TRIS (NONYLPHENYL) PHOSPHITE

CAS-No.: 26523-78-4

EINECS-No.: 247-759-6

SUMMARY RISK ASSESSMENT REPORT

Final report, 2007

France

Rapporteur for the risk assessment of tris(nonylphenyl) phosphite is the Ministry of Ecology and Sustainable Development as well as the Ministry of Employment and Social Affairs in co-operation with the Ministry of Public Health. Responsible for the risk evaluation and subsequently for the contents of this report is the rapporteur.
The scientific work on this report has been prepared by :

Environment risk assessment

National Institute for Industrial Environment and Risks (INERIS)
Direction of chronic risks
Parc Technologique Alata
BP n°2
60550 Verneuil-en-Halatte

Human health risk assessment

Effect assessment, exposure and risk characterisation for consumers

National Institute for Industrial Environment and Risks (INERIS)
Direction of chronic risks
Parc Technologique Alata
BP n°2
60550 Verneuil-en-Halatte

Exposure and risk characterisation for workers

Institut National de recherche et Sécurité (INRS)
Département Risques Chimiques et Biologiques
30, rue Olivier Noyer
75680 Paris cedex 14

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Final report:	**[please year]**

PREFACE

This report provides a summary, with conclusions, of the risk assessment report of the substance tris(nonylphenyl) phosphite that has been prepared by France in the context of Council Regulation (EEC) No. 793/93 on the evaluation and control of existing substances.
For detailed information on the risk assessment principles and procedures followed, the underlying data and the literature references the reader is referred to the comprehensive Final Risk Assessment Report (Final RAR) that can be obtained from the European Chemicals Bureau[1]. The Final RAR should be used for citation purposes rather than this present Summary Report.

[1] European Chemicals Bureau – Existing Chemicals – http://ecb.jrc.it

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1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

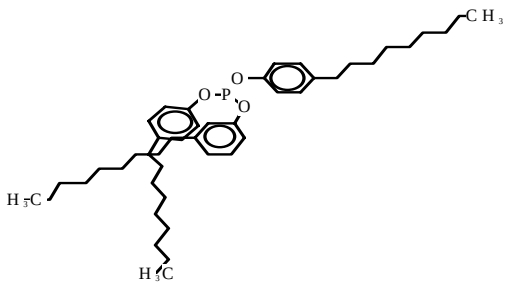
CAS No: 26523-78-4

EINECS No: 247-759-6

IUPAC Name: Phenol, nonyl-, phosphite (3:1)

Molecular formula: $C_{45}H_{69}O_3P$

Structural Formula:



Molecular weight: 689 $g.mol^{-1}$

Synonyms and tradenames: Alkanox

In this assessment, the name Tris(nonylphenyl)phosphite (TNPP) will be used for the substance as this is the most common name.

4.1 PURITY/IMPURITIES, ADDITIVES

4.2 PHYSICO-CHEMICAL PROPERTIES

Table : Summary of physical and chemical properties of the TNPP

Property	Value	Comments
Physical state at ntp	Viscous liquid	
Molecular weight	689 $g.mol^{-1}$	
Melting Point	6°C ± 3°C	Instead of a melting point, a pour point (more appropriate to viscous liquids) was determined
Boiling Point	322°C	Degradation
Relative density	0.98 $g.cm^{-3}$	
Vapour pressure	0.058 Pa at 25°C	extrapolated from results obtained by isoteniscope (method ASTM D2879)
Partition coefficient	Log Kow = 21.6 Log Kow = 8 (EUSES)	Calculated with software ACD/LogP DB
Water solubility	<0.6 $mg.L^{-1}$	A saturated solution was not obtained and the water solubility result corresponds to the detection limit of the analytical method.
Flash point	207°C	Pensky Martin apparatus (closed cup)

Property	Value	Comments
Autoflammability	440°C	Setchkin method
Oxidising properties	No oxidising property	
Henry's law constant	66.6 $Pa.m^3.mol^{-1}$	TGD calculation

4.3 CLASSIFICATION

1.1.1 Classification

Human health effects (adopted classification)

Classification was finalised in the Commission working group on the Classification and Labelling of Dangerous Substances in November 2005 (human health) :

Symbol : Xi
R-phrase : R43 : May cause sensitisation by skin contact.

Environmental effects

To be updated

2 GENERAL INFORMATION ON EXPOSURE

3 ENVIRONMENT

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

4.3.2 Effects assessment

No specific toxicokinetic study was conducted with trisnonylphenyl phosphite (TNPP). However qualitative information can be derived from the physico-chemical properties of the substance. Considering the relatively high molecular weight of the molecule (MW = 689 $g.mol^{-1}$), its extremely low water solubility (< 1 mg/l) and a very high Log P_{ow} (> 6), the absorption of TNPP by the gastro-intestinal tract is expected to be limited as well as the absorption following dermal exposure. Moreover, due to the low vapor pressure of the liquid substance, inhalative exposure can be anticipated only as liquid aerosol.

Based on the physico-chemical properties, default values were chosen for oral, dermal and inhalative absorption:

- oral absorption: as indicated above, the absorption of TNPP by the gastro-intestinal tract is expected to be limited. However no quantitative value is available, then as a worst case assumption for oral route, a default value of 50 % is chosen.

- dermal absorption: a default factor of 10 % is used as MW>500 and Log P_{ow} is higher than 4.

- inhalative exposure: absorption mechanisms via mucous membranes are expected to be the same by oral and inhalation route, thus a default value of 50 % is chosen as a worst case assumption.

Given the animal data, the acute oral, dermal or inhalation toxicity of TNPP is judged to be low and do not justify the classification for acute toxicity endpoints.

Based on the available data on rabbits, TNPP is a very slight to moderate irritant to the skin, and a slight irritant to the eye. In each case, the effects were generally reversed within a few days. According to the cutaneous and eye irritation test methods cited in Annex V, similar to OCDE guideline 404 and 405, TNPP should not be classified as an irritant to skin and eye.

After a 4-hour exposure under semi-occlusive conditions, TNPP is not corrosive on intact skin and hence should not be classified as corrosive to skin or eye according to the criteria of the European Union.

No human data is available for sensitisation endpoint. Results of the two studies available, both conducted on guinea pig and following OECD TG 406, are not in accordance: one Buehler sensitisation test is negative and one Maximisation test is positive. Adjuvant-type tests are likely to be more accurate in predicting a probable skin sensitising effect of a substance in humans than those methods not employing Freunds Complete Adjuvant (FCA), and are thus the preferred methods. Then, the results of the Guinea-Pig Maximisation test will be used for the risk assessment, as this test is considered to be more sensitive than the Buehler test. According to the

criteria of the European union, TNPP needs to be classified as a skin sensitiser Xi, R43 “May cause sensitisation by skin contact”.

With respect to repeated dose toxicity, the studies available provide a profile of limited repeated dose toxicity for TNPP. A 90-day exposure to a dose of 5000 mg/kg/day of TNPP in rat resulted in the observation of toxic symptoms and of pathological changes in the kidney, but no adverse effect was observed at lower doses. Over a longer period (2-year), ingestion of TNPP at a dose level of 10 000 ppm (corresponding to 500 mg/kg/d in rats) led to a slight retardation of growth in male rats, an increase of the liver weight in F0 female rats and a thyroid change (doubtful relationship to dosage) in dogs. One male dog exposed to 10000 ppm also exhibited a renal chronic inflammation in pelvis. Based on these 2-year studies, a NOAEL of 3300 ppm of TNPP in the diet (corresponding to 167 mg/kg/d in rats) was determined and will be used for risk assessment. Classification R48 should not be applied.

With regard to mutagenicity, six well conducted *in vitro* mutagenetic tests (two Bacterial Reverse Mutation Assays, two *in vitro* Mammalian Cell Gene Mutation Tests, and two *in vitro* Mammalian Chromosome Aberration Tests) were realised and did not revealed any genotoxic effect. Although neither human data nor *in vivo* tests are available, the available data from *in vitro* tests support the view that TNPP is a non-genotoxic substance. TNPP is hence not classifiable as mutagenic according to the criteria of the European Union.

Considering carcinogenicity, no reliable study is available. However, on the basis of the information currently available on mutagenicity, TNPP is considered as a non-genotoxic substance, so concerns for cancer caused by a genotoxic mechanism are low. Considering the potential for carcinogenicity by a non-genotoxic mechanism, no evidence of a significant increase of tumour incidence was found in the 2-year chronic studies carried out on a small sample of rats and dogs. Although only limited data are available, these data tend to indicate that TNPP is not of concern for a carcinogenic potential and do not justify a classification as a carcinogen, according to the criteria of the European Union.

TNPP exposure over several generations do not reveal any significant effect on reproduction up to the highest dose tested (500 mg/kg/day) in F0 but a slight reduction of litter size born from F1 and F2 generations, which tended to be confirmed by the OECD 421 study in which a slight but significant litter size reduction was observed at the highest dose (1000 mg/kg/day). In this same study, maternal toxicity was observed at the dose of 1000 mg/kg/day. The decreasing weight ovary of F0 females, associated with the decrease of epididymides weight in F1 males suggest an oestrogen-like activity of the test substance. The NOAELs for reproductive toxicity and for maternal toxicity, were derived from the OECD 421 study and were considered to be 200 mg/kg/day.
No indication of any developmental effect was observed in both studies: $NOAEL_{terato}$ is $\geq$ 1000 mg/kg/day, although these parameters were observed on a very reduced number of animals.
In conclusion, TNPP is not a reproductive toxicant at doses up to 200 mg/kg/day. Effects above this dose may result from the hydrolysis of TNPP to NP providing NP equivalent doses up to 200 mg/kg/day with a 1000 mg/kg/day dose of TNPP. According to the European criteria, this chemical is not classified as toxic to reproduction (fertility and development).

4.1.3 Risk characterisation

No human data are available, so this assessment of hazardous properties of TNPP is based only on animal data.

Route-to-route extrapolation and calculation of internal doses

Occupational exposure may occur by inhalation and dermal route during manufacture of TNPP, manufacture of products and use of preparations containing TNPP. So, inhalation and dermal route are the relevant occupational routes whereas all NOAELs are available by oral route only. Therefore, route-to-route extrapolation has to be done and corrections should be made for differences in bioavailability as determined by percentages of absorption.
There are no data on the absorption of TNPP for the different routes of exposure, so default values were chosen: 50 % for oral and inhalation routes, 10 % for dermal absorption.
Internal doses are presented in table 4.1 via the different routes for each scenario. They are calculated using a human body weight of 70 kg and a ventilation rate of 10 m^3/8 hours.

Table4-1: Calculated internal doses for workers

Scenario	Route of penetration				Combined routes
	Inhalation		Dermal		
	External exposure mg/m^3	Internal dose mg/kg/day	External exposure mg/day	Maximum internal dose mg/kg/day	Internal dose mg/kg/day
1 - TNPP manufacture	2.86	0.20	0 - 42	0.06	0.26
2 - Manufacture of products containing TNPP	8.58	0.61	42 - 420	0.60	1.21
3 - Use of preparations containing TNPP	5.72	0.41	0.42 - 4.2	0.006	0.42

For risk characterisation at the workplace, MOSs should normally be determined for route-specific as well as combined inhalation and dermal exposure. For simplification, only MOSs derived from combined exposure are presented.

Workers

Acute toxicity

Acute dermal toxicity was found to be very low (LD_{50} > 2000 mg/kg). No data is available for acute inhalation toxicity but taking into account the very low acute toxicity by dermal and oral routes and that TNPP is a very slight to moderate irritant, inhalation acute toxicity is likely to be low as well. Acute toxicity is not considered of concern. **Conclusion (ii)**

Irritation

TNPP is considered as a slight skin and eyes irritant and it may be presumed that it does not induce significant respiratory irritation. Therefore irritative effects are not considered of concern. **Conclusion (ii)**

Sensitisation

One study conducted according to Buehler gave a negative response while a positive result was observed in a maximisation test. Thus TNPP is classified as a skin sensitiser.

No human data are available, however, according to the TNPP consortium, no case of sensitisation was observed at existing production sites. There are no data on respiratory sensitisation. Exposure to TNPP during manufacture of the substance, manufacture of products

and use of preparations may lead to concern. Risk reduction measures which should be applied as a result of its classification as the proper use of personal protective equipment can effectively reduce sensitisation at the work place. **Conclusion (iii)**

Repeated dose toxicity

Comparing the estimated combined internal exposure with the NOAELs of 167 mg/kg/day derived from a 2-year study in rats, the following MOSs can be calculated:

Table 4-2: Risk characterisation for repeated dose toxicity

Scenario	Internal Exposure mg/kg/day	Internal NOAEL mg/kg/day	MOS	Conclusion
1 - Manufacture	0.26	83.5	321	(ii)
2 - Manufacture of products	1.21	83.5	69	(ii)
3 - Use of preparations	0.42	83.5	199	(ii)

The effects observed at the LOAEL in the 2-year study in rats (500 mg/kg/day) are changes on growth and liver weight. The main toxic effect is a renal impact observed in a reproductive/developmental toxicity screening test in rats at 1000 mg/kg/day.

A minimal MOS of 50 can be derived from the following assessment factors:

- 10 for interspecies differences (default value)
- 5 for intraspecies differences (homogeneous population)
- 1 for type of the effect
- 1 for the confidence in the data base.

Compared to the minimal MOS, the MOSs are considered acceptable. **Conclusion (ii) for all scenarios**

Mutagenicity

Available *in vitro* data do not reveal a genotoxic potential, effects are not anticipated to occur. **Conclusion (ii) for all scenarios**

Carcinogenicity

Data concerning carcinogenicity are not available. Based on results of mutagenicity testing, TNPP is not anticipated to be a genotoxic carcinogen. There is a low concern for carcinogenicity by a non-genotoxic mechanism too. **Conclusion (ii) for all scenarios**

Toxicity to reproduction

Fertility and reproductive toxicity

Comparing the estimated combined internal exposure with the NOAEL of 200 mg/kg/day derived from a reproductive/developmental study in rats, the following MOSs can be calculated :

Table 4-3: Risk characterisation for reproductive effects by repeated exposure

Scenario	Internal Exposure mg/kg/day	Internal NOAEL mg/kg/day	MOS	Conclusion
1 - Manufacture	0.26	100	385	(ii)
2 – Manufacture of products	1.21	100	87	(ii)
3 – Use of preparations	0.42	100	238	(ii)

The adverse effects observed at 1000 mg/kg/day in the reproductive/developmental study in rats are decrease of ovary weight in F0 females, a decrease of epididymes weight in F1 males and a slight litter size reduction. No other significant reproductive effects were observed.

A minimal MOS of 50 can be derived from the following assessment factors:

- 10 for interspecies differences (default value)
- 5 for intraspecies differences (homogeneous population)
- 1 for the type of the effect
- 1 for the confidence in the data base

Compared to the minimal MOS, the MOSs are considered acceptable. **Conclusion (ii) for all scenarios**

Developmental toxicity

No indication of any developmental effect was observed up to the highest dose of 1000 mg/kg/day. Effects are not anticipated to occur. **Conclusion (ii) for all scenarios**

Consumers

Risk may occur by ingestion of food in contact with plastic containing TNPP. It is the only route of significant exposure for the consumer.

Risk characterisation due to migration from food contact materials

The total daily intake due to food-contact materials has been estimated to 0,0337 mg/day. For an adult with a bodyweight of 70 kg, the systemic dose resulting from this unique route of ingestion is 0,48 µg/kg/day. Systemic and reproductive effects are observed in animals with repeated dose. With the available NOAELs, the following MOSs can be calculated:

Table 4-4: Risk characterisation for systemic effects by repeated exposure

Scenario	Exposure µg/kg/day	NOAEL mg/kg/day	MOS	Concern for risks to human health	Conclusion
Food contact materials	0.48	167	350000	low	(ii)

Table 4-5: Risk characterisation for reproductive effects by repeated exposure

Scenario	Exposure µg/kg/day	NOAEL mg/kg/day	MOS	Concern for risks to human health	Conclusion
Food contact materials	0.48	200	420000	low	(ii)

Summary of risk characterisation for consumers

Repeated dose toxicity and reproductive effects are of low concern (**conclusion ii**).

Human exposed via the environment

This section was not provided as it will be updated in the next version of the environmental risk assessment.

Summary of risk characterisation for exposure via the environment

This section was not provided as it will be updated in the next version of the environmental risk assessment

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

Exposure assessment

The exposure assessment, to the extent it is related to physico-chemical properties, has already been discussed. No specific exposure information is available.

Effects assessment : Hazard identification and dose (concentration) - response (effect) assessment

Explosivity

TNPP has no explosive properties.

Flammability

TNPP has a very low degree of flammability (flash point : 207°C).

Oxidising potential

TNPP has no oxidising potential.

Risk characterisation

TNPP has neither explosive nor oxidising properties. The likelihood of an adverse effect deriving from flammability is very low.

Conclusion (ii) for all scenarios

5 RESULTS

5.1 ENVIRONMENT

To be updated

5.2 HUMAN HEALTH

Workers

Conclusion (iii) There is a need for specific measures to limit the risks; risk reduction measures which are already being applied shall be taken into account.

It is reached because of concerns for sensitisation as a consequence of dermal exposure arising during manufacture of the substance, manufacture of products or use of preparations containing TNPP.

Consumers

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those, which are being applied already.

Humans exposed indirectly via the environment

Risk assessment of human exposed via the environment was not discussed and will be updated following the update of environment risk assessment.

Human health (risks from physico-chemical properties)

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those, which are being applied already.