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Directorate C - Public Health and Risk Assessment
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**SCIENTIFIC COMMITTEE ON TOXICITY, ECOTOXICITY AND THE
ENVIRONMENT (CSTEE)**

Opinion on the results of the Risk Assessment of:

**3, 4-DICHLOROANILINE
HUMAN HEALTH PART**

CAS No.: 95-76-1

EINECS No.: 202-448-4

**Carried out in the framework of Council Regulation (EEC) 793/93 on
the evaluation and control of the risks of existing substances¹**

**Adopted by the CSTEE during the 40th plenary meeting
on 12 November 2003**

¹ Regulation 793/93 provides a systematic framework for the evaluation of the risks to human health and the environment of those substances if they are produced or imported into the Community in volumes above 10 tonnes per year. The methods for carrying out an in-depth Risk Assessment at Community level are laid down in Commission Regulation (EC)1488/94, which is supported by a technical guidance document.

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Terms of Reference

In the context of Regulation 793/93 (Existing Substances Regulation), and on the basis of the examination of the Risk Assessment Report the CSTEE is invited to examine the following issues:

- (1) Does the CSTEE agree with the conclusions of the Risk Assessment Report?
- (2) If the CSTEE disagrees with such conclusions, the CSTEE is invited to elaborate on the reasons for this divergence of opinion.

According to the Technical Guidance Document on Risk Assessment – European Communities 2003:

- conclusion i): *There is a need for further information and/or testing;*
- 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;*
- conclusion iii): *There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.*

OVERALL CONCLUSIONS

The overall quality of this report is sound, bearing in mind the very limited data base from which to assess the risk to workers and the general public from exposure to DCA itself. However the report fails to consider possible contaminants of DCA, in particular 3,3',4,4'-tetrachloroazobenzene which is a potent dioxin like substance.

It is estimated by the CSTEE that the exposure of the general public is likely to be very low since DCA exposure will only occur via the degradation of products that have DCA as part of their structure. For this reason, in respect of consumers conclusion ii) is appropriate.

In the case of workers some exposure will occur. In view of the lack of reliable chronic toxicity data only conclusion iii) can be reached.

EXPOSURE CONSIDERATIONS

There are only two manufacturing plants for 3,4-dichloroaniline (DCA) in the EU. According to the report DCA appears to be used almost entirely as an intermediate in the manufacture of:

- The phenylurea herbicides (propanil, diuron and linuron)
- A bactericide, trichlorocarbanilide
- An azodye, 5-amino-2,3-dimethylbenzenesulphethanolamide.

Any other products are likely to be manufactured in quantities less than one ton.

It is noted by the CSTE that commercial grade DCA contains up to 5% impurities including 3,3',4,4'-tetrachloroazobenzene and various other chloroanilines. No consideration is given in the report to either worker or consumer exposure to these substances.

The report concludes that human exposure to DCA may occur:

- a) in the workplace
- b) through the environment as a consequence of the breakdown of the products manufactured from DCA

a) Workplace exposure

Manufacture of DCA from 3,4-dichloronitrotoluene 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 DCA also appear to use closed systems for the manufacture of the products derived from DCA. It is not clear whether all of the downstream users are covered in this analysis. Nonetheless for down stream users too the most 'at risk' workers would therefore appear to be those involved in the maintenance, cleaning repair, sampling and analysis.

Dermal absorption is a potential route of exposure. Using the EASE model estimated airborne levels of 3.6-6.6 mg/m³ could occur with dermal exposure, assuming no PPE worn, resulting in exposures of 26-260 mg per day. It follows that personal protective equipment (PPE) should be worn by all those who may be exposed to DCA.

Actual inhalation exposure data appears to be rather limited. The highest airborne level report (1 of 17 measurements) is a short-term value reported as 570 µg/m³. All other results were below the limits of detection. This data is insufficient to reach a clear conclusion on the risks from inhalation exposure.

No assessment has been made of the exposure of workers to any of the impurities. It is very important to specify the level of 3,3',4,4'-tetrachloroazobenzene in the products produced in DCA in the EU and to identify the fate of the contaminants that are removed during manufacture.

b) Exposure of the public

There is no data on the amounts of DCA that could be present in consumer products, for example soaps, biocides, paints and plastics.

DCA release by the manufacturing plants is stated to be low with the airborne route being insignificant. However no data is provided to confirm this.

The report concludes therefore that exposure would arise solely from the degradation of the products listed above after they have been distributed in the environment. Diuron for example is known to release DCA in the environment although the levels appear to be very low.

DCA has a low log Pow and therefore accumulation in the food chain is estimated in the report to be low. However direct evidence to support this contention appears to be limited to a single dose study.

Propanil is widely used in rice production but levels of DCA in rice are normally below 1µg/g. Higher levels may however be found in some other foods such as parsley, carrots and onions.

GENERAL COMMENTS ON THE HAZARD ASSESSMENT

The data base for the hazard assessment is weak. The report tries to extrapolate from related chemicals to fill in important gaps in the data. Confidence in this extrapolation must be limited. In such an analysis it is essential to set out the rationale for the selection of some analogues and the exclusion of others. The CSTEE considers that this explanation is inadequate in the report.

Absorption, metabolism distribution and excretion

There is very limited data on the absorption characteristics of DCA. Based on a single study in rats using the oral route the extent of absorption appears too high.

Studies on the onset of methaemoglobinaemia following dermal or inhalation exposure indicate that absorption is rapid.

There is limited data on the biotransformation of DCA. In one study in female rats haemoglobin adducts of DCA were detected. *In vitro* metabolism studies indicate that N-hydroxyDCA and Nacetyl and N formamide metabolites are produced. By extrapolation with other amines it appears likely that a number of other routes of metabolism will arise *in vivo* including ring hydroxylation, O and N hydroxylation. Conjugation with sulphate and glucuronic acid may be anticipated. A similar profile of metabolites is likely to occur in man.

Excretion in rats is prompt, principally in the urine.

Toxicological properties

Acute studies

In none of the reported toxicity findings is the purity of the DCA used described although the commercial grade may contain up to 5% impurities. The report assumes that all of the adverse effects are due to DCA itself.

The most notable acute toxic effect of DCA is methaemoglobinaemia, which at higher doses can give rise to cyanosis, lethargy, dyspnoea and muscle weakness.

The oral LD50 in rats is around 600 mg/kg. By the inhalation route the LC50 ranges from 2.8-4.7 mg/l/4hrs.

A marked species difference in dermal toxicity was observed with rabbits being considerably more sensitive than rats. No human data is described. By extrapolation from some other aromatic amines humans could be considerably more sensitive to methaemoglobin formation than rats.

The report does not discuss the mechanism by which methaemoglobin is formed. The CSTEЕ considers that this should have been included in the risk assessment.

DCA appears to be a mild irritant. It must be assumed, although there is no human data, that DCA is a sensitising agent. This conclusion is based on a single Magnusson Kligman test in which up to 75% of animals exhibited a positive reaction. There is no data on respiratory sensitisation potential of DCA. In view of the effects on the skin in the one animal study the CSTEЕ concludes that DCA should be considered to be a potential respiratory sensitiser.

Repeat dose studies

There is very limited reliable data on the effects of subchronic and chronic exposure to DCA. In a single inhalation study in rats, lasting only two weeks, dose related methaemoglobin and haemosiderin levels were observed along with anaemia and elevated spleen weights.

A 10-day rabbit study using dermal exposure produced qualitatively similar effects to those seen following inhalation exposure.

The limited mutagenicity testing produced equivocal results with a positive SCE test and evidence of the induction of spindle damage while other tests were generally negative. The report places heavy reliance of a negative finding in a single micronucleus test. The CSTEЕ disagrees with the conclusion in the report that the data is sufficient to conclude that DCA is not genotoxic. No carcinogenicity studies have been performed and hence the carcinogenicity potential of DCA remains uncertain. It is noted that a number of aromatic amines produce spleen tumour in rats due to the formation of methaemoglobin.

These studies do not provide a reliable basis for estimating the chronic effects of DCA. The report attempts to get round this problem by considering the toxicology of related chlorinated aromatic amines that have been better studied. However the data is not sufficiently robust or comprehensive to enable a conclusion to be reached on the risk to man from chronic exposure to DCA.

Developmental toxicity

A single developmental study in rats, using the oral route, indicated signs of maternal toxicity at 25mg/kg. However development effects were marginal at the higher dose of 125mg/kg. No specific teratogenic effect was observed.

RISK CHARACTERISATION

The absence of any reliable human data requires that the animal toxicity data be used to assess the human risk. Because rabbits are less sensitive to methaemoglobin formation than rats the report has chosen a somewhat arbitrary extrapolation factor of 2.5 to allow for the putative difference in sensitivity between rats and humans.

It is argued in the report that DCA is probably not a mutagen *in vivo* based on a single negative micronucleus test and hence it is not a genotoxic carcinogen. The report does not discount the potential of DCA to be tumourigenic.

Workers

In view of the absence of data, and the importance of ensuring the protection of the workforce conclusion iii) is appropriate. Moreover the possible effects of contaminants such as the dioxin like 3,3',4,4'-tetrachloroazobenzene have not been taken into account in this assessment.

Consumers

The report states that there is no consumer exposure. This is unlikely to be correct. However, the very limited data available does indicate that consumer exposure is likely to be very low and, therefore conclusion ii) is probably appropriate.