Annex XV report

PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

Substance Name: **TRIS(NONYLPHENYL)PHOSPHITE**

EC Number: 247-759-6

CAS Number: 26523-78-4

Submitted by: France

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Version 2

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TABLES

PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

Substance Name: Tris(nonylphenyl)phosphite

EC Number: 247-759-6

CAS number: 26523-78-4

Registration number (s): -

Purity: 95 – 100% w/w

Impurities:

Nonylphenol (CAS 25154-52-3)

Phenol (CAS 108-95-2)

Di(nonylphenyl)phenylphosphite (CAS 25417-08-7)

TNPP was on the 4th priority list of the Existing Substances Regulation and it is therefore a requirement to harmonise classification for all endpoints justifying classification.

A classification proposal was submitted and discussed at ECB (TC C&L) for health endpoints. Classification R43 was concluded by the TC C&L for health. For information, discussions and conclusions of the TC C&L as reported in summary records of the corresponding meetings are presented in Appendix I of the present report.

The proposal for environmental classification was on hold as additional testing had been requested and was on-going. A summary explanation of the justification for requirement of the new studies according to Commission Regulation (EC) No 466/2008 is presented in Appendix II of the present report.

Further to completion of the required environmental test the whole classification proposal is now submitted to ECHA for all endpoints justifying classification.

Proposed classification based on Directive 67/548/EEC criteria:

Xi; R43
R53

Proposed classification based on GHS criteria:

Skin Sens. 1 – H317
Aquatic Chronic 4 – H413

Proposed labelling:

R-phrases: R43- R53
Symbol(s) : Xi
S-phrases : S24 – S37 – S61

Proposed specific concentration limits (if any): none

Proposed notes (if any): see below.

Some impurities of TNPP, especially nonylphenol, have an harmonised classification and can be present in TNPP in concentration that trigger additional classifications of TNPP as discussed in more details in section 1.2.

However, the classification proposed in this dossier as displayed above does not take into account additional classifications based on the impurities as the impurity content can vary depending on the production process and its possible improvements.

It is therefore recommended that the potential influence of impurities on classification remains of the responsibility of the manufacturer/importer. To inform manufacturer/importer as well as users that it can be necessary to complement the harmonised classification of TNPP based on the impurity content, a new note could be created and added to the TNPP proposal.

It is also noted that as for environmental classification, available data on skin irritation, eye irritation and reproductive toxicity of TNPP are not in agreement with corresponding classifications based on impurity content. These data are therefore displayed in the present dossier for information and possible discussions that may be raised if it is decided that presence of impurities should be taken into account in the harmonised classification.

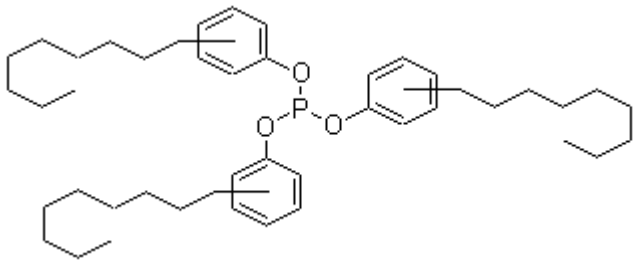
JUSTIFICATION

1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1 Name and other identifiers of the substance

Chemical Name:	Tris(nonylphenyl)phosphite
	Synonyms: Alkanox TNPP, Lowinox TNPP, Irgafos TNPP, Tris(monononylphenyl)phosphite, Tri(nonylphenyl)phosphite, Weston 399, Weston TNPP, Irgastab CH 55, Naugard TNPP, Polygard, Polygard HR, Polygard LC, TNPP, Trisnonylphenylphosphit.
EC Name:	Tris(nonylphenyl)phosphite
CAS Number:	26523-78-4
CAS Name	Phenol, nonyl-,1,1’,1’’-phosphite
IUPAC Name:	Tris(nonylphenyl)phosphite

1.2 Composition of the substance

Chemical Name:	Tris(nonylphenyl)phosphite (TNPP)
EC Number:	247-759-6
CAS Number:	26523-78-4
IUPAC Name:	Tris(nonylphenyl)phosphite
Molecular Formula:	$C_{45}H_{69}O_3P$
Structural Formula:	
Molecular Weight:	689 g/mol
Typical concentration (% w/w):	-

Concentration range (% w/w):

There are two grades of TNPP that are sold in the marketplace.

The purity of the standard TNPP is reported as ca. 95 – 100% w/w. The following impurities may be found in standard TNPP:

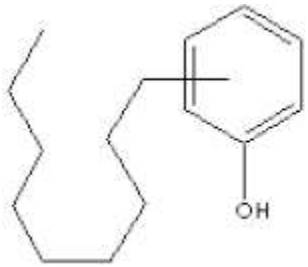
- Nonylphenol (CAS 25154-52-3) < 5% w/w,
- Phenol (CAS 108-95-2) < 0.1% w/w,
- Di(nonylphenyl)phenylphosphite (CAS 25417-08-7) 0.05% w/w,

A high purity grade of TNPP was introduced into the market in the late 1990s. The impurities found in the high purity TNPP are:

- Nonylphenol (CAS 25154-52-3) < 0.1% w/w,
- Phenol (CAS 108-95-2) < 0.1% w/w,
- Di(nonylphenyl)phenylphosphite (CAS 25417-08-7) 0.05% w/w,

TNPP is an unspecific isomeric reaction mass. No information is available on the distribution of the isomers.

Impurities

Chemical Name:	Nonylphenol
EC Number:	246-672-0
CAS Number:	25154-52-3
IUPAC Name:	Nonylphenol
Molecular Formula:	$C_{15}H_{24}O$
Structural Formula:	
Molecular Weight:	220.34 g/mol
Typical concentration (% w/w):	< 5% w/w
Concentration range (% w/w):	-

Classification: The following harmonised classification applies:

According to 67/548/CEE	*According to CLP*
Repr. Cat. 3; R62-63 Xn; 22 C; R34 N; R50-53	Repr. 2; H361fd Acute Tox. 4; H302 Skin Corr. 1B; H314 Aquatic Acute 1; H400 Aquatic Chronic 1; H410

Considering that nonylphenol can be present in TNPP in concentration <5%, the following additional classification can apply for TNPP due to this impurity:

According to 67/548/CEE	According to CLP
N; R50-53	Repr. 2; H361fd Skin Irrit 2 – H315 Eye Dam 1 – H318 Aquatic Acute 1 - H400 Aquatic Chronic 1 - H410 (taking into account a M-factor of 10 for nonylphenol, based on the lowest acute toxicity value reported in the nonylphenol EU RAR).

In the high purity TNPP, nonylphenol can be present in TNPP in concentration <0.1% and the following additional classification can apply for high purity TNPP due to this impurity:

According to 67/548/CEE	According to CLP
R52-53	No classification

Chemical Name: Phenol

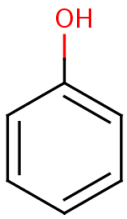
EC Number: 203-632-7

CAS Number: 108-95-2

IUPAC Name: Phenol

Molecular Formula: C_6H_6O

Structural Formula:



Molecular Weight: 94.11 g/mol

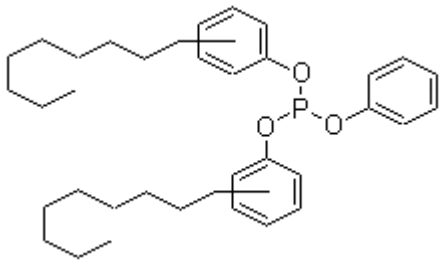
Typical concentration (% w/w): < 0.1% w/w

Concentration range (% w/w): -

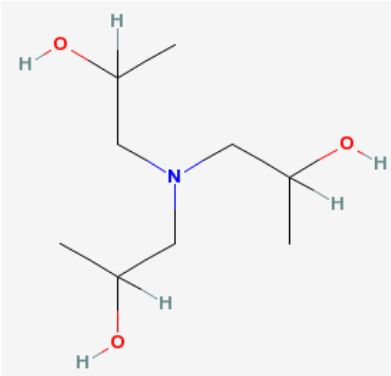
Classification: The following harmonised classification applies:

According to 67/548/CEE	*According to CLP*
Muta. Cat.3; R68 T ; R23/24/25 Xn; R48/20/21/22 C; R34 with SCL : T; R23/24/25: C ≥ 10 % Xn; R20/21/22: 3 % ≤ C < 10 % C; R34: C ≥ 3 % Xi; R36/38: 1 % ≤ C < 3 %	Muta. 2; H341 Acute Tox. 3; H301-H311-H331 STOT RE 2; H373 Skin Corr. 1B; H314 with SCL: Skin Corr. 1B: C ≥ 3 % Skin Irrit. 2: 1 % ≤ C < 3 % Eye Irrit. 2: 1 % ≤ C < 3 %

Considering that phenol can be present in TNPP in concentration < 0.1%, no additional classification applies for TNPP due to this impurity.

Chemical Name:	Di(nonylphenyl)phenylphosphite
EC Number:	-
CAS Number:	25417-08-7
IUPAC Name:	-
Molecular Formula:	$C_{36}H_{50}O_3P$
Structural Formula:	
Molecular Weight:	561.76 g/mol
Typical concentration (% w/w):	0.05% w/w
Concentration range (% w/w):	-
Classification:	No harmonised classification

Additive

Chemical Name:	Triisopropanolamine (TIPA) TIPA is added for hydrolytic stability of TNPP
EC Number:	204-528-4
CAS Number:	122-20-3
IUPAC Name:	1-1',1''-nitrilotripropan-2-ol
Molecular Formula:	$C_9H_{21}NO_3$
Structural Formula:	
Molecular Weight:	191.26 g/mol
Typical concentration (% w/w):	-
Concentration range (% w/w):	0.5 - 1% w/w
Classification:	The following harmonised classification applies:

According to 67/548/CEE	*According to CLP*
Xi; R36 R52-53	Eye Irrit. 2; H319 Aquatic Chronic 3 ; H412

Considering that TIPA can be present in TNPP in concentration 0.5-1%, no additional classification applies for TNPP due to this additive alone.

Only presence of nonylphenol can therefore have an influence on the classification of TNPP.

However, the classification proposed in this dossier as displayed in page 3 does not take into account classifications based on impurities as impurity content can vary depending on the production process and its possible improvements.

It is therefore recommended that the potential influence of impurities on classification remains of the responsibility of the manufacturer/importer. To inform manufacturer/importer as well as users that it can be necessary to complement the harmonised classification of TNPP based on impurity content, a new note could be created and added to the TNPP proposal.

It is also noted that as for environmental toxicity, available data on skin irritation, eye irritation and reproductive toxicity of TNPP are not in agreement with corresponding classifications based on impurity content. These data are therefore displayed in the present dossier for information and

possible discussions that may be raised if it is decided that presence of impurities should be taken into account in the harmonised classification.

1.3 Physico-chemical properties

Table 1: Summary of physico- chemical properties

REACH ref Annex, §	Property	IUCLID section	Value	[comment/reference]
VII, 7.1	Physical state at 20°C and 101.3 kPa	3.1	Viscous liquid at room temperature	
VII, 7.2	Melting/freezing point	3.2	6°C ± 3°C	Reimer&Associates, 2001b
VII, 7.3	Boiling point	3.3	322°C (degradation)	Reimer&Associates, 2001a
VII, 7.4	Relative density	3.4 density	0.98 g/cm^3 at 20°C	Crompton, 2003
VII, 7.5	Vapour pressure	3.6	0.058 Pa at 25°C	Phoenix_Chemical_Laboratory, 1997
VII, 7.6	Surface tension	3.10	No data	
VII, 7.7	Water solubility	3.8	Upper value: <0.05 mg.L^{-1} at 20°C Lower value: 3.10^{-16} mg/L	TNO, 2004 Lower value: value obtained using QSAR calculation
VII, 7.8	Partition coefficient n-octanol/water (log value)	3.7 partition coefficient	Experimental : 14 (T° not known)	OECD guidelines 117 HPLC method (Jakupca, 2007)
VII, 7.9	Flash point	3.11	207°C (closed cup)	Pittsburgh_Testing_Laboratory, 1978
VII, 7.10	Flammability	3.13	No data	
VII, 7.11	Explosive properties	3.14	TNPP is not expected to have explosive properties	On the basis of chemical structure
VII, 7.12	Self-ignition temperature		No data	
VII, 7.13	Oxidising properties	3.15	No oxidising properties	EU RAR, 2002a
VII, 7.14	Granulometry	3.5	No data	
XI, 7.15	Stability in organic solvents and identity of relevant degradation products	3.17	No data	
XI, 7.16	Dissociation constant	3.21	No data	
XI, 7.17,	Viscosity	3.22	6000 cps at 25°C	Crompton, 2003
	Auto flammability	3.12	440°C	United States Testing Company, 1990
	Reactivity towards container material	3.18	No data	
	Thermal stability	3.19	No data	

2 MANUFACTURE AND USES

2.1 Identified uses

Industrial use: stabiliser in the processing of various plastic and rubber products (polyvinylchloride – PVC – film, Polyolefins linear low density polyethylene – LLDPE, High density polyethylene – HDPE rubber).

General public: no identified use

3 CLASSIFICATION AND LABELLING

3.1 Classification in Annex I of Directive 67/548/EEC

No current classification in Annex I of Directive 67/548/EEC or in Annex VI of CLP.

3.2 Self classification(s)

No data.

4 ENVIRONMENTAL FATE PROPERTIES

4.1 Degradation

4.1.1 Stability

Table 2: Degradation of TNPP in air and water

	Value	Reference
Atmospheric degradation (estimated with EPIWIN v3.10)	$kdeg_{air}$ = 3.28 d^{-1} half-life: 0.21 days (5.07 h)	Staples, 2001
Aquatic degradation hydrolysis of TNPP in aqueous media (Test substance: Doverphos HiPure 4-HR (in addition to TNPP, HR grade contains 0.75% of triisopropanol amine, TIPA, CAS n°122-20-3): Purity of TNPP: 99.9%, Residual NP: <0.1%).	0.1% of Nonylphenol formed after 241 h	DAT Laboratories, 2007

Corresponds to IUCLID 4.1

4.1.2 Biodegradation

4.1.2.1 Biodegradation estimation

No data.

4.1.2.2 Screening tests

No data.

4.1.2.3 Simulation tests

Table 3: Summary of simulation tests

Guideline / Test method	Test para-meter	Inoculum		Test substance concentr.	Degradation		Reference
		Type	Adaptation		Incubation period	Degree [%]	
OECD 301D (Test substance: purity of 100% based on a SDS; certificate of analysis not provided)	biological oxygen demand (BOD)	commercial bacterial preparation	No	15.4 mg/L	28 days	< 4% after 28 days	Hydroqual Laboratories Ltd, 2001c
OECD 301B (Purity of TNPP not given)	CO_2 evolution	Sewage activated sludge	Substance preparation was adapted considering the very low solubility of the substance	18.1 mg/L	29 days	1% after 29 days	CIBA-Geigy, 1994

4.1.3 Summary and discussion of persistence

TNPP released to the atmosphere is expected to degrade by reaction with hydroxyl radicals with an estimated half-life of 5.07 hours. With such a low half life, TNPP will be rapidly degraded in the air and it is therefore not expected that TNPP will contribute to ozone depletion in the stratosphere.

TNPP is not readily biodegradable in aquatic environments. However, it has been shown that the substance can be hydrolysed into nonylphenol, this hydrolytic product being readily biodegradable. Indeed, according to the Risk Assessment Report for nonylphenol (EU RAR, 2002b): “the data available indicate that nonylphenol undergoes biodegradation in water, sediment and soil systems. The results from standard biodegradation tests are variable but indicate that nonylphenol is probably inherently biodegradable.”

Although it cannot be totally ruled out that there might be environmental conditions where hydrolysis could occur, hydrolysis of TNPP in the aquatic environment will not be considered as an important phenomenon. This is based on the expected very low water solubility of the substance that would not enable hydrolysis to occur in large amount. Furthermore, the high hydrophobicity of TNPP (high log Kow) will contribute to a large adsorption of the substance on sediment when entering the aquatic compartment thus reducing its availability for hydrolysis.

Based on these available studies, we can conclude that TNPP fulfils the P/vP screening criterion (E.C., 2003). Further testing would be necessary for a definite assignment on the P criterion.

4.2 Environmental distribution

4.2.1 Adsorption/desorption

The partition coefficients for TNPP have been calculated using EUSES (E.C., 2004) based on log Kow of 14. They are presented as an example in the following table:

Table 4: Calculated partition coefficients for TNPP with a Log Kow of 14

K_{oc}	$2.76x10^{11}$	Partition coefficient organic carbon-water ($L.kg^{-1}$)
Kp_{susp}	$2.76\ x10^{10}$	Partition coefficient solid-water in suspended matter ($L.kg^{-1}$)
Kp_{sed}	$1.38\ x10^{10}$	Partition coefficient solid-water in sediment ($L.kg^{-1}$)
Kp_{soil}	$5.51\ x10^{09}$	Partition coefficient solid-water in soil ($L.kg^{-1}$)
$K_{soil-water}$	$8.27\ x10^{09}$	Soil-water partition coefficient ($m^3.m^{-3}$)
$K_{susp-water}$	$6.89\ x10^{09}$	Suspended matter-water partition coefficient ($m^3.m^{-3}$)
$K_{sed-water}$	$6.89\ x10^{09}$	Sediment-water partition coefficient ($m^3.m^{-3}$)

The high hydrophobicity of TNPP (high log Kow) will contribute to a large adsorption of the substance on sediment when entering the aquatic compartment.

Corresponds to IUCLID 4.4.1

4.2.2 Volatilisation

A Henry's law constant between 799 and $1.33x10^{17}$ $Pa.m^3.mol^{-1}$ was calculated from TGD estimation (eq 21) using a vapour pressure of 0.058 Pa, a molecular weight of 689 $g.mol^{-1}$ and a water solubility of <0.05 $mg.L^{-1}$ (the lowest value obtained using the QSAR result for the water solubility was $3x10^{-16}$ mg/L).

The resulting air-water partition coefficient ($K_{air-water}$) would then range between 0.337 and $5.62x10^{13}$ $m^3.m^{-3}$ by EUSES v2.1. However, considering the hydrophobicity and the strong adsorption potential of the substance, volatilisation of TNPP from water is not expected to be a major phenomenon.

Corresponds to IUCLID 4.4.2

4.2.3 Distribution modelling

Table 5: Estimation of removal of TNPP in STPs according to EUSES v2.1

	Log Kow 14 H = 799 $Pa.m^{-3}.mol^{-1}$ (calculated using a solubility of 0.05 mg/L)

% to air	$1.7x10^{-5}$
% to water	8
% to sludge	92
% degraded	0
% removal	92

TNPP being insoluble, not volatile and considered as not biodegradable, releases through production or processing will mainly go to sludge.

4.3 Bioaccumulation

4.3.1 Aquatic bioaccumulation

4.3.1.1 Bioaccumulation estimation

A calculated BCF of 3.162 L/kg has been obtained using EpiWin.

Using EUSES v2.1 calculation, a bioconcentration factor of 479 L/kg could be calculated for fish taking into account a log Kow >10 (the worst case for BCF obtained when using the parabolic equation giving the BCF for fish based on the K_{ow}, (E.C., 2003)).

4.3.1.2 Measured bioaccumulation data

Measured data on bioaccumulation of TNPP are not available.

Bioaccumulation of nonylphenol released from TNPP into the aquatic compartment should also be considered (BCF for NP: 1,280 L/kg for fish - E.C., 2002).

4.3.2 Terrestrial bioaccumulation

For earthworms, a partition coefficient earthworm-porewater could be calculated using EUSES model (v2.1, E.C., 2004): $K_{worm\text{-}porewater} = 1.2x10^{6}$ L/kg taking into account a log Kow of 8 (worst case of the QSAR application range).

4.3.3 Summary and discussion of bioaccumulation

The bioaccumulation factors calculated for TNPP based on log Kow of 8 and >10 as a worst case indicate a high bioaccumulation potential. Nevertheless, the bioaccumulation potential of TNPP based on these calculations should be considered with precaution for the following reasons:

- molar weight is near 700 g/mol (689 g/mol) and certain classes of substances with molecular mass greater than this threshold are not readily taken up by fish and are unlikely to bioaccumulate significantly.

- Information on the molecular size of TNPP is also available (personal communication, Kazumi Kawahara, CERI, 20th October 2005). Based on this study, it seems that, taking into account the calculated molecular size of TNPP, the bioaccumulation potential is negligible. The calculation of the mean diameter for six different three dimension structures of TNPP has led to a lowest value of 13.9 Å. This conclusion has been reached based on a cut-off value for the ability of a chemical to pass through fish gill membrane has been established at 9.5 Å (Opperhuizen *et al.*, 1985). However, it should also be considered that the current cut-off value proposed by the PBT subgroup is a mean diameter higher than 17 angstroms.

- A worst case value has been taken into account for the calculation of BCFs for TNPP. However, there are some indications that the Kow of TNPP could be much higher than this value (HPLC method estimated log Kow of 14).

- The molecular dimensions (D_{max}[1] and D_{eff}[2]) of two representative isomers of commercial TNPP were estimated with a demonstration version of Molecular Operating Environment software (version 2006.08) (Schocken, 2007). The TNPP isomers, comprised of nonylphenol ligands that are "slightly or highly branched" were each sorted into their lowest potential energy state conformations in aqueous solution and the lowest-energy conformations averaged to obtain the requisite molecular dimensions. The approach taken was to use two different programs of MOE, namely, conformational import and dynamics simulation. Results showed that D_{max} average, currently considered the most important molecular dimension and defined as the average diameter of the smallest spheres circumscribing the low-energy conformations for a given TNPP isomer, ranged from 23.7 Å for the slightly branched TNPP isomer to 22.8 Å for the highly branched TNPP isomer using the conformational import approach and from 24.3 Å to 21.2 Å for the slightly branched and highly branched TNPP isomer using the dynamics simulation method, respectively. These values all exceed the 17.4-Å cutoff currently used to preclude absorption of organic chemicals via fish gills. Coupled with TNPP's high experimentally determined log Kow (14) and its high molecular weight (689 grams/mole), it is unlikely that this chemical would be bioaccumulative in the aquatic environment.

- Mammalian toxicity of TNPP is described in section 5 of this report. In animals, TNPP has a very low acute toxicity by the oral route, with a LD50 value of about 19.5 +/- 3.3 g/kg bw for the rat. Two-year studies provide a profile of limited repeated dose toxicity for TNPP. In these 2-year studies, 3300 ppm of TNPP in the diet (corresponding to 167 mg/kg/d in rats), was derived as a NOAEL, both for rat and dog.

The low mammalian toxicity of TNPP could be linked to a limited absorption potential. However in the absence of specific toxicocinetic study, only quantitative information was derived from the physico-chemical properties of the substance.

According to a weight of evidence approach, TNPP does not fulfil the B/vB criterion.

[1] Defined as the diameter of the smallest sphere into which the molecule may be placed.

[2] Defined as the diameter of the smallest cylinder into which the molecule may be placed.

4.4 Secondary poisoning

The biomagnification factor (BMF) should ideally be based on measured data. However, no measured data was available for TNPP so the default values given in TGD Table 21 were used instead. Considering the chosen value for log Kow, a BMF of 1 is applied.

5 HUMAN HEALTH HAZARD ASSESSMENT

5.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

No specific toxicocinetic study was conducted with trisnonylphenyl phosphite.

5.2 Acute toxicity

5.2.1 Acute toxicity: oral

Table 6: Acute toxicity by oral route

Species	LD_{50} (mg/kg)	Observations and Remarks	Ref.
Rat	19.5 +/- 3.3 gram/kg bw (TNPP purity not givzn)	Gross pathological findings included hemorrhagic lesions in the gastric mucosa and/or duodenum in a few rats that died, and hemorrhagic lungs.	Food and Drug Research Laboratories, 1957.
Rat	> 10.0 ml/kg bw (eq. to 9.8 g/kg bw) (TNPP purity: not known; considered to be 100%)	No mortality occurred during the study	Hill Top Research, 1965

5.2.2 Acute toxicity: inhalation

No data

5.2.3 Acute toxicity: dermal

Table 7: Acute toxicity by dermal route

Species	LD_{50} (mg/kg)	Observations and Remarks	Ref.
Rat	> 2000 mg/kg bw (TNPP purity not given)	No mortality occurred during the study	Tay, 2001a

Rat	> 2000 mg/kg bw (TNPP purity > 94%)	No mortality occurred during the study	Ciba-Geigy, 1992

5.2.4 Acute toxicity: intraperitoneal routes

Table 8: Acute toxicity by IP route

Species	LD_{50} (mg/kg)	Observations and Remarks	Ref.
Rat	> 1000 mg/kg bw (TNPP purity not given)	No mortality occurred during the study	Ciba-Geigy, 1983

5.2.5 Summary and discussion of acute toxicity

➔ According to the criteria of the Directive 67/548/EEC and of the CLP Regulation, this chemical doesn't need to be classified on the basis of its acute toxicity (LD_{50} > 2000 mg/kg by oral and dermal route).
Information for this endpoint is given for information only.

5.3 Irritation

5.3.1 Skin

Table 9: Skin irritation

Species	N° of animals	Exposure time (h/day)	conc. (wt/wt)	Dressing : Occlusive semi-occlusive open	Observations and remarks (specify the experimental conditions, score and evaluation method)	Ref.
Rabbit	3	4 hours	A dose of 0.5 ml liquid test substance (TNPP purity: 99.3%)	Semi-occlusive	Very slight erythema was observed in three out of three rabbits following a 4-hour exposure. By the 24-hour observation point, the irritation was reversed. OECD 405 Reactions graded according to the Draize scoring scale.	Tay, 2001b
Rabbit	6	24 hours	A dose of 0.5 ml liquid test substance (TNPP purity not given)	Occlusive	In 3/6 animals, the application sites showed necrosis. In 5/6 animals the erythemas extended beyond the treated areas. Erythema and edema of intact skin were reversed within 7 days. Reactions graded according to the Draize scoring scale.	Ciba-Geigy, 1981

5.3.2 Eye

Table 10: Eye irritation

Species	N° of animals	Exposure time (h/day)	conc. (wt/wt)	Observations and remarks (specify the experimental conditions, score and evaluation method)	Ref.
Rabbit	4	Single instillation, unrinsed (TNPP purity: 99.3%)	0.1 ml of the undiluted test substance	Slight conjunctival redness and chemosis were observed at the 1-hour observation point and were resolved within 24 to 48 hours. OECD 404	Tay, 2001c

Rabbit	6	Single instillation rinsed within 30 seconds in half on the animals (TNPP purity not given)	0.1 ml of the undiluted test substance	Reversible slight redness of conjunctiva and chemosis were observed. Mean scores for conjunctive redness were 1, 0.3 and 0.7 at 24, 48 and 72h, respectively in non rinsed eyes (mean 0.7). Mean scores for chemosis were 1, 0.3 and 0.3 at 24, 48 and 72h, respectively in non rinsed eyes (mean 0.6).	Ciba-Geigy, 1981

5.3.3 Respiratory tract

No data

5.3.4 Summary and discussion of irritation

➔ According to the criteria of the Directive 67/548/EEC and of the CLP Regulation, this chemical doesn't need to be classified as an irritant to the skin nor to the eye.

Indeed, for skin irritation, the conclusion is based on the guideline study with semi-occlusive application that shows mean 24-48-72h scores of 0 for both erythema and edema (reversibility of erythema already observed at 24h).

For eye irritation, reversible effects were observed on conjunctiva with mean 24-48-72h scores below 2 in both studies.

Information for this endpoint is given for information only.

5.4 Sensitisation

5.4.1 Skin

Table 11: Skin sensitisation

Species	Type o f test	N° of animals (c, t)	Incidence of reactions observed (c, t)	Ref.
Guinea pig	Maximisation Test OECD 406 (TNPP purity > 94%) Induction with 5% TNPP intradermal and 10% topical. Challenge with 1% TNPP.	c : 10 t : 20	There were 12/20 (60%) and 15/20 (75%) positive animals respectively 24h and 48h after occlusive epidermal application (showing erythema scores of 1 to 2) and none in the negative control group.	Ciba-Geigy, 1992d
Guinea pig	Buehler Sensitisation Test OECD 406 Challenge and induction with neat substance. (TNPP purity: 99.3%)	c: 15 t : 20	All animals showed no sign of erythema or oedema at the 24 and 48-hour observation points for the challenge phase.	Tay, 2001d

c : control group ; t : test group

5.4.2 Respiratory system

No data

5.4.3 Summary and discussion of sensitisation

➔ The positive result in the maximisation test (more than 30% of animals with a positive reaction in an adjuvant type guinea pig test method) warrants classification with R43 (Skin Sens. 1 – H317 according to CLP).

5.5 Repeated dose toxicity

5.5.1 Repeated dose toxicity: oral

Table 12: Repeated toxicity by oral route

Species	Dose mg/kg/body weight mg/kg diet	Duration of treatment	Observations and Remarks	Ref.
Rat	NOAEL = 1% TNPP in the diet (about 1000 mg/kg bw)	90 days	Pathological changes were observed in the lung and the kidney.	Food and Drug Research Laboratories, 1957
Rat	NOAEL = 3300 ppm in the diet (about 167 mg/kg bw)	2 years	Limited observed effects (slight retardation of growth in males and elevation of the liver weight in F0 females at the highest dose level).	Food and Drug Research Laboratories, 1961
Dog	NOAEL = 3300 ppm in the diet	2 years	Limited observed effects (chronic inflammation in renal pelvis in one male dog at the highest dose level, slight to moderate degree of hyperplasia of the thyroid (with focal collections of lymphocytes) in two female dogs at the highest dose level) group	Food and Drug Research Laboratories, 1961
Rat	NOAEL = 200 mg/kg bw for males NOAEL > 1000 mg/kg bw for females	4 weeks for F0 males 10 weeks for F0 females 85 days for F1 generation	Renal lesions observed in F0 and F1 males.	Tyl et al., 2002

5.5.2 Repeated dose toxicity: inhalation

No data

5.5.3 Repeated dose toxicity: dermal

No data

5.5.4 Summary and discussion of repeated dose toxicity:

➔ According to the criteria of the Directive 67/548/EEC and of the CLP Regulation, this chemical doesn't need to be classified on the basis of its repeated dose toxicity (absence of significant and/or severe effects at doses relevant for classification).

Information for this endpoint is given for information only.

5.6 Mutagenicity

Not evaluated in this dossier

5.7 Carcinogenicity

Not evaluated in this dossier

5.8 Toxicity for reproduction

5.8.1 Effects on fertility

Table 13: Effects on fertility

Species	Route	Dose	Number of generations exposed	Observations and Remarks	Ref.
Rat	Oral	50, 167 and 500 mg/kg/d NOAEL for reproduction ≥ 10 000 ppm (500 mg/kg/day) (TNPP purity not given)	3 (F0 to F3)	Growth was normal at all dosage levels in F0, F1 and F2 females. At the dose level of 500 mg/kg/d, there was a slight but statistically significant retardation in growth of the F2 (p=0,001) and F3 (p=0,05) males and of the F3 females (p=0,001), along with a decrease in the efficiency of food utilisation for F2 males (p=0.05) at the highest dose and F3 females at the 2 highest doses used (p=0.001). In F3 females, the decrease of food utilisation efficiency was dose related. There was no indication of adverse effect in the F0 generation at any dose level. Diminution in the number of pups born per litter in the F1 and F2 high dose groups, and a small decrease in the fertility and viability indexes in F2 at this same high dose level exposure were observed (see table 14a below).	Food and Drug Research Laboratories, 1961
Rat	Oral	50, 200 and 1000 mg/kg/d NOAEL for maternal and offspring toxicity = 200 mg/kg/day (TNPP	1 (F0 to F1) Modified OECD 421*	Effects were only observed in the highest dose group and were the following : - Three of ten pregnant F0 females at 1000 mg/kg/day died in late pregnancy (gestation day 22). These deaths may have been related to dystocia, since the dams appeared to be unable to deliver their normal appearing pups. Two F0	Tyl et al., 2002

		purity: 99.98%)		females respectively exposed to 50 mg/kg/day (during gestation) and 1000 mg/kg/day (during lactation) were also found dead. But these deaths were attributed to dosing errors and were not considered treatment related. - Ovary weights (absolute and relative to terminal body and brain weights- see table 14b for details) were significantly decreased at 1000 mg/kg/day in F0 but not F1 adult females. These findings were not related to microscopic findings - There was a reduction of the litter size on pnd0 observed at 1000 mg/kg/d (see table 14c below). - In F1 males, paired epididymides weight, relative to terminal body weights, were significantly decreased at 1000 mg/kg/day. Mating, fertility, pregnancy and gestational indices were equivalent across groups ; gestational length was equivalent across all groups. Andrology parameters, time of vaginal opening, preputial separation, normality and length of oestrous cycles were also checked and did not reveal any changes compared to control.	

* The modified OECD TG 421 exceeds the OECD TG 421 study design as follows : enhanced evaluation of toxicity in the F0 generation, including the evaluation of a recovery group of males ; evaluation of developmental landmarks in the F1 generation (time of vaginal opening or preputial separation, normality and length of oestrous cycle) ; and following the F1 offspring to adulthood, with continued exposure and assessment of reproductive structures and functions including potential effect on sperm.

Table 13a : Comparison of first two matings in three generations of rats (FDRL, 1961)

Dose	**Generation**	**Total No. of mating**	**No. litters born alive**	**Pups born alive**	**Pups per litter born**	**No. litters weaned**	**Average weight of pups at weaning[1]**	**F.I.[2]**	**G.I.[3]**	**V.I.[4]**	**L.I.[5]**
Mg/kg							**Gm**				
None	**F0**	49	41	328	8.0	34	40.0	98.0	82.9	87.2	96.2
	F1	20	19	216	11.3	19	36.3	95.0	100.0	87.0	89.5
	F2	20	17	151	8.9	16	42.7	90.0	94.5	93.2	87.5
50	**F0**	49	40	354	8.8	36	36.5	91.8	90.0	91.8	88.0
	F1	20	20	213	10.7	20	41.6	100.0	100.0	96.0	90.0
	F2	20	19	159	8.4	16	40.0	95.0	94.5	87.6	81.1
167	**F0**	50	45	415	9.2	41	37.9	94.0	95.7	95.7	87.7
	F1	20	20	212	10.6	20	40.1	100.0	100.0	95.5	94.5
	F2	20	19	151	8.0	12	42.6	95.0	100.0	94.5	71.0
500	**F0**	48	40	337	8.4	37	36.0	100.0	83.3	93.8	87.3
	F1	17	16	113	7.0	13	36.0	100.0	100.0	93.5	96.0
	F2	20	17	122	7.3	13	43.8	85.0	100.0	79.7	89.7

[1]At 21 days
[2]Fertility index = (No. pregnancies / No. matings) X 100
[3] Gestation index = (No. litters born alive / pregnancies) X 100
[4] Viability index = (No. pups at 1d. / No. pups born alive) X 100
[5] Lactation index = (No. pups at 21d. / No. pups at 1d.) X 100

Table 13b : Summary and Statistical analysis of the F0 female paired ovary weight (absolute and relative) (Tyl et al., 2002)

	Trisnonylphenyl Phosphite (mg/kg/day)			
	0	50	200	1000
Paired ovary weight (g)	0.1488 ± 0.0041 N = 10	0.1426 ± 0.0062 N = 9	0.1512 ± 0.0077 N = 10	0.1137 ± 0.0010 ** N = 5[a]
Relative Paired ovary weight (% sacrifice weight)	0.0456 ± 0.0016 N = 10	0.0458 ± 0.0028 N = 9	0.0466 ± 0.0023 N = 10	0.0355 ± 0.0009 N = 5[a]

** p< 0.01 ; Dunett's test for pairwise comparisons to control
* p< 0.05 ; Dunett's test for pairwise comparisons to control
[a] Decrease in N is due to one paired ovary weight being a statistical outlier and therefore it was excluded.

Table 13c : Summary of F1 offspring toxicity (Tyl et al., 2002)

	Trisnonylphenyl Phosphite (mg/kg/day)			
	0	50	200	1000
N° of live litters Postnatal Day 0	10	8	10	7
N° of live litters Postnatal Day 4	10	7*	10	7
Average number of live pups per litter (pnd 0)	14.9 ± 0.5	12.8 ± 1.6	15.9 ± 0.6	12.0 ± 1.4
Average number of live pups per litter (pnd 4, precull)	14.8 ± 0.5	14.3 ± 0.6	15.6 ± 0.5	12.0 ± 1.4

* The entire litter for female 30 was missing and presumed dead on postnatal day 4.

5.8.2 Developmental toxicity

Table 6: Developmental toxicity

Species	Route	*dose mg/kg/day ppm **Conc. (mg/L)	Exposure period : - number of generations or - number of days during pregnancy	Observations and remarks	Ref.
Rat	Oral	NOAEL terato > 1000 mg/kg/day (TNPP purity: 99.98%)	Exposure during the whole pregnancy Modified OECD 421*	No OECD TG 414 test was provided. Information on developmental toxicity was derived from a screening test according to a modified OECD TG 421*. In this study, no developmental effect was observed, up to the dose level of 1000 mg/kg/day, whether on pnd4 or 21.	Tyl et al., 2002

* The modified study design used in this study provides, for continuation of the F1 offspring, with continuing exposure until sexual maturity. Thus, to provide data on the pnd 4 pups, the pups culled to standardise litters on pnd 4 were euthanised and subjected to complete gross necropsy, but this was done on a very reduced number of pups, since F1 litters were culled on pnd 4 to yield, as nearly as possible, five males and five females per litter. This leads to nearly 2 animals in the highest dose group and 4 in the other groups. The other pups were subjected to a complete gross necropsy at weaning (pnd 21), except for at least one male and one female per litter that were selected to continue treatment for seven more weeks.

5.8.3 Human data

No data

5.8.4 Summary and discussion of reproductive toxicity

➔ According to the criteria of the Directive 67/548/EEC and of the CLP Regulation, this chemical doesn't need to be classified as toxic to reproduction based on the following rationale:

- The effect on reproductive organ weight seen at a high dose in the screening one-generation study (OECD 421) is not considered sufficient to provide evidence of a toxicity to fertility in absence of histological damages or direct effects on fertility in this study and considering the absence of effects related to fertility in the 3-generation study. Phenomenon of dystocia observed in dams at the highest dose in the study of Tyl (2002) is viewed as maternal toxicity, due from the adjustments of dosing volume on gd 14 and especially on GD 20, resulting in over dosing the dams in late gestation.

- Absence of observation of significant developmental effects.

Information for this endpoint is given for information only.

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Not evaluated in this dossier

7 ENVIRONMENTAL HAZARD ASSESSMENT

Due to limits of analytical methods (the water solubility of TNPP is below the detection limit of the substance) all the test results for TNPP are based on nominal concentrations.

7.1 Aquatic compartment (including sediment)

7.1.1 Toxicity test results

7.1.1.1 Fish

Acute toxicity to fish

The following table shows a summary of the acute toxicity tests that were performed with fish species. The toxicity limits reported are above the upper limit of the estimated water solubility (solubility < 50 µg/L).

Table 7: Acute toxicity to fish

Test #	Species	References	Comment	Validity*
1	Species: *Oncorhynchus mykiss* LC_{50} (96 hours) > 100 mg/L Method: OECD GL 203 (TNPP purity: 99.8%)	Guterson, 2001	Concentrations tested were far above the solubility of the substance. No effect was seen at the highest concentration tested although no analytical monitoring was performed.	2
2	Species: *Brachydanio rerio* LC_{50} (96 hours) = < 10 mg/L LC_{50} (48 hours) = 16 mg/L Method: Dir. 84/449/EEC C.1 (TNPP purity > 94%)	CIBA-Geigy, 1992a	The tested concentrations were probably very far above the actual water solubility of the substance. No analytical follow-up of the test concentrations was performed. As there was no equilibration time to allow dissolution of the substance during the preparation of the test concentration, it is not even clear that the maximum solubility in the test medium was achieved. The report mentions that undissolved substance was observed at all test concentrations. All fish died at the lowest test concentration during aeration of the test system at t = 48 h. No LC50 could be estimated	3
3	Species: *Leuciscus idus* LC_{50} (48 hours) = 7.1 mg/L Method: DIN 38412-L15 (Purity of TNPP: commercial grade; no further information available.	CIBA-Geigy, 1988a	Concentrations tested were above the solubility of the substance and the results show no effect below the estimated upper limit of the water solubility of TNPP.	3

* 1 = valid; 2 = valid with restrictions; 3 = invalid; 4 = not assignable

Chronic toxicity to fish

No chronic toxicity test with fish is available.

7.1.1.2 Aquatic invertebrates

Acute toxicity to aquatic invertebrates

The following table shows a summary of the acute toxicity tests that were performed with aquatic invertebrate species.

Table 8: Acute toxicity to aquatic invertebrates

Test #	Species	References	Comment	Validity
1	Species: Daphnia magna NP (estimated) EC50 (48 hours) = 0.009 mg/L Method: OECD GL 202 (Test substance: Hydrolyzed solution of tris-nonylphenyl phosphite (TNPP; CAS n° 26523-78-4; from Dover Chemical Corporation): Purity of initial TNPP, 99.8% (stock solution)).	Hydroqual Laboratories Ltd, 2001a	The test was performed on hydrolysis products of TNPP obtained after leaving TNPP for 78h at room temperature. The supernatant containing the hydrolysis products of TNPP was then decanted for preparation of the test solutions. A stock was prepared from the hydrolyzed TNPP solution by diluting 100 mL of the supernatant with 900 mL of dilution water (10.00 mg/L nominal). This solution was then serially diluted with laboratory dilution water to obtain the other eight test concentrations (5.00, 2.50, 1.25, 0.63, 0.31, 0.16, 0.08, and 0.04 mg/L). The samples of the test solutions were analysed for the major hydrolysis product of TNPP, nonylphenol. Toxicity values were derived based on nominal concentrations for the mixture of TNPP hydrolysis products (based on total mass of TNPP initially added). These nominal values were likely higher than actual concentrations because of the sparingly soluble nature of the test substance and hydrolysis products. The concentrations and 95 % confidence limits of the hydrolysis products that immobilized 50 % of the daphnids at 24 and 48 h were 2.2 mg/L (1.7 to 3.0 mg/L) and 0.3 mg/L (0.2 to 0.4 mg/L), respectively. The highest concentrations of hydrolysis products that produced no significant immobility relative to controls at 24 and 48 h were 1.25 and 0.16 mg/L, respectively (NOEC). The degree of immobilization increased with an increasing concentration of the hydrolyzed test substance as expected (normal dose and response relationship). Nonylphenol was only detected in the highest treatment at test initiation (0.3 mg/L based on the results of duplicate analyses; detection limit of 0.2 mg/L). The toxic response and presence of detectable levels of the hydrolysis product in solution confirmed that the TNPP had undergone hydrolysis during preparation of the stock solution. TNPP is not soluble in water and the only major hydrolysis product is nonylphenol. Hence, nonylphenol is likely the toxic agent present in the test solutions..Toxicity values were derived based on this measured concentration of nonylphenol. The test concentrations for toxicity values were derived from the single value for nonylphenol (starting value that was serially divided by a factor of 2 to obtain the numerical values for the test concentrations, all of which were below the detection limit of 0.2 mg/L for nonylphenol).	2
2	Species: *Daphnia magna* EC_{50} (48 hours) = 0.42 mg/L Method: Dir. 84/449/EEC C.2 (Purity of TNPP > 94%)	CIBA-Geigy, 1992b	No analytical monitoring was conducted neither for TNPP nor for its degradation product (nonylphenol). However, test result is comparable with the results of test #1 and other tests conducted with nonylphenol.	3

* 1 = valid; 2 = valid with restrictions; 3 = invalid; 4 = not assignable

Chronic toxicity to aquatic invertebrates

The following table shows a summary of the chronic toxicity tests that were performed with aquatic invertebrate species.

Table 9: Chronic toxicity to aquatic invertebrates

Test #	Species	References	Comment	Validity*
1	Species: *Daphnia magna* NOEC (21 days) ≥ 100% WAF of 0.1 mg/L LOEC (21 days) > 100% WAF of 0.1 mg/L Method: OECD GL 211, OECD Series on Testing and Assessment Number 23 (OECD, 2000) (Test substance: Doverphos 4 High Pure (DP4HP, with less than 0.1% NP remaining as impurity))	Sayers, 2009	The test was conducted as a limit test at a single nominal concentration of 100% Water Accommodated Fraction of a 0.10 mg/L stock solution. No analytical monitoring was conducted neither for TNPP nor for its degradation product (nonylphenol).	2

* 1 = valid; 2 = valid with restrictions; 3 = invalid; 4 = not assignable

7.1.1.3 Algae and aquatic plants

The following table shows a summary of the toxicity tests that were performed with algae species.

Table 10: Algae and aquatic plants toxicity

Test #	Species	References	Comment	Validity*
1	Species: *Selenastrum capricornutum* NOEC (72 hours) 100 mg/L (growth rate) Method: OECD GL 201 (Test substance: purity of 100% based on SDS; certificate analysis not provided)	Hydroqual Laboratories Ltd, 2001b	No significant effects upon algae growth were observed at any test concentration. On the contrary, it seems that the hydrolysis of TNPP during the experiment has increase the phosphorous content of the test medium causing growth stimulation.	2
2	Species: *Scenedesmus subspicatus* NOEC (72 hours) 100 mg/L (biomass) Method: Dir. 87/302/EEC, part C., p. 89 (Purity of TNPP > 94%)	CIBA-Geigy, 1992c	No significant effects upon biomass were observed at any test concentration.	2

* 1 = valid; 2 = valid with restrictions; 3 = invalid; 4 = not assignable

7.1.1.4 Sediment organisms

The following table shows a summary of the toxicity tests that were performed with sediment species.

Table 19: Toxicity to sediment organisms

Test #	Species	References	Comment	Validity
1	Species: *Lumbriculus variegatus* Reproduction and biomass: LOEC(28 days) = 63 mg a.i./kg NOEC (28 days) < 63 mg a.i./kg Estimated NOECs: $EC10_{(reproduction)}$ = 44 mg a.i./kg $EC10_{(biomass)}$ = 25 mg a.i./kg Method: OECD GL 225 (Doverphos 4 Hi Pure (DP4HP, CAS No.: 26523-78-4): Purity: 99.9% as tris (nonylphenyl) phosphate with less than 0.1% NP remaining as impurity)	Picard, 2008	No analytical monitoring was conducted neither for TNPP nor for its degradation product (nonylphenol). Deviation: the total ammonia content was analysed only in Solvent control and in the highest dose instead of "at least in one replicate of the controls and in one test vessel of each concentration level at the start of the exposure period, and subsequently 3 x per week".	1

* 1 = valid; 2 = valid with restrictions; 3 = invalid; 4 = not assignable

This study is described for information although it has no implication for classification.

7.1.1.5 Other aquatic organisms

No data available.

7.1.2 Calculation of Predicted No Effect Concentration (PNEC)

Not relevant for this type of dossier.

7.2 Terrestrial compartment

7.2.1 Toxicity test results

No data available.

7.2.1.1 Toxicity to soil macro organisms

No data available.

7.2.1.2 Toxicity to terrestrial plants

No data available.

7.2.1.3 Toxicity to soil micro-organisms

No data available.

7.2.1.4 Toxicity to other terrestrial organisms

Toxicity to birds

No data available.

Toxicity to other above ground organisms

No data available.

7.2.2 Calculation of Predicted No Effect Concentration (PNEC_soil)

Not relevant for this type of dossier.

7.3 Atmospheric compartment

No data available.

7.4 Microbiological activity in sewage treatment systems

7.4.1 Toxicity to aquatic micro-organisms

The following table shows a summary of the toxicity tests that were performed with micro-organisms.

Table 20: Toxicity to aquatic micro-organisms

Test #	Species	References	Comment	Validity*
1	STP activated sludge 1.6-1.7 g/L IC_{50} = 16 mg/L NOEC: n.d. Method: OECD GL 209 (Purity of TNPP: commercial grade; further information not available)	CIBA-Geigy, 1988b	Instead of a centrifuged sludge, a settled sludge was used. Due to the very low solubility and the expected low toxicity of the substance, only one concentration (100 mg/L) was tested in duplicates during three hours. The test substance was directly added to the test vessel. In one replicate no inhibition was recorded, in the other an inhibition of 24% was observed. This test must be considered invalid as 25% inhibition were found in a replicate.	3

Test #	Species	References	Comment	Validity*
2	STP activated sludge NOEC = 18.1 mg/L Method: OECD GL 301B (Purity of TNPP not given)	CIBA-Geigy, 1994	After 7 days and 20 days, the biodegradation of the reference substance (Sodium benzoate) reaches respectively 71 and 86%. The controls of reference and reference together with the test substance meet the specification for ready biodegradability. Therefore, it can be concluded that the test substance has no inhibitory effect on the bacteria at the concentration tested (18.1 mg/L) which is above the solubility limit of TNPP.	2

* 1 = valid; 2 = valid with restrictions; 3 = invalid; 4 = not assignable

7.4.2 PNEC for sewage treatment plant

Not relevant for this type of dossier.

7.5 Calculation of Predicted No Effect Concentration for secondary poisoning (PNEC_oral)

Not relevant for this type of dossier.

7.6 Conclusion on the environmental classification and labelling

➔ The short-term toxicity test available performed with fish and algae and that were considered as valid (validity of 1 or 2) did not conclude on a toxic effect of TNPP and do not justify a classification.

The acute toxicity test of Hydroqual Laboratories Ltd (2001) conducted with *Daphnia magnia* is not used for the classification of TNPP. Indeed, the toxicity test results were based on TNPP hydrolysis products and not based solely on TNPP. The toxic response and presence of detectable levels of the hydrolysis product in solution confirmed that TNPP had undergone hydrolysis during preparation of the test solution. TNPP is not soluble in water and the major hydrolysis product is nonylphenol. Hence, nonylphenol is likely to be the toxic agent present in the test solutions. The low effect concentration could also be attributed to physical effect although there was no identification of the presence of undissolved material during the test. Therefore, no explanation can be found to explain the toxicity observed during this short-term toxicity testing with daphnids. Indeed, the toxicity observed could not be attributed solely to nonylphenol measured in the test medium if we refer to toxicity of NP as reported in the EU risk assessment available on this substance: "the lowest acute toxicity value for *Daphnia magna* from a fully valid study is a 48-hour $EC_{50(Immobilisation)}$ of 0.085 mg/L" for nonylphenol (EU RAR, 2002b). The test results present some uncertainties so it was not taken into account for the classification of TNPP. The other short-term test available on *Daphnia magna* is not considered valid. Besides, the results from available valid acute studies performed on TNPP with other species conclude to an absence of effect and **does not support a classification for short-term toxicity.**

Based on the chronic toxicity test of Sayers (2009) conducted with *Daphnia magna*, no effects were observed at the solubility limit. Additional testing to further define the EC_{50} value was not conducted since the nominal concentration tested is considered to be representative of the functional solubility limit of the test substance under the test conditions maintained. According to these results, TNPP may not cause short and long-term adverse effects in the aquatic environment. However, the degradation product of TNPP, the NP is classified in Annex I to Directive 67/548/EEC as N; R50-53 without specific concentration limits. So as the degradation product of TNPP may cause long-term adverse effects in the aquatic environment and as TNPP is poorly water-soluble, not readily biodegradable and has a log Kow ≥ 3, it is covered by the **R 53** criterion set out in Annex VI to Directive 67/548/EEC.

On the same rationale, classification **Aquatic Chronic 4 – H413** is proposed according to CLP regulation.

Proposed classification based on Directive 67/548/EEC criteria:

R 53

Proposed classification based on CLP criteria:

Aquatic Chronic 4 – H413

JUSTIFICATION THAT ACTION IS REQUIRED ON A COMMUNITY-WIDE BASIS

TNPP was on the 4th priority list of the Existing Substances Regulation and it is therefore a requirement to harmonise classification for all endpoints justifying classification.

A classification proposal was submitted and discussed at ECB (TC C&L) for health endpoints. Classification R43 was concluded by TC C&L for health. For information, discussions and conclusions as reported in summary records of the corresponding meetings are presented in Appendix I of the present report.

The proposal for environmental classification was on hold as additional testing had been requested and was on-going.

Further to completion of the required test the whole classification proposal is now submitted to ECHA for all endpoints justifying classification.

When considered useful in the view of a discussion on the relevance of classification due to impurities on in relation to the discussion of environmental fate in section 4.3.3, some additional toxicological data are displayed in the present dossier for information.

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APPENDIX I

Collection of discussions on TNPP classification at ECB

TNPP classification was first discussed in written procedure of TC NES III 04. For health effects, it was then discussed at the Technical Committee of Classification and Labelling (TC C&L) in March 2005 and in November 2005. Health classification was concluded at the TC C&L in November 2005. Environmental effects were not further discussed.

Extract from document ECBI/141/04 Rev. 4 - Final Summary table of the written procedure for Substances from TCNES III 04

Substance (Rapporteur)	Index No	Current Classification-S-Phrases	Proposed Classification- S-Phrases	Comments to proposal (HH: human health, ENV: environment)	**Revised Classification S-Phrases**	Comments to revised proposal
TNPP, Tris (nonylphenyl) phosphite (France)	Not listed CAS 26523-78-4		HH: R43 ENV: N: R50-53 S: (2-)46-24-37-60-61	**BE**: HH: agrees. **EL**:HH: agrees. **IRL**: HH: agrees but add Xi (substance is a skin sensitiser) and revise S Phrases to: S24-37-60/61. **NL**: HH: agrees with R43 but R62 should also be discussed. Provide additional information on old skin/eye irritation test. **UK**: HH: agrees. **S**: HH: agrees. **DK**: HH: suggests also application of Repr. Cat. 3 R62. **DE**: HH: Revise chapter on reproductive toxicity according to comments. **UK:** HH: agrees. **S**: ENV: agrees, but give a better rational for classification	----------	

Extract from document ECBI/55/05 - Draft Summary Record - Meeting of the Technical Committee C&L on the Classification and Labelling of Dangerous Substances - Arona, 15-18 March 2005

TNPP, Tris (nonylphenyl) phosphate (F) Not in Annex I CAS 26523-78-4 Proposal: R43 ENV: N: R50-53 S: (2-) 46-24-37-60-61

Documents:

ECBI/141/04 Rev. 4 ECB, Final Summary of proposals and comments distributed instead of substance sheets

ECBI/127/04 FR, C&L proposal

F presented their proposal. They proposed no classification for skin irritation and for skin sensitisation based on results of guinea pig maximisation test. Concerning reprotoxic effects there were for fertility two oral studies on rats. A decrease in the number of pups born was seen at 500 mg and a small decrease in fertility. In the other studying the absence of systemic toxicity deaths were seen at the higher dose (1000 mg/kg) – probably due to distoxia – that was discussed at TCNES and considered as a reprotoxic effect. **The Group** provisionally agreed for R43. IND could react in the follow-up period. Based on the possible reaction, MS might comment and reconsider their decision. **NL** had no concerns for R62.

Repr. Cat 3 – R62

D could not find anything in the dossier on quantitative data. They wanted to have quantitative data. They thought that it was a case between R62 and no classification. **F** said that they would revise the proposal upon further discussions of Industry. **NL** and **DK** agreed with that.

ECB said that TNPP will end up now in the regular follow-up as the written procedure was over and the substance is in the pipeline for the normal procedure. Reprotoxicity was postponed to the next meeting.

7.6.1.1 Conclusion: The TC C&L agreed to classify the substance as R43. The Repr. Cat. 3; R62 classification will be discussed at the next meeting.

Extract from document ECBI/60/05 Rev. 3 - Draft Summary Record of the Meeting of the Technical Committee on the Health Effects of New Substances, Pesticides, Biocides, Existing Chemicals, and on General Issues –

Ispra, 14 - 17 November 2005

TNPP, Tris(nonylphenyl)phosphite (F042)

(CAS number 26523-78-4, EC number 247-759-6)

Not in Annex 1

Proposal: R43 - N; R50-53

ECBI/127/04 Classification proposal and Rev. 1

In **March 2005** R43 was provisionally agreed. Some member states were concerned over the reproductive toxicity and France submitted a revised document (Rev 1) in the follow-up period.

France introduced their paper (Rev 1) in which, following earlier requests, a detailed review of fertility data had been undertaken. The paper concluded that there was no case for classification for fertility.

With the exception of Denmark, who expressed a strong reservation, the Group agreed that no classification for fertility was required.

APPENDIX II

Summary explanation why the new studies have been required by Commission Regulation (EC) No 466/2008 :

Decisions taken to perform tests on TNPP result from the last TC NES meeting (TC NES I '08).

- **Acute toxicity test with *Daphnia magna* and long term *Daphnia* test (depending on outcome of acute *Daphnia* test):** The Rapporteur had identified some uncertainties in the acute toxicity test with *Daphnia* and the test had been redone with measurements of both TNPP and NP. The test would provide more information on the formation of NP during the toxicity tests. The Rapporteur expected that NP would not be formed in the toxicity tests. It was discussed during the last TC NES meeting that for poorly soluble substances it might take time before effects could be observed and that might be a reason for not seeing effects in short term tests, whereas effects might be shown in long term tests. Moreover, the results of the acute test could eventually be used to determine the test concentration range of the long term *Daphnia* study. Consequently, a long term *Daphnia* test has been required in order to know the effects of TNPP on aquatic organisms. Indeed, due to the low solubility of the substance uptake by filtering organisms such as *Daphnia* occurred not only via water but also via suspended matter, for example through adhesion to algae.

- **Information on structure of TNPP:** Information on structure of TNPP has been required for the evaluation of the bioaccumulation potential of the substance. Indeed, the molecular dimensions Dmax and Deff had been estimated with Molecular Operating Environment (MOE) software. In the discussions of the PBT WG it had been noticed that the MOE software seemed not to calculate the parameter Dmax. UK recommended during the TC NES meeting to double check what exactly had been calculated and if possible to compare with OASIS prediction. ECB concluded that the Rapporteur was asked to have further look into the calculations used for the molecular diameter and to base the conclusion on bioaccumulation potential on an evaluation of all weight of evidence including the (lack of) toxic effects. *(This information is not available at this time).*

- **Information on solubility:** The improvement of the analytical method led to perform a new water solubility measurement. This need was confirmed by the QSARs estimate which showed that TNPP is insoluble in water.

- **Log Kow determination:** ECB noted that in this section the basis was laid for the sensitivity analysis using a range of log Kow values from 7 – 22. Industry recommended the use of a higher value of log Kow in the sensitivity analysis. Industry believed that a log Kow of 7 was not reliable. Industry emphasised that it was not likely that TNPP does bioaccumulate in fish, a higher value was also supported by QSAR estimates. Industry concluded that the higher value of log Kow was more realistic. The Rapporteur explained that the upper value of the log Kow range had been chosen because it was the highest value obtained with QSARs. The Rapporteur reminded though that the QSARs could not be considered valid above log Kow of 10, as indicated in the TGD. Therefore the Rapporteur was reluctant to use the upper value in the risk assessment. The Rapporteur noted that the value of 7 might be too low, but the true hydrophobicity of TNPP was unknown.

Consequently, the TC NES supported the request to do a Kow measurement using HPLC method based on OECD guideline 117. We noted that log Kow was used for the evaluation of the bioaccumulation potential of the substance.

- **Hydrolysis test:** ECB noted that the hydrolysis study was a crucial test and the conclusions from the test affected the rest of the risk assessment.
  The first hydrolysis study (2001) suffered from serious problems. It was not known what was happening in that study. There was a lack of material balance. The LOQ was high and that was assumed to be the water solubility. Therefore the study was interpreted improperly. Then industry had asked TNO to provide a new hydrolysis study according to the OECD guidelines. TNO had established a much lower LOQ and they used an indirect way to show whether TNPP did hydrolyse or not because it is insoluble in water. They did this both by measuring in the calibration solutions which showed that the amount of nonylphenol was the same. Then they used the water samples where TNPP was added to show if nonylphenol was formed. TNO was not able to detect more nonylphenol then was present initially in the samples as impurity, thereby showing that no further nonylphenol was formed in the 24h study that they conducted.

  Industry informed the meeting on recent developments on the hydrolysis study of 2004. The testing laboratory had used TNPP with linear NP as reference standard. Also a sensitive method was developed for the detection and quantification of linear NP. Commercial NP contained largely branched NP. So if NP would be formed, it would be the branched NP and that would not have been detected in the 2004 hydrolysis study. Therefore the relevance of the 2004 study was questionable. Industry was looking further into the possibilities of doing a new test. ECB noted that this particular hydrolysis study was very relevant for the whole risk assessment as the meeting had come to the conclusion that hydrolysis of TNPP did not take place under environmental conditions on the basis of this study. Therefore if this study was questioned, large parts of the risk assessment would have to be revisited on the basis of these comments. ECB noted that a repeat study might be necessary. Industry agreed that a new study was urgently needed to measure hydrolysis. ECB asked the Rapporteur to evaluate the results of the new study and to consider the results in a revised risk assessment.

- **Sediment test with *Lumbriculus variegatus*:** it appeared that the target environmental compartment was sediment due to the low water solubility and high log Kow of TNPP. The Rapporteur pointed out that conclusion (i) was proposed for sediment for all stages of the life cycle of TNPP because of the absence of data on toxicity of TNPP towards benthic organisms. Considering the low solubility in water and the suspected high adsorption potential of TNPP toxicity to sediment dwelling organisms should be studied.
  UK agreed that further sediment testing could be useful given all difficulties to test surface water exposure with *Daphnia*. Perhaps a single limit test with *Lumbriculus* could be done just to test out that there is no observed chronic toxicity. Maybe that could be combined with some bioaccumulation testing to get some idea on this at the same time. *Lumbriculus* was the preferred species because the ingestion route was addressed. If the test showed no long term toxicity, this would mean that the substance was not bioavailable. The TC NES agreed to ask for a *Lumbriculus* test.

- **Monitoring data for sites with PEC/PNEC>1:** Monitoring data have been required in order to refine the PEC value and then recalculate the Risk Characterisation Ratio when it was higher than 1. *(This information is not available at this time).*