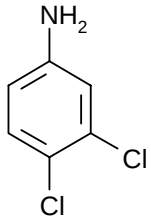
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	95-76-1
Chemical Name	3,4-Dichloroaniline
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Like other chloroanilines, the primary toxic effect of 3,4-dichloroaniline (3,4-DCA) is methaemoglobin formation. Acute intoxication is indicated by methaemoglobinemia (cyanosis), fatigue, dyspnoea, and muscle weakness.

In vitro studies on rat liver and kidney slices indicated that 3,4-DCA may have a hepatotoxic and nephrotoxic potential as other structurally related compounds observed after single in vivo applications.

3,4-DCA has demonstrated for rats moderate acute toxicity after oral application and after inhalation (LD50 values of 530 – 880 mg/kg bw and a LC50 of 3300 mg/m^3 (4 h) in a test according to OECD TG 403). Acute dermal toxicity demonstrated great species differences: In tests with rats the dermal LD50 was detected to exceed 1000 mg/kg bw (no mortalities and no toxic signs) whereas a test with male rabbits demonstrated a dermal LD50 of 300 mg/kg bw.

In a Draize test with rabbits according to OECD TG 404 3,4-DCA caused mild skin irritation. In two Draize eye tests with rabbits according OECD TG 405 moderate reversible irritation of conjunctivae, iris and cornea occurred, but corneal vascularization was observed 7-14 days after instillation of the substance into eyes.

In humans, cyanosis, methaemoglobinemia, eye and skin irritation were observed after prolonged occupational exposure to mixed chemicals including 3,4-DCA.

3,4-DCA has no local corrosive properties, but demonstrated skin sensitizing properties in a Magnusson Kligman test with guinea pigs according to OECD TG 406. Sensitization of humans is not reported.

In rats, mice, and rabbits repeated inhalation, oral or dermal exposure to 3,4-DCA or structurally related compounds resulted primarily in methaemoglobinemia and hemolytic anemia. Spleen weight increase, microscopically hemosiderosis in the spleen, liver, and/or kidneys and increased compensatory erythropoeisis were observed as main effects. From the 14-day inhalation study with 10, 45, or 200 mg/m^3 3,4-DCA to rats (OECD TG 412, 6 h/d, 5 d/week) a LOAEC of 10 mg/m^3 was derived based on significant increase of methaemoglobin levels. Similar effects were seen on male rabbits after daily application of 60 mg/kg bw to the dorsal skin on 10 days. 3,4-DCA did not induce gene mutations in all bacterial tests according to OECD TG 471.

In vitro tests were negative for gene mutations with CHO cells (OECD TG 476) and for chromosomal aberrations with human lymphocytes (OECD TG 473). Limited evidence for a mutagenic potential may be derived from a positive a mitotic spindle damage test with V79 cells. The clearly negative *in vivo* micronucleus tests according

OECD TG 474 indicate that this potential is unlikely to be expressed *in vivo*.

No data on the cancerogenic potency of 3,4-DCA itself is available. From data on the structurally related compound 4-chloroaniline some concern may be derived that 3,4-DCA might have carcinogenic properties, too. However, the available metabolic data give no evidence for an in vivo dehalogenation of 3,4-DCA to 4-chloroaniline. Thus this suspicion is considered to be negligible.

The assessment of data from the available teratology gavage study with rats according to OECD TG 414 did not indicate any significant developmental toxicity (doses of 5, 25, or 125 mg/kg bw/d). Borderline developmental toxicity occurred at the clearly maternally toxic high dose level of 125 mg/kg bw/d in form of a slight but not statistically significant increase in resorptions and consequently post-implantation loss. Also a significant delay in ossification of a few skeletal elements was observed. Thus, the NOAEL for developmental toxicity is 25 mg/kg bw/d, whereas that for maternal toxicity is 5 mg/kg bw/d (reduced food consumption and average body weight gain).

There are no adequate data available on fertility impairment. Limited data from short term repeated dose toxicity studies on structurally related compounds such as 2-chloroaniline and 2,5-DCA did not reveal changes in male reproductive organs. However, 3,4-DCA is one of the metabolites which are formed in vivo from the herbicide diuron. In a 2-year study in dogs administration of up to 1250 mg/kg food (highest dose, equivalent to 62.5 mg/kg bw/d diuron) resulted in formation of 1.2% 3,4-DCA. No histopathological changes in gonads and uterus were reported at this dose of 62.5 mg/kg bw/d diuron (NOAEL) which represents an internal exposure to 3,4-DCA of 0.75 mg/kg bw. The weight of evidence indicates that there is no evidence of effects on fertility; therefore, no further testing is necessary.

Environment

3,4-DCA has a Koc of 334 l/kg calculated from a log Pow of 2.7, a water solubility of 580 mg/l and a vapor pressure of 0.184 Pa at 20°C. Based on a Henry`s law constant of 0.05 Pa m^3mol^{-1}, only a low volatilization from the hydrosphere is to be expected. According to the Mackay fugacity model level I calculation, the favorite target compartment of DCA is water with 91.38 %, followed by soil with 3.62 %, sediment 3.38% and air 1.62%.

3,4-DCA is not readily and not inherently biodegradable. In surface waters, the substance is removed by photolysis and by chemisorption onto the organic matter of sediments.

In agricultural soils, DCA is formed by biodegradation of the plant protection agents. Within some days, DCA forms covalent bounds with soil organic matter. The reaction product is extremely slowly biodegraded and accumulates when the agents are periodically applied.

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 h-LC50 of 0.23 mg/l and a 96 h LC50 of 0.16 mg/l could be found. The most sensitive species in long-term tests are *Brachydanio rerio* and *Poecilia reticulata* with 42d-NOECs of 2 µg/l. A PNEC of 0.2 µg/l was determined on the available data basis using an AF of 10. For the sediment one long-term test with *Lumbriculus variegatus* with a NOEC of 5 mg/kg dw for the endpoint total number of worms is available. With an assessment factor of 100, a PNECsediment of 0.05 mg/kg is calculated.

For the terrestrial compartment long-term data are available for plants, micro-organisms and invertebrates. The most sensitive species appears to be the micro-organisms with a 28 d-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.

Exposure

In the European Union, in the period 1996 – 1998 13,500 – 15,500 t/a 3,4-DCA were produced, from this 3,700 – 4,600 t were exported. 3,4-Dichloroaniline (DCA) is produced by hydrogenation of 1,2-dichloro-4-nitrobenzene. More than 99% of the production volume are processed by phosgenation to the 3,4-dichlorophenylisocyanate. At the

present for 3,4-DCA there is only one producer in the EU. 3,4-DCA is exclusively used as an intermediate in the chemical industry primarily for the synthesis of 3,4-dichlorphenylisocyanate as intermediate for the production of herbicides. Only small amounts of 3,4-DCA are used for the synthesis of the bactericide trichlorocarbanilide and an azo dye.

Manufacture of 3,4-DCA from 3,4-dichloronitrobenzene takes place in a closed environment. Therefore provided the integrity of the system is maintained there should be no human exposure during manufacture, Exposure could occur however during maintenance, cleaning or repair work or by taking samples and analysing them. The down stream users of EU produced 3,4-DCA also appear to use closed systems for manufacture of the products derived from 3,4-DCA.

The exposure of the general public is likely to be very low, since 3,4-DCA exposure will only occur via degradation of products that have 3,4-DCA as part of their structure.

During production 3,4-DCA it released via waste water into the hydrosphere. Further releases into the hydrosphere are expected from processing of the isocyanate compound to the pesticides diuron, linuron, and propanil.

A direct use of 3,4-DCA by consumers does not exist. There might be the possibility of a very low exposure of 3,4-DCA due its metabolic formation from diuron containing products. The herbicide diuron and paint formulations with this substance do not contain 3,4-DCA.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical possesses properties indicating a hazard for human health (skin and eye irritation, sensitization, methaemoglobinemia, developmental toxicity at maternally toxic doses). Based on data presented by the sponsor country, exposure to humans and the environment is anticipated to be low, and therefore this chemical is currently of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the sponsor country.

Note: A risk assessment performed in the European Union in the context of the EU Existing Substances Regulation reveals concern for several toxicological endpoints. A finalized risk reduction strategy for workers concluded, that the legislation for workers protection currently in force in the EU is considered to give an adequate framework to limit the risk of the substance to the extent needed.

Environment: The chemical possesses properties indicating a hazard for the environment. Based on data presented by the sponsor country, exposure to humans and the environment is anticipated to be low, and therefore this chemical is currently of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the sponsor country.

Note: This substance has been assessed in the European Union Risk Assessment program under Regulation EEC/793/93. A finalized risk reduction strategy for the environment concluded, that there is no longer a risk identified in the risk assessment from production and processing in the EU.
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 characterization, 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.