,4-dichloroaniline of 0.75 mg/kg bw (1.2% of total metabolites). For 3,4-dichloroaniline no significant adverse effects on embryonic/fetal development were revealed from an oral teratology study (according to OECD-Guideline 414) in rats. The NOAEL for developmental toxicity is 25 mg/kg bw/day. There are no studies in humans available on toxicity for reproduction.

4.3 RISK CHARACTERISATION

4.3.1 Workers

Workplace exposure to 3,4-dichloroaniline is restricted to production and further processing in the chemical industry. For the purpose of risk assessment, it is assumed, that inhalation of vapour/particles and skin contact are the main routes of exposure. There is only one exposure scenario for repeated inhalation exposure during production and further processing. Average air concentrations lay below the detection limit of 0.07 mg/m³, as short-term value 0.57 mg/m^3 is reported. Dermal exposure to the molten 3,4-dichloroaniline is assessed to be low, because highly accepted use of functioning PPE is assumed. However, for cleaning, maintenance and repair tasks occasional dermal exposure to the cooled substance (pure and in mixtures) cannot be ruled out. As a worst-case estimate an exposure level of 26-260 mg/person/day is given for the unprotected worker. Under normal working practices oral exposure is not considered to be relevant.

3,4-dichloroaniline is a methaemoglobin generating aromatic amine. With reference to data on interspecies differences for similar substances (aniline and acetanilide) species extrapolation for 3,4-dichloroaniline is a crucial issue in risk evaluation. Workers are considered to be more susceptible than rats. For the oral and dermal route a rat-to-human assessment factor of 1/10 is used. For inhalation exposure, expressed as concentration of the substance in air, this factor reduces to 1/2.5 because of the approximately 4 times higher respiratory minute volume of rats compared to humans on the basis of bodyweight.

Comparing the rat LC_{50}-value of 3,300 mg/m^3 with the highest short-term exposure concentration of 0.57 mg/m^3 a MOS of 5,789 is calculated, which indicates that lethality is not expected following acute inhalation exposure at these workplaces (**Conclusion (ii)** for acute inhalation toxicity/lethality). In addition dose response data on methaemoglobin formation in rats do not indicate a risk of cyanosis, assuming that in humans a methaemoglobin blood level in the range of 10% and above can lead to cyanosis (**Conclusion (ii)** for cyanosis following acute inhalation exposure).

Risk assessment for acute dermal toxicity primarily is based on a rabbit LD_{50} of 300 mg/kg. For a body weight of 70 kg a LD_{50} of 21,000 mg/person is calculated. On the basis on a maximum dermal exposure of 260 mg/person/day the lowest MOS of 81 (21,000/260) is not considered to be of concern. In addition, available toxicological data for 3,4-dichloroaniline does not indicate a risk of cyanosis after skin contact (overall **Conclusion (ii)** for acute dermal toxicity).

3,4-dichloroaniline is slightly irritant to the skin of rabbits. Irritation potency is not considered to be sufficient for classification. No concern for workers is derived (**Conclusion (ii)** for dermal irritation).

Based on rabbit data 3,4-dichloroaniline may result in serious damage to the eyes. It is assumed that suitable PPE usually is worn in the chemical industry. However, unintended contact by non-proper use of eye glasses may occur. Therefore a risk of eye irritation has to be considered. On the grounds that control measures exist, which should be able to efficiently reduce exposure, conclusion ii is proposed. However, control measures must be implemented and complied with to reduce the risk of damage to the eyes (**Conclusion (ii)** for eye irritation).

Based on studies in animals 3,4-dichloroaniline is considered to be sensitising to the skin. Dermal exposure critically depends on the proper use of suitable gloves. In the case that use of functioning gloves is highly accepted (handling of the molten substance) the risk of skin sensitisation is anticipated to be negligible. However during cleaning, maintenance and repair work relevant dermal exposure against 3,4-dichloroaniline (cooled substance) cannot be excluded. The risk of workers to develop contact allergies therefore is considered to be of concern (**Conclusion (iii)** for skin sensitisation). Data on respiratory sensitisation in man (e.g. case reports) and in animals are not available. Inhalation exposure is not suspected to result in respiratory tract sensitisation (**Conclusion (ii)** for respiratory sensitisation).

Risk assessment for repeated dose toxicity (by inhalation and by dermal contact) primarily relies upon the results of a two-week inhalation study in rats. At the lowest tested air concentration of 10 mg/m^3 slight erythrotoxicity, interpreted as an early indicator of chronic toxicity, has been observed. Taking into account metabolic rate scaling and the lack of a NOAEL, a critical exposure level of about 1 mg/m^3 is used for risk evaluation. Repeated inhalation exposure during production and further processing (<0.07 mg/m³) is at least 10 times below the critical exposure level (**Conclusion (ii)** for repeated dose toxicity by inhalation; systemic effects). Significant dermal exposure levels only have to be considered during cleaning, maintenance and repair work. This contact however is reported to occur only occasionally and is therefore not relevant under the aspect of chronic toxicity (**Conclusion (ii)** concerning repeated dose toxicity by dermal contact). Concerning adverse effects in the respiratory tract the 2-week exposure of 3,4-dichloroaniline led to no local effects up to air concentrations of 200 mg/m^3 (**Conclusion (ii)** for repeated dose toxicity; local effects).

Carcinogenicity data on 3,4-dichloroaniline is not available. Based on negative results from *in vivo* micronucleus tests, a risk of carcinogenicity (via a genotoxic mechanism) is not expected (**Conclusion (ii)** for mutagenicity and carcinogenicity).

Experimental studies on fertility impairment of 3,4-dichloroaniline are not available. No effects were observed in testes and epididymides in a 2-week inhalation study in male rats up to the highest concentration of 200 mg/m^3. In a 2-year feeding study in dogs with diuron, a herbicide that is partly metabolised to 3,4-dichloroaniline, no histopathological changes in gonads and uterus were reported at the highest dose tested, which may be assumed to correspond to an internal exposure to 3,4-dichloroaniline of 0.75 mg/kg/day. In combination with the fact that inhalation exposure at the workplace is reported to be below the detection limit of 0.07 mg/m^3 and dermal exposure occurs only occasional, no request for further testing and no concern was derived (**Conclusion (ii)** for fertility impairment). Based on the negative results of a teratology study in rats 3,4-dichloroaniline is not considered to be a developmental toxicant (**Conclusion (ii)** for developmental toxicity).

In summary, worker exposure against 3,4-dichloroaniline generally is low except for occasional dermal contact during cleaning, maintenance and repair work. On that background concern for skin sensitisation (**Conclusion (iii)**) is expressed. For all other toxicological endpoints, a risk assessment perspective did not result in concern. However, repeated dose toxicity of

3,4-dichloroaniline is considered to be significant. Corresponding toxicological data principally could be used for the establishment of a health-based occupational exposure limit.

4.3.2 Consumers

Since there is no consumer exposure, a health risk of consumers is not expected. **Conclusion (ii)**.

4.3.3 Humans exposed via the environment

The total daily intake of 3,4-dichloroaniline for oral exposure via drinking water and fish and from plants has been calculated to amount up to about $4 \cdot 10^{-3}$ mg/kg bw/day.

4.3.3.1 Repeated dose toxicity

No data from an oral study following 3,4-dichloroaniline administration are available. Therefore, for the risk characterisation the total daily intake resulting from the three scenarios is compared with a converted NOAEL of 2.88 mg/kg bw/day which was derived from a 14-day inhalation study on rats. The margin of safety expressed by the magnitude between the calculated exposure value and the NOAEL is considered to be sufficient. Thus, the substance is of no concern in relation to indirect exposure via the environment. **Conclusion (ii)**.

4.3.3.2 Reproductive Toxicity

Studies on the reproductive function or capacity of 3,4-dichloroaniline is not available. From a two-year feeding study on dogs with the herbicide diuron, which is metabolised to 3,4-dichloroaniline *in vivo*, no histopathological changes in gonads and uterus were reported at the highest dose tested. At this dose the animals were internally exposed to 0.75 mg 3,4-DCA/kg bw. From the results of an OECD-Guideline 414 study with oral application to rats a NOAEL for embryonic/fetal effects of 25 mg/kg bw/day was derived. Taking into account the low exposure of up to $4 \cdot 10^{-3}$ mg/kg bw/day it can be concluded that the margins of safety for both toxicity to reproduction and developmental toxicity are considered to be sufficient. Thus, there is no concern in relation to indirect exposure via the environment. **Conclusion (ii)**.

5 RESULTS

5.1 ENVIRONMENT

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

This conclusion is reached because of

- the non-agricultural use of diuron on sealed areas as total herbicide,

which is expected to cause a risk to the aquatic environment including sediment.

An environmental pollution of 3,4-dichloroaniline from the use of diuron as antifouling agent and as algicide in the construction sector has to be expected. These releases could not been taken into account in the risk characterisation, as neither sufficient exposure relevant information nor an appropriate exposure model are available. Diuron is more toxic than 3,4-DCA and probably occurs in higher concentrations, thus the 3,4-DCA exposure from these applications should be covered by a diuron assessment. It is recommended to perform an assessment for diuron in the frame of the Biocide Directive 98/8/EU.

Conclusion (i) There is a need for further information and/or testing.

For the releases of 3,4-DCA from the non-agricultural use of diuron on sealed areas as total herbicide the PEC/PNEC ratio for sediment is above 1. The data basis can be improved by performing a long term test with a third sediment organism representing a further exposure pathway (*Hyalella azteca*). However, the requirement for further testing should await the outcome of the risk reduction strategy for the aquatic (surface water) compartment, since the sediment PECs will be directly affected by any measures to reduce concentrations in water.

5.2 HUMAN HEALTH

5.2.1 Human health (toxicity)

Workers

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Based on the available information the exposure of workers against 3,4-dichloroaniline generally is low with the exception of occasional dermal contact during cleaning, maintenance and repair work. On that background for skin sensitisation concern has to be raised.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

For the other toxicological endpoints the risk orientated conclusions result in no concern with the consequence that risk reduction measures are of low priority. Although the hazard assessment revealed significant toxicological properties for 3,4-dichloroaniline, exposure levels reported at the workplace are below the concern range.

5.2.1.1 Consumers

Conclusion (ii) There is at present no need for further information and/or testing or for risk reduction measures beyond those which are being applied already.

5.2.1.2 Humans exposed indirectly via the environment

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

5.2.2 Human health (Physico-chemical properties)

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already

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DG Joint Research Centre, Institute of Health and Consumer Protection
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EUR 22234 EN **European Union Risk Assessment Report**
3,4-dichloroaniline

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The summary report provides the comprehensive risk assessment of the substance 3,4-dichloroaniline. It has been prepared by Germany in the frame of Council Regulation (EEC) No. 793/93 on the evaluation and control of the risks of existing substances, following the principles for assessment of the risks to humans and the environment, laid down in Commission Regulation (EC) No. 1488/94.

Part I - Environment

This part of the evaluation considers the emissions and the resulting exposure to the environment in all life cycle steps. Following the exposure assessment, the environmental risk characterisation for each protection goal in the aquatic, terrestrial and atmospheric compartment has been determined.

The environmental risk assessment concludes that there is concern for the aquatic environment as a consequence of exposure arising from the non-agricultural use of diuron as total herbicide on sealed areas.

There is a need for further information to adequately characterise the risks to the aquatic ecosystem arising from the release form non-agricultural use of diuron on sealed areas as total herbicide and performing a long term test with a third sediment organism representing a further exposure pathway (Hyalella azteca). However, this requirement for further testing was awaiting the outcome of the risk reduction strategy for the aquatic compartment. Because the measures recommended are expected to sufficiently reduce concentrations in the aquatic compartment, the test is now no longer deemed necessary.

Part II – Human Health

This part of the evaluation considers the emissions and the resulting exposure to human populations in all life cycle steps. The scenarios for occupational exposure, consumer exposure and humans exposed via the environment have been examined and the possible risks have been identified.

The human health risk assessment concludes that there is concern for workers with regard to skin sensitisation as a consequence of dermal exposure arising form cleaning, maintenance and repair work in the production and further processing of 3,4-dichloroaniline. For consumers and humans exposed via the environment there is no concern

For human health as far as physico-chemical properties are concerned there is no concern.

The conclusions of this report will lead to risk reduction measures to be proposed by the Commission’s committee on risk reduction strategies set up in support of Council Regulation (EEC) N. 793/93.

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