EUROPEAN COMMISSION

Health & Consumer Protection
Directorate-General

Scientific Committee on Health and Environmental Risks

SCHER

Risk Assessment Report on Diphenylamine

Human Health Part

CAS No.: 122-39-4

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Scientific Committees
on consumer products
on emerging and newly identified health risks
on health and environmental risks

The SCHER adopted this opinion at its 21st plenary on 15 January 2008

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Three independent non-food Scientific Committees provide the Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. The Committees also draw the Commission's attention to the new or emerging problems which may pose an actual or potential threat.

They are: the Scientific Committee on Consumer Products (SCCP), the Scientific Committee on Health and Environmental Risks (SCHER) and the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) and are made up of external experts.

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SCHER

Questions relating to examinations of the toxicity and ecotoxicity of chemicals, biochemicals and biological compounds whose use may have harmful consequences for human health and the environment.

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1. BACKGROUND

Council Regulation 793/93 provides the framework for the evaluation and control of the risk of existing substances. Member States prepare Risk Assessment Reports on priority substances. The reports are then examined by the Technical Committee under the regulation and, when appropriate, the Commission invites the Scientific Committee on Health and Environmental Risks (SCHER) to give its opinion.

2. TERMS OF REFERENCE

On the basis of the examination of the Risk Assessment Report the SCHER is invited to examine the following issues:

1) Does the SCHER agree with the conclusions of the Risk Assessment Report?
2) If the SCHER disagrees with such conclusions, it is invited to elaborate on the reasons.
3) If the SCHER disagrees with the approaches or methods used to assess the risks, it is invited to suggest possible alternatives

3. OPINION

3.1. General comments

The health part of the document is of good quality and both the exposure and effects assessment follow the TGD. However, it has to be highlighted that many studies are described as cited in the JMPR report on DPA (1998), since the original publication was not available.

DPA is currently produced by two companies in the European Union. The EU market volume is about 10 000 t/a. Most of the DPA is processed as a chemical intermediate (approximately 97.5%, according to information provided by Industry). Indeed, DPA is an important intermediate for the production of antioxidants, antiozonants, phenothiazine, dyes and other products. It is also used in the post-harvest treatment and as an antioxidant for lubricants. In the past DPA was used as an additive to gas oil. After August 2002, EU legislation (2001/574/EC, notified under document number C(2001)1728) prescribed the use of Solvent Yellow 124 (derivate of aniline) as the primary marker to identify this fuel and DPA is no longer listed as a possible marker.

3.2 Specific comments

3.2.1 Exposure assessment

DPA is a colourless solid (vapour pressure 0.03 Pa at room temperature) with a floral odour.

At the workplace, the relevant routes of exposure are by inhalation and by skin contact.

The route of exposure to consumers is the oral intake through residues present in fruits and vegetables, which have been preserved with DPA; dermal exposure is also possible by the use of lubricants.

The SCHER agrees with the choice of the scenarios regarded as relevant for occupational exposure, that is:

1. Production of diphenylamine and further processing

   For the large-scale chemical industry high standards of control at the workplaces are assumed to be practised. Inhalation exposure in other fields is normally minimised by technical equipment. Model estimates (0.7 - 1 mg/m³) and measured exposure levels are in the same range (90^{th} percentile: 1.05 mg/m³).

For assessing the health risks from daily dermal exposure in the area of production handling the solid (flakes) and the liquid substance is considered. Due to the melting temperature of 53°C, the liquid substance is transferred and filled at elevated temperatures (T>60°C). As a consequence workers avoid any dermal contacts. For handling the solid (flakes, contact the cooled, solidified substance), since no measurement results are available, an attempt is made to quantify dermal exposure by the EASE model. Dermal exposure is estimated to be 21 – 210 mg/person/day. The use of suitable gloves reduces dermal exposure to 10% leading to exposure of 2.1 – 21 mg/person/day. The upper value is regarded to represent the reasonable worst case. Exposure to the eyes is largely avoided by using eye protection.

2. Use of lubricants.

For activities without the formation of aerosols the inhalation exposure to diphenylamine is considered to be negligible (non-volatile substance, vapour pressure 0.03 Pa at room temperature). The SCHER agrees with this conclusion.

The estimation of dermal exposure has been performed for the unprotected worker (personal protective equipment is not generally worn during e.g. decanting or draining of lubricants or by cleaning works. The estimated exposure levels (42 – 126 mg/person/day) have been calculated for a formulation containing 1 % DPA an exposed area of 840 cm².

3.2.2 Effect assessment

Orally administered DPA is well absorbed (80-90 %) from the gastrointestinal tract in man and in several animal species. DPA is readily biotransformed to hydroxylated metabolites and their conjugates and excreted; consequently no potential for bioaccumulation is expected.

Absorption of 100% for the oral route has been taken for the risk characterisation; there are no data on dermal or inhalation absorption, although they are relevant route of exposure. A default absorption value of 100% is assumed for inhalation uptake. Based on the physicochemical properties of DPA (molecular weight: 169 g/mol; log Pow 3.4; water solubility: 40 mg/l), the default dermal absorption value should be 100%. However, based on the comparison of NOAELs from oral and dermal experimental toxicity data, a dermal bioavailability of about 5% (4.2%) is calculated. This value has been used for risk characterisation; the SCHER supports this conclusion considering the justification for deviation from the 100 % default adequate.

Regarding DPA acute oral toxicity, the SCHER disagrees with the conclusion that DPA is to be classified as harmful and labelled with R 22, harmful if swallowed, which has been proposed on the basis of results from an usual acute toxicity study (administration of three doses for 3 consecutive days) on Syrian hamsters (LD_{50} =600 mg/kg bw/d); rats and Mongolian gerbils (LD_{50} >800 mg/kg bw/d). Since valid studies, compliant to OECD Test Guidelines and GLP, reported LD_{50} values>2000 mg/kg bw, the SCHER opinion is that DPA does not meet the criteria for acute oral toxicity classification.

SCHER agrees that DPA has a low potential for skin irritation; data on DPA-induced eye irritation are conflicting and in some cases poorly documented. However, a guideline-compliant study reported severe eye irritation caused by DPA, still present after 21 days. SCHER agrees that DPA may pose a risk of serious damage to eyes and consequently appropriate labelling with R41 "Risk of serious damage to eyes" is necessary.

Based on the results of animal and human studies, DPA did not result as a skin sensitizer.

For assessment of DPA repeated dose toxicity, data are reported after oral and dermal route of administration. No data on effects after repeated inhalation of DPA are available.

In agreement with some relatively old studies, some recent guideline-conform repeated dose toxicity studies on mice and rats (Botta, 1992; Krohmer, 1992) have been

described in the JMPR report (1998), indicating that the primary target organs after short- and long-term dietary exposure of DPA are the haematological system (critical target for NOAEL derivation) and the kidneys, spleen, and liver. No marked species differences were evident (LOAEL values = 25 mg/kg bw/d are the same in rats and dogs); the lowest NOAEL (7.5 mg/kg bw/d) for adverse effects after chronic exposure is derived from the two-year carcinogenicity study on rats (Botta 1994b), based on haematological and histological effects at the higher dose (LOAEL=25 mg/kg bw/d).

SCHER agrees on the proposal to base risk characterisation for dermal exposure (systemic effects) on the NOAEL of 500 mg/kg bw/d from the 90-day study on rats. Indeed, the effect (i.e. dark red foci) seen in the stomach of two rabbits at the same dose 500 mg/kg bw/d in a 21-day dermal toxicity study were not observed in the longer 90-day study.

DPA was negative in two Salmonella gene mutation tests and not or very weakly genotoxic to mammalian cells in vitro. Negative results from an in vivo micronucleus test indicate that no mutagenic effects are expressed in vivo. On the basis of whole amount of data, SCHER agrees that DPA should be not considered as genotoxic.

Quite a number of relatively old investigations do not report any DPA-related neoplastic alterations. In addition, although reported only in the above mentioned JMPR document (1998), guideline compliant long term studies in mice and rats (Botta et al. 1994a, 1994b), as well a 1-year study in beagle dogs (Botta 1994c) found no evidence for increased tumour incidence. SCHER agrees that DPA should not be classified as a carcinogen.

Regarding reproductive and developmental effects, data from laboratory animals are limited to studies with the oral route. Both impairment of reproduction as well as any specific embryo-/fetotoxic or teratogenic potential capability are unlikely to occur in the absence of parental toxicity (reduced body weight, decrease in food consumption and pathological findings in spleen, kidney and liver). SCHER agrees with the recommended NOAEL values to be used for risk characterisation purposes, that is: NOAEL/fertility of 131 mg/kg bw/d, and NOAEL/developmental toxicity of 46 mg/kg bw/d.

3.2.3 Risk characterization

The risk characterization performed in the RAR uses the MOS approach and is performed for inhalation and dermal occupational exposures as well as for dermal consumer exposure.

The SCHER agrees with the procedure used to convert the oral NOAEL into an inhalatory NOAEC and with conclusions ii)[1] for all the considered occupational exposure scenarios regarding acute and repeated inhalation and dermal exposures, due to high MOS values. Regarding the risk of severe irritation to the eyes, conclusion ii) is proposed on the grounds that control measures exist and are usually in place as documented by Industry which can minimise exposure, thereby reducing concern. The SCHER agrees with this consideration. In addition, there is no reason for concern with respect to sensitization properties.

Regarding consumer exposure, it can be assumed that it is primarily due to oral exposure from eating fruits and vegetables treated with DPA. This kind of oral exposure is covered by the legislation on plant protection products, and no risk characterisation has been performed in the RAR.

[1] *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.*

Dermal exposure of consumers is possible by the use of lubricants; considering the low vapour pressure of DPA, inhalation exposure can be neglected. Due to high MOS values, conclusions ii) is accepted for all the considered exposure scenarios.

Finally, although conclusion ii) for the local scenario of indirect environmental exposure (caused by the application of sewage sludge from a municipal WWTP) is accepted for the moment, the SCHER agrees that it should be considered provisional. Indeed, it may have to be revised as soon as further knowledge, e.g. on PEC regional or the sludge application scenario becomes available, since the applied model calculations are of preliminary nature.

4. LIST OF ABBREVIATIONS

DPA	Diphenylamine
EASE	Estimation and Assessment of Substance Exposure
LOAEL	Lowest Observed Adverse Effect Level
MOS	Margin of Safety
NOAEC	No Observed Adverse Effect Concentration
NOAEL	No Observed Adverse Effect Level
PEC	Predicted Environmental Concentration
RAR	Risk Assessment Report
TGD	Technical Guidance Document
WWTP	Waste Water Treatment Plant

5. REFERENCES

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