



EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL
Directorate C - Public Health and Risk Assessment
C7 - Risk assessment

SCIENTIFIC COMMITTEE ON HEALTH AND ENVIRONMENTAL RISKS
SCHER

Opinion on

Risk Assessment Report on
Tris (nonylphenyl)phosphite (TNPP)

HUMAN HEALTH PART

CAS N°: 26523-78-4
EINECS N°: 247-759-6

Adopted by the SCHER
during the 12th plenary of 4 July 2006

TABLE OF CONTENTS

1. BACKGROUND..... 3

2. TERMS OF REFERENCE..... 3

3. OPINION 3

 3.1 General Comments 3

 3.2 Specific Comments 3

 3.2.1 Uses and exposure assessment 3

 3.2.2 Effect assessment 4

 3.2.3 Risk characterisation 5

4. LIST OF ABBREVIATIONS 6

5. REFERENCE 6

6. ACKNOWLEDGEMENTS 6

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 document is well written and in accordance with the requirements of the TGD; all relevant endpoints are addressed. The SCHER agrees with the proposed conclusions, and has only a few minor comments.

TNPP is a viscous liquid with a very low vapour pressure (0.05 Pa at 25°C), and a very high octanol-water partition coefficient of >8 (the SCHER notes that in the human health part of the RAR, the abbreviation Pow is used whilst in the glossary only the term Kow is explained). The purity of TNPP is reported as 95-100% with the main impurities being nonylphenol (< 5%) and phenol (<1%). Commercial products may contain 1,1',1''-nitritotripropan-2-ol as an additive in concentrations of up to 1%. In Europe, TNPP is produced in closed systems at three sites, and about 25 to 35 facilities are processing TNPP.

3.2 Specific Comments

3.2.1 Uses and exposure assessment

The main use of TNPP is as a stabilizer and antioxidant in the processing of various plastic materials (PVC, LLDPE, HDPE and rubber), where it is used in concentrations of between 0.05 and 3%. Other uses are considered to be negligible.

Occupational exposure may occur through the respiratory and the dermal routes with highest exposures occurring during the manufacture of TNPP containing materials and a worst case inhalation exposure level of 8.58 mg/m³ (related to mixing or transforming activities at high temperatures). The highest dermal exposure may occur during transfer of the substance.

Afterwards TNPP is enclosed in a polymer matrix and exposure is considered to be negligible. With the EASE model, a dermal exposure of 0.1-1 mg/cm²/day was estimated.

Consumer exposure may occur through use of plastic products containing TNPP, mainly through food-contact materials. The total daily intake due to food-contact materials has been estimated to be 0.0337 mg/day (corresponding to about 0.48 µg/kg bw/day for a person of 70 kg bw).

3.2.2 *Effect assessment*

No toxicokinetic, metabolism or distribution studies in animals were performed with TNPP. A relative high molecular weight (689 g/mol), extremely low water solubility and a very high log Kow indicate poor absorption via the oral or dermal routes of exposure. Inhalation of vapours is considered to be negligible due to the low vapour pressure. Hydrolysis of TNPP results in the formation of nonylphenol; it was calculated that a oral dose of 1000 mg TNPP/kg bw could result in a nonylphenol dose of up to 200 mg/kg bw.

TNPP is of low acute oral and dermal toxicity in animals (LD₅₀ values of greater than 10,000 mg/kg bw for the oral and of > 2000 mg/kg bw for the dermal route with no specific signs of toxicity). Only very limited information is presented in the RAR with regard to a potential neurotoxicity of TNPP. Based on the lack of clinical and electron microscopical signs of delayed neurotoxicity after a single exposure to 4000 mg TNPP/kg bw to chickens, the potential to induce neurotoxicity was however considered to be low.

TNPP was only slightly irritating to the skin and eyes of rabbits. While no sensitisation reaction was found in a Buehler test with Guinea pigs, 12/20 and 15/20 animals showed reactions indicative of a sensitisation at 24h and 48h, respectively, after occlusive epidermal challenge with TNPP in a Maximisation Test according to Magnusson and Kligman. Data on the sensitisation potential in humans were not available.

For the assessment of repeated dose toxicity, a rat study according to an enhanced OECD TG 421 protocol (Tyl et al., 2002), a 90-day study with rats and two-year rat studies over three generations (FDA, 1957 and 1961), as well as a two-year study with dogs (FDA, 1961) were available. In all studies the route of exposure was oral. The kidney was the main target organ in the OECD TG 421 gavage study (LOAEL: 1000 mg/kg bw/day based on absolute kidney weight increase and mineralization of the kidneys in F0 and F1 males; NOAEL: 200 mg/kg bw/day; note that no microscopic examination was performed for the 200 mg/kg bw/day dose group). At 1000 mg/kg bw/day, excessive rooting behaviour in males and females was observed, most probably a sign of taste aversion. After repeated exposure of rats to TNPP via the diet for 90 days, 8 of 9 animals showed acute and chronic pyelonephritis with foci of calcification at 5000 mg/kg bw/day (NOAEL: 1000 mg/kg bw/day). In the 2-year feeding study with rats, an oral dose of 10,000 ppm (corresponding to 500 mg/kg bw/day) led to a few effects on growth in male rats and to an increase of the liver weight in female rats. A NOAEL of 3300 ppm, corresponding to 167 mg/kg bw/day was derived. In the two-year feeding study with dogs, a dose level of 10,000 ppm induced chronic inflammation in the renal pelvis in one male dog, and a slight to moderate hyperplasia of the thyroid in two female dogs (NOAEL: 3300 ppm in the diet). No reliable repeated dose toxicity studies were available for the respiratory and dermal routes of exposure.

No data was available on the genotoxicity of TNPP in humans. TNPP was tested negative in two Ames tests, two *in vitro* mammalian cell gene mutation tests and two *in vitro* chromosome aberration tests. There were no *in vivo* studies available.

There were no epidemiology data on the carcinogenic potential of TNPP available. No evidence of a significant increase in tumour incidence was found in the 2-year chronic studies carried out on rats and dogs.

In the two-year rat feeding study over three generations, no pathological findings related to reproductive parameters were noted in the F0 generation, but there was a slight reduction of litter size in the F1 and F2 generations at 500 mg/kg bw/day (NOAEL for reproduction 167 mg/kg bw/day). A reproductive toxicity screening test was performed according to OECD TG 421 with oral administration (gavage) of TNPP to CD rats. In addition to the parameters requested by the OECD TG 421, the following examinations were performed: an enhanced evaluation of toxicity in the F0 generation, including the evaluation of a recovery group of males; an enhanced evaluation of developmental landmarks in the F1 generation (time of vaginal opening or preputial separation, normality and length of oestrous cycle); and a follow-up of the F1 offspring to adulthood, with continued exposure and assessment of reproductive structures and functions including potential effect on sperm. Based on a slight reduction of the litter size, on a slight decrease in relative epididymides weight in F1 males and on signs of maternal toxicity (death on gestation day 22, decrease in ovary weight) at 1000 mg/kg bw/day, NOAELs for maternal and offspring toxicity of 200 mg/kg bw/day were derived from this study. No indication of any developmental effect was observed in the studies (NOAEL: 1000 mg/kg bw/day).

3.2.3 Risk characterisation

Workers: Whilst the most relevant occupational exposure routes are the dermal and the respiratory routes, the available repeated dose toxicity data is limited to the oral route. Hence, route-to-route extrapolation was necessary. In the absence of substance-specific data for TNPP, default values of 10%, 50% and 50% were chosen for the absorption by the dermal, respiratory and oral routes of exposure, respectively, based on the physico-chemical properties of TNPP. Based on the available data, SCHER finds the assumptions reasonable and agrees with the proposed default values.

Comparing anticipated human internal doses for combined dermal and respiratory exposure (0.26 – 1.21 mg/kg bw/day) with the NOAELs revealed large MOS for acute and repeated dose toxicity, and for toxicity to reproduction. There were no concerns identified for irritation, mutagenicity and carcinogenicity. Even at a 20% conversion of TNPP to NP, a large MOS for NP toxicity at this level is observed (Tyl et al, 2006). The SCHER therefore agrees with the conclusion (ii)¹ for all occupational scenarios with regard to acute toxicity, irritation, repeated dose toxicity, mutagenicity, carcinogenicity, and toxicity to reproduction.

The SCHER also agrees with the conclusion (iii) for sensitisation, because of concerns as a consequence of dermal exposure during TNPP manufacture, and the manufacture of products or use of preparations containing TNPP.

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.*

Consumers: Significant exposure of consumers to TNPP may only occur through the ingestion of food in contact with plastic containing TNPP with a maximum estimated daily exposure of about 0.48 µg/kg bw. This results in large MOS with regard to acute toxicity, repeated dose toxicity and reproductive toxicity effects. There were no concerns identified for irritation, mutagenicity and carcinogenicity, or for sensitisation via the oral route. The SCHER therefore agrees with the conclusion (ii) for all endpoints.

Humans exposed via the environment: The SCHER notes that the risk characterisation for humans exposed via the environment has still to be completed.

4. LIST OF ABBREVIATIONS

EASE	Estimation and Assessment of Substance Exposure Physico-chemical properties
Kow	n-octanol-water partition coefficient
LD50	Median Lethal Dose
LLDPE	Linear Low Density Polyethylene
LOAEL	Lowest Observed Adverse Effect Levels
MDPE	Medium Density Polyethylene
MOS	Margin of Safety
NP	Nonylphenol
NOAEL	No Observed Adverse Effect Levels
Pow	n-octanol-water partition coefficient
PVC	polyvinyl chloride
RAR	Risk Assessment Report
TGD	Technical guidance Document
TNPP	Tris(nonylphenyl)phosphite

5. REFERENCE

Tyl RW, Myers CB, Marr MC, Castillo NP et al (2006) Three-generation evaluation of dietary para-nonylphenol in CD(Sprague-Dawley) rats. *Toxicol Sci* 92: 295-310, 2006.

6. ACKNOWLEDGEMENTS

Prof. H. Greim (rapporteur) is acknowledged for his valuable contribution to this opinion.