EUROPEAN COMMISSION

Health & Consumer Protection
Directorate-General

Scientific Committee on Health and Environmental Risks

SCHER

Risk Assessment Report on 2,4-dinitrotoluene

Human Health Part

CAS No.: 121-14-2

EINECS No.: 204-450-0

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

About the Scientific Committees

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.

In addition, the Commission relies upon the work of the European Food Safety Authority (EFSA), the European Medicines Evaluation Agency (EMEA), the European Centre for Disease prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

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.

In particular, the Committee addresses questions related to new and existing chemicals, the restriction and marketing of dangerous substances, biocides, waste, environmental contaminants, plastic and other materials used for water pipe work (e.g. new organics substances), drinking water, indoor and ambient air quality. It addresses questions relating to human exposure to mixtures of chemicals, sensitisation and identification of endocrine disrupters.

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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 RAR is written in accordance with the requirement of the TGD, and all relevant endpoints are addressed. The document is slightly unbalanced, very extensive and academic review of ADME and genotoxicity. Non-compliance studies, when properly conducted studies are available, should not be included. What is the difference between sub-acute and sub-chronic studies – they both refer to 28 days study. It is recommended that the RAR is carefully edited, e.g. all abbreviations used in the text should be in the list, it is stated that 2,4-DNT is a liquid at room temperature in spite of a melting point of 69.90 C°**.**

3.2 Specific comments

3.2.1 Exposure assessment

The major routes of occupational exposure are through inhalation and dermal contacts. It is anticipated that the skin may be the major route of absorption. The exposure was estimated at three different scenarios, Production and processing of 2,4-DNT, explosives manufacturing and use of explosives. Inhalation and dermal exposures were determined using the EASE model. The use of these models tends to overestimate the exposure, especially through the skin (Creely, 2005).

Exposure scenario 2 (production and processing scenario) the RWC for inhalation was based upon actual measured values rather that the estimate made by the EASE model. SCHER agrees with the concern expressed in the RAR of using EASE for dermal exposure due to the shortcoming as expressed by Creely, and disagreement with actual measured values. However, the RAR estimates the RWC on the modelled data taking PPE into consideration and assumes only 10% penetration. However, the value is still higher than the 50-percentile determined by analysis of skin wipe from workers.

Exposure scenario 2 (explosive manufacture) for inhalation is based upon the EASE model as no reliable measurement has been made. SCHER agrees with the pragmatic approach of using half of the RWC as the typical exposure, which also brings it into line with scenario 1.The RISIKOFDERM exposure model has been used to assess dermal uptake. However, SCHER lacks proper argument for using 820 cm^2 for exposed area in scenario 2 compared to 210 cm^2 in scenario 1. SCHER suggests taking the use of PPE into consideration, as has been done in scenario 1 thus reducing the RWC value.

In exposure scenario 3 (use of explosives) the exposure has been modelled using the EASE model as no measured data is available. In this scenario yet another exposure area, 420 cm^2 is used and does not take the required PPE into consideration. SCHER recommends standardizing the dermal exposure default values, or providing evidence for the differences.

No consumer exposure is anticipated, as 2,4-DNT is not used in consumer products.

The indirect exposure via the environment is estimated by using the EUSES model, and the oral intake via food and drinking water is the major route, whereas the contribution by inhalation is negligible.

3.2.2 Effect assessment

The relevant route of exposure is by inhalation and dermal contact, but in general the effect assessment is based upon oral administration.

The ADME is covered in very great details and many different species and at different levels of biological organisation. No proper studies on the uptake of 2,4-DNT by dermal and inhalation was reported. In absence of other data, the RAR used the assumption of 100% for both routes of exposure based upon oral absorption data. SCHER supports the notion for inhalation, but is however confused on dermal exposure. Based upon dermal absorption data from 2,6-DNT, that have similar MW and physical properties, a dermal penetration rate of 10% is considered acceptable.

2,4-DNT is rapidly absorbed from the gastrointestinal-tract and metabolites excreted into urine. The metabolism is qualitatively similar in humans and rodents, and metabolism by the bacterial flora appears to be important for the formation of carcinogenic metabolites. The section should be focused as it is currently 20% of the RAR. SCHER disagrees with the statement that the presence of urinary metabolites is evidence that absorption occurs via inhalation under occupational settings, as other reported studies show that dermal absorption can be a significant route of entry, and the biomarker cannot discriminate between the two exposure pathways. There is no need to repeat the summary of the ADME conclusions in the risk characterization.

Acute toxicity shows that 2,4-DNT is classified as harmful by inhalation and oral routes of studies based upon rodent studies (LD_{50} 434-743 mg/kg bw and 1250-2178 mg/kg bw for rats and mice respectively). SCHER disagrees with the suggestion that the risk characterisation should be based upon cat data, as this study is based upon 2 cats per group and 2 doses, and as the purity of the compound is not given.

SCHER supports the use of a LOAEL on 0.57 mg/kg bw/day based upon reproductive toxicity for chronic exposure conducted in concordance with OECD guidelines, but disagrees of using the cat NOAEL (10 mg/kg bw) for acute exposure.

SCHER aggress that 2,4-DNT is classified as a category 3 mutagen as it is a *in vivo* mutagenic agent in somatic cells. This conclusion is mostly based upon the study of Ellis et al (1979) but the dose is not given in table, only as % in food. There are limited data on human carcinogenicity, but a recent case report (Harth, 2005) supports the notion that occupational exposure is associated with an increased risk of urothelial cancer. Furthermore, 2,4-DNT is an in vivo mutagen and is carcinogenic in animals. Thus the SCHER supports the notion that 2,4-DNT is classified as a category 2 carcinogen.

3.2.3 Risk characterization

The risk characterization is based upon the MOS approach for the non-genotoxic endpoints and the life-time cancer risk approach based upon the HT25 estimate for cancer risk. The HT25 used in the risk characterization is based upon hepatocellular carcinoma in mice. The risk assumption on exposure via the dermal route may be an overestimate if PPE is taken into considerations, i.e., protective equipment (PPE is required). In determination of risk, a dermal uptake of 10%, based upon the data from 2,6-DNT was used, however the protective effect of PPE, a factor 10%, as proposed

under exposure scenario 1, has not been included in the risk characterisation, although it results in additional reduction of the estimated exposure used in the RAR.

Occupational

SCHER supports conclusions (ii)[1] for acute toxicity, irritation and corrosivity and sensitisation for all scenarios, and for chronic toxicity following inhalation in scenarios 1 and 3.

SCHER supports conclusion (iii) for carcinogenicity in all three scenarios.

SCHER supports conclusion (ii) for reproductive toxicity in scenarios 1 and 3 for inhalation, for scenario 1 for dermal exposure, and for developmental toxicity in all scenarios.

Consumers

2,4-DNT is primarily used as a chemical intermediate, and there is no information on its use in consumer products. Thus no exposure is anticipated.

Humans exposed via the environment

The areas of concern are mutagenicity and carcinogenicy and the risk has been estimated for 4 different scenarios. The risk, using the calculated life time cancer risk was tolerable in three of these scenarios, but there was concern at one location. The recommendation (iii) should be modified and not include inhalation as a route of exposure, as 2,4-DNT is crystalline with low vapour pressure, and the contribution from air is less than 1/1000 of the estimated exposure.

4. LIST OF ABBREVIATIONS

2,6-DNT	2,6-dinitrotoluene
ADME	Absorption, Distribution, Metabolism, Excretion
DNT	2,4-dinitrotoluene
EASE	Estimation and Assessment of Substance Exposure
HT25	Dose at which 25% of exposed Human will develop Tumour
LOAEL	Lowest Observable Adverse Effect Level
MOS	Margin of Safety
NOAEL	No Observed Adverse Effect Level
PPE	Personal Protective Equipment
RAR	Risk Assessment Report
RWC	Reasonable Worst Case
TGD	Technical Guidance Document

5. REFERENCES

Creely KS, Tickner J, Soutar AJ et al (2005) Evaluation and further development of EASE model 2.0 Ann Occup Hyg 49: 135-145.

[1] [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

Harth V, Bolt HM, Brüning T (2005) Cancer of the urinary bladder in highly exposed workers in the production of dinitrotoluene: a case report. Int Arch Occup Environ Health 78: 677-680.