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Toxicological Evaluation and Limit Values for Nonylphenol, Nonylphenol Ethoxylates, Tricresyl, Phosphates and Benzoic Acid

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1 General description

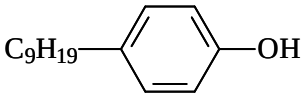
1.1 **Identity**

Nonylphenol (NP) is the commercially most important member of the group of alkyl phenols. The term “nonylphenol” represents a large number of isomeric compounds, varying in the point of attachment of the nonyl group to the phenol molecule, and in the degree of branching in the nonyl moiety. Commercially produced nonylphenols are predominantly 4-nonylphenol (para-nonylphenol) with a varied and undefined degree of branching in the alkyl group, while very little straight chain nonylphenol is present (EU-RAR 1998).

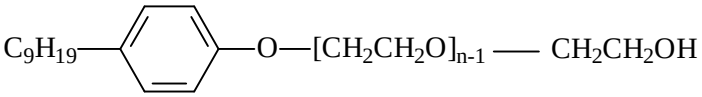
Similarly, nonylphenol ethoxylate (NPE) is the most important alkylphenol ethoxylate. NPE accounts for approximately 85% of alkylphenol ethoxylate production (Anonymous 1997). An NPE is composed of a nonyl chain, usually branched, attached to a phenol ring (hydrophobe moiety) which is combined, via an ether linkage, with one or more ethylene oxide or polyoxyethylene units (hydrophile moiety).
A particular NPE is identified by the length of the polyoxyethylene chain (average number of ethylene oxide units, abbreviated EO). NPEs of a particular average ethylene oxide chain length, produced by different manufacturers, may differ in ranges of ethylene oxide chain lengths.

Molecular formula: NP: $C_{15}H_{24}O$
NPE: $C_{15}H_{24}O(C_2H_4O)_n$

Structural formula:



Nonylphenol



Nonylphenol ethoxylate, generalised formula
n = number of ethyle oxide units

Molecular weight: NP: 220
NPE: 220 + n x 44
where n is the number of ethoxylene units (n can vary from 1-100).

CAS-no.: Nonyl phenol: 84852-15-3

Nonylphenol ethoxylate: A number of CAS numbers exist for the various NPEs
with EO=1: 104-35-8, 27986-36-3
with EO>1: 9016-45-9, 26027-38-3, 68412-54-4
with EO=2: 20427-84-3, 27176-93-8
with EO=4: 7311-27-5
with EO=8: 27177-05-5
with EO=9: 26571-11-9
with EO=10: 27177-08-8

Synonyms: Nonylphenol: NP; isononylphenol; phenol, nonyl-, branched; para-nonylphenol; monoalkyl (C_{3-9}) phenol.

Nonylphenol ethoxylate: NPE; nonylphenol polyoxyethylene ether; nonylphenol polyethylene glycol; nonylphenol polyethylene glycol ether; polyoxyethylene nonylphenol ether.

1.2 **Physical / chemical properties**

Description: NP is a clear to pale yellow viscous liquid with a slight phenolic odour (Merck 1996).

NPEs with between 1 and 13 ethylene oxide units are liquid. NPEs with 14 and 15 ethylene oxide units are paste-like liquids. Viscosity increases with increasing ethylene oxide chain length, and NPEs with 20 or more ethylene oxide units are waxy solids. Colour varies from colourless to light amber. NPEs with higher numbers of ethylene oxide units are opaque. (CIR 1983).

Purity: NP: 90% w/w. Impurities: 2-nonylphenol (5% w/w); 2,4-dinonylphenol (5% w/w) (EU-RAR 1998).

NPE: no data have been found. The same impurities as in the starting material (NP) may be expected. Possible content of traces of ethylene oxide or its degradation product, 1,4-dioxane (CIR 1983).

Melting point: NP: Substances of this type (oily) do not have a clear melting point. Various values have been reported, probably owing to differences in the alkyl chain structure. The values are: -10°C, -8°C, 10 °C , and <20 °C.

NPE: “Solidification points” for nonylphenols

	with varying average lengths of the ethylene oxide chain: -6°C (EO=7), -1.0-1.1 °C (EO=8.5), -2.5-4.0 °C (EO=9.5), 6 °C (EO=13), 19-21 °C (EO=15), -5.0- -3.0 °C (EO=30), 67 °C (EO=40).
Boiling point:	NP: 290-310°C. However, some thermal decomposition probably occurs before this temperature is reached. NPE: -
Density:	NP: 0.95 g/ml (at 20°C) NPE: 0.98-1.08 (at 25°C)
Vapour pressure:	NP: 0.0023 mmHg (0.3 Pa) at 20°C NPE (9 EO): <0.075 mm Hg (<10 Pa)
Concentration of saturated vapours:	-
Vapour density:	-
Conversion factor:	1 ppm = 9.15 mg/m^3 20°C 1 mg/m^3 = 0.109 ppm 1 atm
Flash point:	NP:141-155°C NPE: >150 °C
Flammable limits:	-
Autoignition temp.:	NP: 370°C NPE: (with 9 ethylene oxide): 425 °C
Solubility:	NP: Water: Practically insoluble, 6 mg/100 ml (at 20°C). NPE: Water: >0.1 g/100 ml (at 20°C) (9 EO). For NPEs, water solubility is increased by alkyl branching and is directly proportional to the number of ethylene oxide units. NPEs are water soluble when the number of ethylene oxide units exceeds 6. The NPE most commonly used in cleaning products has 9-10 ethylene oxide units.
$logP_{octanol/water}$:	NP: 4.48 NPE: -
Henry's constant:	NP: 1.02 Pa m^3/mole NPE (with 6 ethylene oxide units):4.1 x 10^{-12} atm x m^3/mol (HSDB 1997).

pK_a-value:	NP: Estimated value 10.25 NPE: -
Stability:	-
Incompatibilities:	-
Odour threshold, air:	-
References:	CIR (1983), EU-RAR (1998), HSDB (1997), IUCLID (1996), Superfos Kemi a/s (1997) Talmage (1994).

1.3 **Production and use**

Nonylphenol
NP is manufactured by reacting mixed nonenes with phenol. The nonyl group, which may be branched or linear, may be linked to the ring either ortho, meta or para to the OH group. In the EU, 78,000 tonnes of nonylphenol were produced in 1994 (EU-RAR 1998).

NP is used as a starting material in the synthesis of NPEs, and as a monomer in polymer production.

Nonylphenol ethoxylate
NPEs are manufactured by reacting NP with ethylene oxide. A polyethylene oxide chain of any desired length can be built up by continued introduction of ethylene oxide into the reaction mixture. Such a reaction yields NPEs with a mixture of ethylene chain lengths, and the number of ethylene units used to describe the product is the average number (Swisher 1970). During base catalysed ethoxylation of nonylphenol, ethylene oxide preferentially reacts with the free nonylphenol and only when this has all reacted do longer ethylene oxide chains form. Nonylphenol ethoxylates have much narrower homologue distributions than alcohol ethoxylates (ICI datasheet for Synperonic NP surfactants).
880 million pounds (4 mio metric tonnes) of alkyl phenol ethoxylates are used annually throughout the world. 80-85% are sold as nonylphenol ethoxylate (NPE), over 15% as octylphenol ethoxylate, and 1% each as dinonylphenol and dodecylphenol ethoxylates (Anonymous 1997).
In the EU, 109,808 tonnes of nonylphenol ethoxylates were produced in 1994 (EU-RAR 1998).

NPEs are non-ionic surfactants. They are used industrially, as ingredients in institutional cleaners and detergents, and in household cleaning and personal-care products. Industrially, NPEs are used for emulsion polymerisation and polymer stabilisation, textile processing, in agricultural chemicals, pulp and paper processing, metal and mineral processing, latex paints, wetting agents and emulsifiers, foaming agents, inks, adhesives, and pharmaceuticals (Anonymous 1997).

1.4 **Environmental occurrence**

NP and NPE are not known to exist in nature.

NP is released to the environment from production and use as a chemical intermediate, in the polymer industry, and as nonylphenol itself. The major part (95%) is released to water. The proportion released to air is low (1%), while approximately 4% is released to soil. Further, NP is released from NPE. NP has a low vapour pressure, a low water solubility, and has a strong tendency to adsorb to soils and sediments.

NPE is primarily released to the environment as a result of use. As for NP, the major part (85%) is released to water, while the release to soil amounts to 13%, and to air 2.5% (EU-RAR 1998).

Air
NP: NP has not been measured in the atmosphere (EU-RAR 1998).
NPE: No data have been found.

Water
NP has been found in surface water, sea water, and ground water (data from Switzerland, United Kingdom, USA, and Croatia). A typical value was 1 µg/l, and the highest value measured was 180 µg/l (River Aire, UK) (EU-RAR 1998).

NPEs have been found in European surface water in concentrations ranging from below the limit of detection to 59µg/l (Talmage 1994).

Soil
In sludge from waste water treatment plants, concentrations of NP in the order of gram per kg dry weight have been found. In soil treated with sludge, 4.7 mg/kg has been found (EU-RAR 1998).

In river sediments, NPE concentrations of the order of mg per kg dry weight have been measured (Talmage 1994).

Foodstuffs
NP was detected in raw beef samples, concentration not stated (HSDB 1997).

1.5 **Environmental fate**

NP is not readily biodegradable. Several mechanisms of microbial aromatic ring degradation have been reported, the most common being formation of catechol from phenol, followed by ring scission between or adjacent to the two hydroxyl groups (Talmage 1994).

NPEs may degrade into nonylphenol. During degradation NPEs' ethylene oxide units are cleaved off the ethylene oxide chain until only short-chain NPE remain, typically mono- and diethylene oxides. Oxidation of these oligomers creates the corresponding carboxylic acids. This leaves several degradation products: short-chain ethoxylates, their carboxylic acids, and nonylphenols (Anonymous 1997). The rate of biodegradation seems to

decrease with increasing length of the ethylene oxide chain (Talmage 1994).

Air
NP released to the atmosphere will exist in the vapour phase and is thought to be degraded by reaction with photochemically produced hydroxyl radicals, with a calculated half-life of 0.3 days.

No data have been found for NPE.

Water
Abiotic degradation of NP is negligible. Biodegradation does not readily take place. The half-life in surface water may be around 30 days (EU-RAR 1998).

No data have been found for NPE.

Soil
NP in soil will have no mobility (HSDB 1997). Biodegradation of NP in soil is slow, and may occur in steps, each step characterised by a certain rate of degradation, as shown in field tests. The half-life in soil is probably around 30 days (EU-RAR 1998).

No data have been found for NPE.

Bioaccumulation
NP bioconcentrates to a significant extent in aquatic species. Excretion and metabolism is rapid (EU-RAR 1998).

No data have been found for NPE.

1.6 **Human exposure**

The possible routes of human exposure to NP and NPEs are dermal contact and inhalation by workers involved in the manufacture and use, dermal and inhalation exposure of consumers from household pesticide products, dermal contact to cleaning products and cosmetics, mucous membrane contact to spermicides; inhalatory exposure via the environment through air, and oral exposure via the environment through drinking water and food.

2 Toxicokinetics

2.1 **Absorption, distribution**

Inhalation
No data have been found for either NP or NPE.
However, on the basis that NP appears to be readily absorbed from the gastrointestinal tract and in view of its high partition coefficient (approximately 4.5) (EU-RAR 1998) it is assumed that significant absorption via the inhalation route will occur.

Oral intake
Knaak et al. (1966) administered ^{14}C-labelled nonylphenol, ^{14}C-labelled nonylphenol ethoxylate (9 ethylene oxide units), and ^{14}C-labelled polyoxyethylene, orally or intraperitoneally to male rats (4 rats per group). Daily urine and faeces samples were collected and analysed for ^{14}C over a 7-day period, while exhaled CO_2 samples were collected and analysed for ^{14}C over a 4-day period. For NP and NPE, a similar pattern of excretion was found. About 70% of the administered radioactivity was excreted via faeces, and 20% via the urine. Most of the radioactivity was excreted within 4 days after administration. No radioactivity was detected in exhaled CO_2. The main part of the urinary NP and NPE metabolites were found to be acidic and were believed to be glucuronic acid conjugates of nonylphenol.

The toxicokinetic behaviour of radiolabelled nonylphenol was investigated in two male volunteers, aged 29 and 58 years (Müller 1997 - quoted in EU-RAR 1998). Ring ^{14}C-labelled nonylphenol was administered to one volunteer as a single oral dose of 5 mg (66 µg/kg bodyweight) and to the second volunteer as a single intravenous dose of 1 mg (14 µg/kg). Blood, urine and faeces were collected from the first volunteer at intervals for up to 56 hours after administration. Blood samples only were taken from the second volunteer, for up 24 hours. The biological samples were analysed for nonylphenol and nonylphenol conjugates (glucuronide and sulphate) by gas chromatography/mass spectrometry (it is not clear why radiolabelled nonylphenol was used). Recovery experiments using spiked blood, urine, faeces and adipose tissue samples confirmed the efficiency of the analytical extraction technique. Following oral administration, the concentration of nonylphenol and nonylphenol present as conjugates in the blood both peaked at about 1 hour; peak concentration of nonylphenol present as a conjugate was 86 ng/g blood, which was some 100-fold greater than that of unconjugated nonylphenol. For intravenous administration, the highest concentrations of nonylphenol, at 0.6 and 0.2 ng/g blood for unconjugated and conjugated compound, respectively, were seen at the first sampling point of 30 minutes; at all time points the concentrations of unconjugated and conjugated nonylphenol were of the same order of magnitude. For both the oral and intravenous routes, the time courses of blood concentration were indicative of an initial phase of distribution from the blood to a second compartment (presumably the lipid compartment) followed by a slower elimination phase. Comparison of the AUCs for the oral and intravenous

routes suggested that oral bioavailability of unconjugated nonylphenol was about 20%. Analysis of the urine samples showed that about 10% of the oral dose was excreted in urine as unconjugated or conjugated nonylphenol, most of which was eliminated within eight hours. Only about 1.5% of the oral dose was excreted in the faeces during the 56-hour collection period.

Müller (1997 - quoted in EU-RAR 1998) also measured the nonylphenol content of 25 samples of adipose tissue taken at autopsies of persons thought to have had no occupational exposure to alkyl phenols. The measured tissue concentrations were all within the range of background contamination found in the analytical "blank" samples. The author indicated that all reasonable precautions were taken to minimise contamination during analysis.

Dermal contact
No data have been found. On the basis that nonylphenol appears to be readily absorbed from the gastrointestinal tract, and in view of its high partition coefficient, and since dermal LD_{50}-values have been determined for NP and NPE, it is assumed that significant absorption via the dermal route will occur. The limited dermal toxicity data that are available indicate that the oral and dermal LD_{50}-values for nonylphenol are similar.

2.2 **Elimination**

See above

2.3 **Toxicological mechanisms**

There are no data on toxicological mechanisms for either NP or NPE with the exception of oestrogenic effects of NP. NP is believed to interact directly with the oestrogen receptor (Odum et al. 1997).

3 Human toxicity

3.1 **Short term toxicity**

Inhalation
No data have been found.

Oral intake
No data have been found.

Dermal contact
Cosmetic formulations containing NPEs with 4, 9, or 12 ethylene oxide units in varying concentrations have been tested for skin irritation in human volunteers (CIR 1983). The results show a range of effects from no to mild skin irritation.

NPEs with 4, 9, 15, or 50 ethylene oxide units were non-sensitising in human test subjects (CIR 1983).

Mucous membrane contact
A 10% NPE spermicidal film caused mild local vaginal irritation in 2 out of 30 women (CIR 1983).

3.2 **Long term toxicity**

No data have been found.

3.3 **Reproductive / developmental effects**

APEs and NPEs (of ethoxylate chain length 9 and 11) are used as spermicides. The results of three large-scale epidemiological studies do not indicate a relationship between use of spermicides and delivery of malformed infants (IPCS 1998).

3.4 **Genotoxic effects**

No data have been found.

3.5 **Carcinogenic effects**

No data have been found.

4 Toxicity, animal data

4.1 **Short term toxicity**

Inhalation

nonylphenol

The LC_{50}-value of NP is unknown. Four hours was the maximum survival time for rats inhaling a "concentrated vapour" of NP, the concentration was not stated (Smyth et al. 1962, 1969 - quoted from Talmage 1994).

The sensory irritation potential of nonylphenol has been investigated (EU-RAR 1998). Atmospheres of saturated vapour concentration and one tenth saturated vapour concentration, nominally 3636 mg/m^3 (400 ppm) and 267 mg/m^3 (30 ppm), respectively, were tested. Groups of five female CD-1 mice were exposed, nose only, to each concentration and the respiration rate was monitored using pressure plethysmography. The duration of exposure to the nonylphenol vapour was not reported. The proportion of liquid particulate material in the test atmospheres was determined, and found to be approximately 1% of the nominal concentration, an amount considered unlikely to have a significant influence on the results. At 3636 mg/m^3 a mean respiratory rate depression of about 25% was found during exposure. However, at 267 mg/m^3 there were no changes in the respiratory rate. These results suggest that nonylphenol can cause mild sensory irritation to the respiratory tract at high exposure levels.

nonylphenol ethoxylate

The LC_{50}-value for NPE is unknown, although several studies of acute inhalatory toxicity have been performed (Table 1). No further details about the concentrations of the test atmospheres were given in the reports.

Table 1. Inhalatory toxicity of nonylphenol ethoxylates with various ethylene oxide (EO) chain lengths (compiled from CIR 1983 (C) and Talmage 1994 (T))

Number of EO units	Test atmosphere	Design	Result (Reference)
4	1% aqueous aerosol dispersion; 0.0213 ml/l	6 male rats exposed for 8 h; 14-day observation period	no mortality (Mellon Institute, 1963 (C))
7	1% aqueous aerosol dispersion; 0.025 ml/l	6 male rats exposed for 8 h; 14-day observation period	no mortality (Mellon Institute, 1963 (C))
7	concentrated vapour at ambient temperature	6 male rats exposed for 6 h, 10-day observation period	no mortality (Monsanto Chemical

			Company, 1972 (T))
9	concentrated vapour at ambient temperature	6 male rats exposed for 8 h; 14-day observation period	no mortality (Mellon Institute, 1963 (C))
9	concentrated vapour at 179 °C.	6 male rats exposed for 4 h; 14-day observation period	no mortality (Mellon Institute, 1963 (C))

Oral administration

nonylphenol

Three unpublished studies performed according to OECD test guideline 401 have yielded oral LD_{50} values of 1200 to 2400 mg/kg for males, and 1600 to 1900 mg/kg for females; presumably the test species was the rat (EU-RAR 1998).

LD_{50} values for NP of 580 (Texaco Chemical Company 1985 - quoted from Talmage 1994), 1300 (Monsanto Chemical Company 1985 - quoted from Talmage 1994), and 1620 mg/kg in rats (Smyth et al. 1969 - quoted from Talmage 1994) have been reported.

nonylphenol ethoxylate

A number of oral LD_{50} values for NPE with various ethylene oxide chain lengths have been reported. These values are presented in Table 2.

Table 2. Oral LD_{50}-values for nonylphenol ethoxylates with various ethylene oxide (EO) chain lengths (compiled from CIR 1983 (C) and Talmage 1994 (T))

Number of EO units	LD_{50} (mg/kg)	Species (Reference; quoted from)
2	3550	rat (Consumer Product Testing Co., 1978; C)
4	5000	rat (Schick, 1967; T)
4	4290	rat (Schick, 1967; T)
4	4800	rat (Monsanto Chemical Company, 1975; T)
4	7400	rat (M.B. Research Labs, 1978; C)
4	4300	rat (Mellon Institute of Industrial Research, 1963; C)
4	>5000	rat (Texaco Chemical Company, 1991; T)
4	5000	guinea pig (Schick, 1967; T)
5	3250	rat (Monsanto Chemical Company, 1975; T)
6	1980	rat (Consumer Product Testing Co., 1978; C)
7	3600	rat (Monsanto Chemical Company, 1975; T)
7	3670	rat (Schick, 1967; T)
7	3670	rat (Mellon Institute of Industrial Research, 1963; C)
8-9	3000	rat (Schick, 1967; T)
8-9	2000	guinea pig (Schick, 1967; T)
9	2600	rat (Smyth & Calandra, 1969)
9	2600	rat (Schick, 1967; T)
9	5600	rat (Monsanto Chemical Company, 1975; T)
9	1410-3000	rat (Mellon Institute of Industrial Research, 1963; C)
9	620	rabbit (Mellon Institute of Industrial Research, 1963; C)
9	4400	rabbit (Industrial Toxicology Labs., 1960; C)
9	840	guinea pig (Mellon Institute of Industrial Research, 1963; C)
9	2000,	guinea pig (Industrial Toxicology Labs., 1960; C)
9	4290	mouse (Mellon Institute of Industrial Research, 1963; C)
9.5	3300	rat (Texaco Chemical Company, 1991; T)
9-10	1600	rat (Olson et al., 1962; T)
10	1300	rat (Mellon Institute of Industrial Research, 1963; C)
10.3	4800	rat (Monsanto Chemical Company, 1975; T)
10.5	2500	rat (Schick, 1967; T)
12	2170	rat (Monsanto Chemical Company, 1975; T)
12	3900	rat (Texaco Chemical Company, 1991; T)
12	5100	rat (Consumer Product Testing Co., 1978; C)
12	871-1050	rabbit (Monsanto Chemical Company, 1959; T)
13	3730	rat (Mellon Institute of Industrial Research, 1963; C)
13	5600	rat (Monsanto Chemical Company, 1975; T)
13.5	2500	rat (Schick, 1967; T)
15	2500	rat (Industrial Biology Research and Testing Labs., 1960; C)
15	4000	rat (Schick, 1967; T)
20	15900	rat (Schick, 1967; T)
20	>16000	rat (Schick, 1967; T)

Dermal contact

For NP, a dermal LD_{50}-value of 2031 mg/kg in rabbits has been reported (EU-RAR 1998)

For NPE, the acute dermal toxicity for a number of NPEs with a varying number of ethoxylene oxide units has been determined in rabbits (Table 3).

Table 3. Dermal LD_{50}-values in rabbits for nonylphenol ethoxylates with various ethylene oxide (EO) chain lengths (compiled from CIR 1983 (C) and Talmage 1994 (T))

Number of EO units	LD_{50} (mg/kg)	Reference; quoted from
4	>2000	Monsanto Chemical Company, 1975; T
4	2500	Mellon Institute of Industrial Research, 1963; C
4	>3000	Texaco Chemical Company, 1992; T
5	>3160	Monsanto Chemical Company, 1975; T
7	>3160	Monsanto Chemical Company, 1975; T
7	1800	Mellon Institute of Industrial Research, 1963; C
9	>5010	Monsanto Chemical Company, 1975; T
9	4400	Consumer Product Testing Co., 1978; C
9	2830	Mellon Institute of Industrial Research, 1963; C
9.5	>3000	Texaco Chemical Company, 1992; T
10	>2000	Monsanto Chemical Company, 1975; T
10	2000	Mellon Institute of Industrial Research, 1963; C
12	>10000	Monsanto Chemical Company, 1975; T
12	>3000	Texaco Chemical Company, 1992; T
13	>7940	Monsanto Chemical Company, 1975; T
13	3970	Mellon Institute of Industrial Research, 1963; C
40	>10000	Monsanto Chemical Company, 1975; T
40	>5000	Mellon Institute of Industrial Research, 1963; C

Irritation
NP is corrosive on contact with skin and is a severe eye irritant. Exposure to the saturated vapour may lead to mild sensory irritation of the respiratory tract (EU-RAR 1998).

4.2 **Long term toxicity**

Inhalation
No data have been found.

Oral administration
NP 28-day study
In a 28-day study (quoted in IUCLID 1996) performed according to OECD guideline 407 (in 1981), doses of 0, 25, 100 or 400 mg/kg/day of NP were administered to Sprague-Dawley rats in the diet. At the highest dose level, body weight, food consumption, and food utilisation was statistically significantly reduced in both sexes. Also at the highest dose level, for male animals only, relative kidney, liver and testes weights were statistically significantly increased (by 20%), blood urea and cholesterol levels were statistically significantly increased, and glucose was statistically significantly reduced. Histopathological examination revealed hyaline droplet accumulation in the renal proximal tubules, and a minor vacuolation in the periportal hepatocytes. Females did not show these effects. In the EU-RAR (1998), the NOAEL is considered to be 100

mg/kg/day.

NP 90-day study

In a 90-day study performed according to EPA guidelines and of GLP quality, Sprague-Dawley rats were administered NP in the diet at concentrations of 0, 200, 650, or 2000 ppm; corresponding to a calculated (in the report) intake of 0, 15, 50 or 150 mg/kg/day (Cunny et al 1997). At the highest dose level, body weight, food consumption, and food utilisation was statistically significantly reduced for both sexes. Haematology, serum chemistry, and ophthalmoscopy findings, oestrous cycle pattern, and spermatogenesis were not affected by treatment. In males, a statistically significant dose-related increase in absolute and relative kidney weight, without accompanying histopathological or clinical-chemical findings was found (actually, a *de*crease in the occurrence of hyaline droplets was found at the highest dose level). In females of the highest dose group, absolute ovary weight was slightly decreased, without accompanying histopathological changes. Relative ovary weight was not affected. Relative liver weight was increased by 10% in both sexes at the highest dose, and in males only at the next-highest dose level. The NOAEL was considered by the authors to be 50 mg/kg b.w./day.

NP multigeneration study

Further information on repeated dose toxicity can be derived from a good-quality multigeneration study (NIEHS 1998 - quoted in EU-RAR 1998). This study is also described in section 4.3. Groups of 30 male and 30 female Sprague-Dawley rats were exposed to nonylphenol in the diet at concentrations of 0 (control) 200, 650 or 2000 ppm over three generations. Calculated nonylphenol intakes were, respectively, about 0, 15, 50 and 160 mg/kg/day during non-reproductive phases. The F0 generation were exposed for 15 weeks, the F1 and F2 generations from soon after birth to about 20 weeks of age and the F3 generation from birth to about 8 weeks of age.

Evidence of general toxicity was seen in adults of all generations, although there were no treatment-related clinical signs, mortalities or adverse effects on food consumption. At 160 mg/kg/day, bodyweight gain was reduced in comparison with controls in adults across all generations, with the terminal bodyweight being about 10% lower than the controls. Similar reductions in bodyweight gain were also seen at 50 mg/kg/day in F1 females, F2 males and F3 females. Relative kidney weights were increased at 50 and/or 160 mg/kg/day in adult males of the F0, F1 and F2 generations and also at 160 g/kg/day in F1 adult females. Histopathological examination revealed an increase, although often without a convincing dose-response relationship, in the incidence of renal tubular degeneration and/or dilatation in adult males from all generations and all nonylphenol treated groups; similar findings were reported for adult females at 160 mg/kg/day in the F1, F2 and F3 generations and at 15 and 50 mg/kg/day in the F3 generation. These data are shown in table 4a and b.

Table 4a Number of animals with histopathological abnormalities in the kidney (n=10) Males

Gen	Finding	Dose level (mg/kg/day)			
		0	15	50	160
F_0	Renal tubule degeneration	1	3	5	5
	Renal tubule dilatation	0	1	0	0
F_1	Renal tubule degeneration	1	2	7	8
	Renal tubule dilatation	1	1	0	2
F_2	Renal tubule degeneration	3	6	6	6
	Renal tubule dilatation	1	2	0	4
F_3	Renal tubule degeneration	0	7	10	2
	Renal tubule dilatation	0	0	3	3

Table 4b Number of animals with histopathological abnormalities in the kidney (n=10) Females

Gen	Finding	Dose level (mg/kg/day)			
		0	15	50	160
F_0	Renal tubule degeneration	3	3	0	0
	Renal tubule dilatation	0	0	1	0
F_1	Renal tubule degeneration	0	1	1	6
	Renal tubule dilatation	0	0	0	3
F_2	Renal tubule degeneration	1	2	0	4
	Renal tubule dilatation	0	0	0	1
F_3	Renal tubule degeneration	0	8	9	7
	Renal tubule dilatation	0	0	1	1

NPEs 90-day studies

Smyth & Calandra (1969), reported on toxicity studies on alkyl phenol ethoxylates including NPEs. Ninety-day feeding studies in rats have been performed with NPEs with 4, 6, 9, 15, 20, 30, and 40 ethylene oxide units. Test materials were of commercial grade and were added to the diet. The various studies were performed at five different laboratories in the years 1959-65 using individual test protocols. Results are thus not directly comparable. Dose groups consisted of 10 male and 10 female rats, except for one study (Shelanski), where groups consisted of 15 rats of “mixed sexes”. The results are presented in Table 5.

In the five studies by Industrial Bio-Test laboratories (NPEs with 4, 6, 15, 20, or 30 ethylene oxide units; doses are shown in Table 5) haematology was studied in 5 rats of each sex from the highest dose level and

the control group before treatment and after 11 weeks. All rats were studied for gross pathology. Livers, kidneys, and testes were weighed, and 33 tissues were examined histopathologically from 5 rats of each sex at the highest and control levels. In order to discriminate between poor palatability and toxic effect, 25-day paired-feeding studies were performed at dose levels for which weight gains were shown to be lower than those of the control groups. For NPEs with 4 or 6 ethylene oxide units, effects included growth retardation and increased absolute and relative liver weight. For NPEs with 15 or 20 ethylene oxide units only retarded growth was found. All effects on growth rate were judged to be due to poor palatability of the diets. With respect to the increased liver weights (for NPEs with 4 or 6 ethylene oxide units), no accompanying histopathological findings were found (however, only the highest dose level was examined histopathologically). The liver response was interpreted by the authors as an increase in parenchymatous tissue resulting from increased enzyme activity in relation to metabolism of the test substances. For NPE with 30 ethylene oxide units no effects at all were found.

In the study of NPE with 9 ethylene oxide units by Mellon Institute gross pathology was studied on all rats at sacrifice, livers and kidneys were weighed, and 16 tissues were studied from 12 controls and from 8 rats from the highest dose group, while only 3 tissues were examined in 10 rats on the other two dose levels. Effects included growth retardation and increased relative liver weight at the two highest dose levels (250 or 1250 mg/kg/day). The liver weight increase was accompanied by cloudy swelling, intracellular lipoid, and reduced polysaccharide, while focal hepatic cell necrosis was found at the highest dose level.

In the study by Shelanski of NPE with 9 ethylene oxide units, the 2 lightest male and female rats in each group were sacrificed after 8 weeks. Gross examination was made. On animals from the highest dose group, histopathological examination of 19 tissues was made. After 90 days, all remaining rats were sacrificed and subjected to macroscopic examination. Nine organs were weighed, and histopathological examination was made of 19 tissues from the 2 lightest males and females in each group. In the highest dose group, 11 of 15 rats died during the study. At 0.64% (300 mg/kg/day) and more in the diet, weight gain was retarded. In the two highest dose groups, rats were emaciated. This was judged to be referable to poor palatability by the authors. Food intake, however, was not significantly lower. This apparent contradiction was not discussed by the authors. No histopathological changes indicating toxic effects were seen.

In the Dow studies of NPE with 9 or 40 ethylene oxide units, haematocrit, white blood cell total and differential counts, and haemoglobin were determined on 5 females of the control and the two highest dose levels prior to sacrifice. Six organs were weighed and 8 organs were studied histopathologically. For NPE with 9 ethylene oxide units, at the lowest dose level, 0.1% (100 mg/kg/day), no effects at all were found. At 0.3% (200 mg/kg/day) and above, relative liver weights were high. At the highest dose level, 1.0% (900 mg/kg/day), relative kidney and spleen weights were high, and growth was reduced. In the liver, petecchial areas of central lobular granular degeneration and necrosis were seen. For NPE

with 40 ethylene oxide units, no effects were found at or below 0.3% (200 mg/kg/day). At 1% (700 mg/kg/day)and above relative liver weights of male rats were non-significantly heavier than controls, with general cloudy swelling and slight central lobular granular degeneration and necrosis at 3% (2000 mg/kg/day).

Table 5. Results of 90-day feeding studies in rats with nonyl phenol ethoxylates of various ethylene oxide (EO) chain lengths (compiled from Smyth & Calandra 1969)

Laboratory and year (EO)	Dose levels (mg/kg b.w./day)	Growth retardation	Increased absolute liver weight	Increased relative liver weight	Histopathology of liver	Other effects
Ind. Bio-Test	40					
Lab. 1963-65	200			x	n.d.	
(4)	1000	x	x	x	no	
Ind. Bio-Test	40			x	n.d.	
Lab. 1963-65	200		x	x	n.d.	
(6)	1000	x	x	x	no	
Mellon Inst.	10					
1959-65	50					x [1]
(9)	250	x		x	x[2]	
	1250	x		x	x[3]	
Shelanski 1960	4 (0.01%)					
(9)	20 (0.04%)					
*)	60 (0.16%)					
	300 (0.64%)	x				
	1300 (2.5%)	x				
	5% in diet	x				x, mortality
Dow 1961	100 (0.1%)					
(9)	200 (0.3%)			x	x[4]	
*)	900 (1.0%)	x		x	x[4]	x[5]
Ind. Bio-Test	40					
Lab. 1963-65	200	x			n.d.	
(15)	1000	x			no	
Ind. Bio-Test	200					
Lab 1963-65	1000					
(20)	5000	x				
Ind. Bio-Test	200					
Lab 1963-65	1000					
(30)	5000					
Dow 1961	20 (0.03%)					
(40)	70 (0.1%)					
*)	200 (0.3%)				x[6]	
	700 (1.0%)					
	2000 (3.0%)					

1) Low kidney weight in females.
2) Cloudy swelling of central hepatic cords, intracellular lipoid, reduced polysaccharide.
3) Focal hepatic-cell necrosis, intracellular lipoid, reduced polysaccharide.
4) Slight petecchial areas of central lobular granular degeneration and necrosis.
5) Increased relative spleen weight in females & increased relative kidney weight in males.
6) Slight central lobular granular degeneration and necrosis with general cloudy swelling.

n.d.) not done (only the highest dose group was examined histopathologically)

*) In the original report, dose was given as % in diet, and was subsequently calculated in mg/kg/day, based on food consumption data, by the rapporteur.

NPE toxicity in dogs

In the same report (Smyth & Calandra 1969), investigations of NPE toxicity in dogs was described (Table 6). Each dosage of NPE with 4, 6, 15, 20 and 30 ethylene oxide units was administered orally in gelatine capsules to 2 male and 2 female dogs. NPE with 9 ethylene oxide units was administered in the diet, a single dog per dose, and 3 dogs in the control group.

Table 6 Results of 90-day feeding studies in dogs with nonyl phenol ethoxylates of various ethylene oxide (EO) chain lengths . Data for EO=4, 6, 15, 20, 30 from Industrial Bio-Test Labs. (1963-65). Data for EO= 9 from Shelanski (1960). (Both sources quoted from Smyth & Calandra 1969).

No. of EO units	Dose levels (mg/kg b.w./day)	Growth retardation	Increased relative liver weight	Emesis	Other effects
4	40				
	200		x	x	
	1000	x	x	x	
6	40				
	200			x	
	1000		x	x	
9	40				
	640	x			
	50000	x			
15	40				
	200			x	
	1000			x	
20	40				x[1)]
	200		x	xx	
	1000	x	x	x	x[2)]
	5000	x	x		x[2)]
30	200				
	1000				

1) Focal myocardial necrosis or degeneration (microscopically).
2) Death, grossly detectable focal myocardial necrosis, lung hyperaemia.

Cardiotoxicity in the dog

A number of exploratory/confirmatory experiments, with cardiotoxicity as the endpoint of interest, reported by Smyth & Calandra (1969), are presented in Table 7. The details of these studies are not well-described in the publication.

Table 7 Results of studies in dogs with nonyl phenol ethoxylates of various ethylene oxide (EO) chain lengths. Endpoint of interest was myocardial degeneration (compiled from Smyth & Calandra 1969).

Test materials	Size of study	Dose levels and schedule	Cardiac effects
Two NPEs with 20 EO	4 dogs: Each compound was given to 1 male and 1 female	Divided daily doses totalling 1 g/kg/day for 14 days	Focal myocardial necrosis
Two NPEs with 15 EO, one with 17.5 EO, three NPEs with 20 EO; and one with 25 EO	14 dogs: Each compound was given to 1 male and 1 female	1 g/kg/day for 14 days.	One type of NPE with15 EO, NPE with17.5EO, and two types of NPE with 20 EO all caused focal myocardial degeneration.
NPE with 9 EO	not reported	0.0088 g/kg/day for 2 years	No myocardial necrosis
NPEs with 15, 20, 30, or 40 EO	8 dogs: each compound was given to 1 male and 1 female	1 g/kg/day for 30 days	NPEs with 15 or 20 EO caused myocardial degeneration or necrosis, with 30 EO slight changes were seen. With 40 EO normal myocardium.
NPE with 20 EO	2 dogs: 1 male and 1 female	0.20 g/kg/day for 34 days	Myocardial necrosis
NPE with 20 EO	4 dogs: 2 males and 2 females	0.20 g/kg/day; increased gradually to 0.55 g/kg/day; reduced to 0.50 g/kg/day total duration not stated (probably>50 days)	Myocardial degeneration
NPE with 20 EO	4 dogs; 2 dogs in one group,1 dog per group in 2 groups (sex not reported)	1 g/kg/day for ? days. Co-treatment with potassium or thiamine	Myocardial degeneration. No effect of intervention.

(Continued)

Table 7 Results of studies in dogs with nonyl phenol ethoxylates of various ethylene oxide (EO) chain lengths. Endpoint of interest was myocardial degeneration (compiled from Smyth & Calandra 1969).

Test materials	Size of study	Dose levels and schedule	Cardiac effects
NPE with 20 EO	5 dogs; 2 dogs per group in 2 groups,1 dog in 1 group (sex not reported	10 g/kg/day for 12 days. Co-treatment with potassium or thiamine	Focal myocardial degeneration, death. No effect of intervention
NPE with 15 EO	2 puppies (8-10 wks) and 2 adult dogs (>3 yrs)	0.2 g/kg/day	No cardiotoxicity
NPE with 15 EO	4 dogs, 2 male, 2 female	0.2 g/kg/day for 60 days	No cardiotoxicity

Cardiotoxicity in other species

Three cats and 3 rabbits were dosed by gavage with 0.7 g/kg of NPE with 20 ethylene oxide units daily for 14 days. These two species did not develop focal myocardial necrosis (Smyth & Calandra 1969).

Nineteen guinea pigs received doses of 1 g/kg of NPE (2 different commercial varieties) with 20 ethylene oxide units daily for 2 or 3 days. Nine of these animals developed myocardial lesions interpreted as early stages of necrosis (Smyth & Calandra 1969).

Rats did not show any heart lesions after 90 days' feeding at 5 g/kg/day (Smyth & Calandra 1969).

2-year oral administration

NPEs with 4 and 9 ethoxylene oxide units have been administered orally to rats and dogs over periods of 2 years (Smyth & Calandra 1969). Results are shown in Table 8.

rats

Groups of 35 male and 35 female Sprague-Dawley rats, with 5 male and 5 female rats in addition in the highest and control groups received NPE with 4 ethoxylene oxide units at 3 dose levels plus control. After 12 months 5 rats of each sex from the highest dose and control group; and 3 of each sex from the two lower-dosage groups were sacrificed. After 24 months all rats were sacrificed. Livers, kidneys, and testes were weighed. Histopathological examination of 28 tissues was done on 5 rats of each sex in the highest dose and control group. At 200 mg/kg/day females showed a reduced weight gain after 12 months, but not after 24 months. At 1000 mg/kg/day, this effect was also found in male rats.

NPE with 9 ethoxylene oxide units was administered to 3 dose groups plus a control group of 36 male and 36 female Carworth-Elias rats for 2 years. Sixteen rats of each sex were interim sacrificed, at 6 and 12 months. At sacrifice livers and kidneys were weighed, and 11 tissues were histopathologically examined. There was no difference between control and treated rats in any observation made.
No increased frequency of tumours was reported in either rat study.

dogs

NPE with 4 ethoxylene oxide units was administered for 2 years to groups of 3 male and 3 female Beagle dogs in gelatine capsules in dosages 40, 200, and 1000 mg/kg/day. An untreated control group was present.. Haematology and blood and urinary clinical-chemical parameters were measured repeatedly during the study. At sacrifice, liver, kidneys, spleen, heart, brain and testes were recorded, and 28 tissues were examined microscopically. At 200 mg/kg/day, and more pronounced at 1000 mg/kg/day, there was a moderate elevation in serum alkaline phosphatase and relative liver weight, without histopathological changes.
NPE with 9 ethoxylene oxide units was administered in the diet in concentrations of 0, 0.03, 0.09, and 0.27%, corresponding to 0, 8.5, 28, and 88 mg/kg/day (author's calculation), to groups of 3 male and 3 female Beagle dogs for 2 years. Haematology and blood and urinary clinical-chemical parameters were measured repeatedly. At sacrifice liver, kidneys, and heart was weighed, and 21 tissues were examined histopathologically. NPE with 9 ethoxylene oxide units caused an increased relative liver weight at 0.27% in the diet (88 mg/kg/day) without accompanying histopathological findings.

Table 8 Results of 2-year oral studies with nonyl phenol ethoxylates of various ethylene oxide (EO) chain lengths (compiled from Smyth & Calandra 1969) .

No. of EO units, species	Dose levels (mg/kg b.w./day)	Growth retardation	Increased relative liver weight	Other effects
4	40			
rat	200	x		
	1000	x		
9	0			
rat	0.03			
	0.09			
	0.27% in diet			
4	40			
dog	200		x	increase in ALP
	1000		x	increase in ALP
9	8.5			
dog	28			
	88		x	

ALP: alkaline phosphatase

Dermal contact
No data have been found.

4.3 **Reproductive / developmental effects**

Oestrogenic effects of NP and NPE
Some alkyl phenols have been implicated in the hypothesis that low-level exposure can disrupt the human endocrine system, that is, that alkyl phenols may act as endocrine disrupters. Alkyl phenols, including NP, have been shown in laboratory studies to mimic the effects of oestrogen in vitro and in vivo (Lee & Lee 1996, Odum et al. 1997).

The oestrogenic effect of nonylphenol and nonylphenol ethoxylates in fish and Daphnids has been studied by a number of authors. Generally the work shows that nonylphenol and nonylphenol ethoxylates do exhibit oestrogenic activity. For nonylphenol ethoxylates the activity was found to increase with decreasing chain length, with nonylphenol showing the greatest activity. (EU-RAR 1998).

The oestrogenic activity of nonylphenol has been investigated in a number of studies using either recombinant yeast, oestrogen sensitive human breast tumour MCF-7 cells, or a rodent uterotrophic assay response. None of these assays have been validated as an internationally accepted toxicity test method, although the MCF-7 and uterotrophic assays have been established for a number of years as standard assays for oestrogenic activity. It should be noted that the significance to human health of oestrogenic activity detected in these assays has yet to be established. (EU-RAR 1998).

NP effects in rodent uterotrophic assay
The oestrogenic activity of nonylphenol in mammals has been assessed in several studies using an assay based upon the uterotrophic response in the rat. Although not stated, it is assumed that the studies have been performed with commercial grade NP which is the branched type.

In the first study, five groups of immature (aged 20 - 22 days) female rats (six in each group) of a Wistar derived strain received single oral gavage doses of nonylphenol in corn oil on each of three consecutive days (ICI 1996 - quoted in EU-RAR 1998). The dose levels ranged from 9.5 to 285 mg/kg/day. Vehicle and positive (oestradiol benzoate 8 µg/kg, by subcutaneous route) groups were included. One day after the final dose the females were killed and the uterus was removed from each animal and weighed. Absolute uterus weight and bodyweight related uterus weight were statistically significantly increased, in a dose-dependent manner, at levels of 47.5 mg/kg/day and above. The NOAEL was 9.5 mg/kg/day. The uterine response seen in the positive control group was much greater than that of the nonylphenol groups, although a direct comparison of potency is not possible given the differing exposure routes. Similar data from the same laboratory have also been presented in peer-review literature (Odum et al. 1997). This latter report also included oral positive control groups (17ß-oestradiol, 10-400 µg/kg), which indicated that oestradiol was about 1000 times more potent in this assay than nonylphenol.

In a similar assay, groups of ten ovariectomised female Sprague-Dawley rats were dosed once daily for three consecutive days with ethanol/oil suspensions of nonylphenol at levels of 0 (vehicle control), 30, 100 and 300 mg/kg/day (Chemical Manufacturers Association 1997b - quoted in EU-RAR 1998). Positive control groups received ethynyloestradiol in ethanol at levels of 10, 30 and 80 µg/kg/day according to the same dosing regimen. The route of administration was not stated. One day after the final dose the females were killed and the uterus was removed from each animal and weighed. Uterus weights at 300 mg/kg/day were significantly increased (1.5-fold) in comparison with the vehicle control group. A slightly greater response (a 2-fold increase) was seen in the 30 and 80 µg/kg/day positive control groups.

In another uterotrophic assay, groups of three immature (aged 20-21 days) Sprague-Dawley rats each received a single intraperitoneal injection of nonylphenol at dose levels of 0, 1, 2 or 4 mg/animal (approximately 25, 50 or 100 mg/kg) (Lee and Lee 1996). Oestradiol, administered by the same route, served as a positive control. The animals were killed 24 hours later and each uterus was removed, weighed and analysed for protein and DNA content and peroxidase (thought to be a uterotrophic marker enzyme) activity. There was a dose-dependent and statistically significantly increase in uterine weight at all levels, with associated increases in uterine protein and DNA content and uterine peroxidase activity. In further experiments, the uterotrophic activity of nonylphenol was found to be blocked by the co-administration ICI 182,780, an oestrogen antagonist, providing evidence that the effect of nonylphenol is mediated through the oestrogen receptor. Also, the potency was compared with oestradiol; in this assay oestradiol was found to be about 1000 - 2000 times more potent than nonylphenol.

Overall, these *in vitro* and *in vivo* studies show that nonylphenol has oestrogenic activity of a potency that is between 3 to 6 orders of magnitude less than that of oestradiol. The oestrogenic effect of NP appears to be mediated through the oestrogen receptor since its action can be blocked by oestrogen antagonists. The structure of the aliphatic side-chain (nonyl) is believed to be highly important for oestrogenic activity. Linear NP is not oestrogenic, while one or more of the branched-chain isomers may be able to mimic oestradiol in binding to the oestrogen receptor. (Odum et al. 1997).

NP oestrogenic effect in 28- and 90-day study
In the 28-day and 90-day studies of NP described in section 4.2 sexual organ morphology, oestrous cycle pattern, and spermatogenesis were not found to be affected by treatment at any dose level. In the 90-day study the absolute, but not relative, ovary weight in the highest dose group was slightly decreased without accompanying histopathological changes.

NIEHS three-generation study of NP
The effects of nonylphenol on fertility and reproductive performance have been investigated in a comprehensive, good-quality multigeneration study, conducted in compliance with GLP (NIEHS 1998 - quoted in EU-RAR 1998). The overall study design was based on the OECD two-

generation reproduction toxicity study guideline, with an extension to include the production of an F3 generation. This study has previously been described in the present report in relation to long term toxicity. Groups of thirty male and thirty female Sprague-Dawley rats were exposed to nonylphenol via incorporation in the diet at concentrations of 0 (control) 200, 650 or 2000 ppm over three generations. Calculated nonylphenol intakes were, respectively, about 0, 15, 50 and 160 mg/kg/day during non-reproductive phases and rising to around 0, 30, 100 and 300 mg/kg/day during lactation. Nonylphenol exposure commenced for the F0 generation at about 7 weeks of age and continued until study termination when the F3 generation were about 8 weeks old. F0 animals were mated (one male with one female) within each dose group to produce the F1 generation, selected F1 animals were similarly mated to produce the F2 generation and selected F2 animals were mated to produce the F3 generation. For the F0 generation and retained F1, F2 and F3 animals, clinical signs of toxicity, bodyweights and food consumption were reported. Oestrous cycles were monitored prior to mating. At the necropsy of adult animals, sperm samples were taken (but not from the F3 generation) for analysis of density, motility (using a computer assisted sperm motion analysis system, only conducted on control and high dose group males) and morphology, a number of organs were weighed and selected organs were sampled for histopathology. Additionally, testicular spermatid counts were made. Parameters assessed in the young offspring included litter size, bodyweights, survival, gross appearance, ano-genital distance, sexual development and, for animals killed at weaning, gross appearance of organs at necropsy and reproductive organ weights. There was evidence of general toxicity in adults of all generations, seen as a reduction in bodyweight gain at 50 and 160 mg/kg/day and histopathological changes in the kidneys at all dose levels. Considering the reproduction-related parameters, there were no adverse effects on fertility or mating performance. However, several other parameters were affected. Oestrous cycle length was increased by about 15% in the F1 and F2 females at 160 mg/kg/day, in comparison with controls. The timing of vaginal opening was accelerated by 1.5-7 days at 50 mg/kg/day and by 3-6 days at 160 mg/kg/day in females of the F1, F2 and F3 generations. Also, absolute ovarian weights were decreased at 50 mg/kg/day in the F2 generation and at 160 mg/kg/day in the F1, F2 and F3 generations; however, no effect on ovarian weight was apparent in the F1 and F3 generations when analysed as an organ-to-bodyweight ratio. In males, changes in sperm endpoints were seen only in the F2 generation; epididymal sperm density was decreased by about 10% at 50 and 160 mg/kg/day and spermatid count was decreased by a similar amount at 160 mg/kg/day. However, there may have been methodological problems with the epididymal sperm density measurements, because the density in all F2 generation groups, including controls, was considerably greater (by about 25-40%) than reported for the F0 and F1 generation males; the age of each generation was similar at necropsy, so major differences in the sperm density would not be expected.

NP effects on the foetus

In a study performed according to OECD guideline 414, of GLP quality, female rats were administered corn oil solutions of NP (presumably by gavage) at dose levels of 0, 75, 150, and 300 mg/kg/day from gestational day 6 to 15. Females were killed on day 20 of gestation, and foetuses

were examined. At the highest and second-highest dose levels, maternal toxicity was evident, with mortality of two females. No maternal toxicity was found at 75 mg/kg/day. Post-implantation loss, litter size, foetal weights, and incidence of foetal abnormalities was not affected, even at dose levels which caused maternal toxicity (EU-RAR 1998).

NPE effects on the foetus
Meyer et al. (1988) administered NPE with 9 or 30 ethylene oxide units (NPE 9, NPE 30) to pregnant rats from gestational day 6 to 15. Doses of NPE 9 were 50, 250, or 500 mg/kg/day by gavage. A satellite group received 500 mg/kg/day by gavage on gestational day 1-20, and two further groups received 50 or 500 mg/kg/day dermally on gestational day 6-15. NPE 30 was given at 50, 250, or 1000 mg/kg/day by gavage on gestational day 6-15, with a satellite group receiving 1000 mg/kg/day on gestational day 1-20. The rats were killed on day 21 and the foetuses examined. NPE 30 did not cause any toxic effects on dams or foetuses. NPE 9, at 500 mg/kg, caused an increase in extra ribs in the foetuses. This dose caused a decreased weight gain in the dams.

4.4 Genotoxic effects

Nonylphenol
NP appears to be negative in the Ames test (*Salmonella typhimurium*), however, a study of sufficient quality has not been found (EU-RAR 1998). In an *in vitro* mammalian cell gene mutation test performed according to the OECD test guideline 476, and of GLP quality, and confirmed by a second independent experiment, NP was found non-mutagenic. The dose level may not have been high enough (EU-RAR 1998).

Nonylphenol ethoxylate
An NPE with unknown ethylene oxide chain length was found negative in the Ames test, using Salmonella typhimurium (CIR 1983). NPEs with 9 or 30 ethylene oxide units have been found negative in the Ames test (*Salmonella typhimurium*) (Meyer et al. 1988).

4.5 Carcinogenic effects

For nonylphenol, no data have been found (EU-RAR 1998).

NPEs with 4 and 9 ethoxylene oxide units have been administered orally to rats for 2 years (Smyth & Calandra 1969). The group size was 35 of each sex for NPE with 4 ethylene oxide units, and 5 of each sex were interim sacrificed at 12 months. Histopathological examination was done on 28 tissues on 5 rats of each sex from the control and highest dose group.
For NPE with 9 ethylene oxide units the group size was 36 of each sex, with 16 rats of each sex interim sacrificed at 6 and 12 months. Histopathology was performed on 11 tissues and all neoplasms.
No increased frequency of tumours was reported in either study.

5 Regulations, limit values

Ambient air
-

Drinking water
Denmark: 0.5 µg/l (measured as phenol C_6H_5OH) (MM 1988).

Soil
-

Sewage sludge
In Denmark, a cut-off value of 50 mg NP/kg (dry weight) has been set for sewage sludge intended to be spread on agricultural fields. After 1st of July, 2000, a cut-off value of 10 mg NP/kg is effective (MM 1996).

OELs
-

Classification
NP and NPE are not adopted on the List of Chemical Substances (Annex 1).

IARC/WHO
-

US-EPA
-

6 Summary

Description
NP is a clear to pale yellow viscous liquid with a slight phenolic odour. NPEs vary from liquids to paste-like liquids to waxy solids. Viscosity and water solubility increases with increasing ethylene oxide chain length.

Environment
NP and NPEs do not occur as natural substances.
NP is released to the environment from production and use as a chemical intermediate, in the polymer industry, and as nonylphenol itself. The major part is released to water, while small percentages are released to air and soil. NP is thought to be degraded in air by reaction with photochemically produced hydroxyl radicals.

Human exposure
The routes of human exposure to NP and NPEs are dermal contact and inhalation by workers involved in manufacture and use, dermal and inhalation exposure of consumers from household pesticide products, dermal contact to cleaning products and cosmetics, mucous membrane contact to spermicides; and exposure via the environment through drinking water, air, and food.

Toxicokinetics
After oral administration, absorption of NP in humans may be significant. Limited data indicate that first pass metabolism may account for inactivation by conjugation of a major part of the NP present in blood. The main part of NP and NPE metabolites are believed to be glucuronic acid conjugates, which are excreted via the kidney. No data exist regarding inhalation or dermal exposure, but it is assumed that absorption will occur.

Human toxicity
There are no data on human oral or inhalatory toxicity of NP or NPE.

Animal toxicity
single exposure
The LC_{50} of NP and NPE by inhalation is unknown. For NP, no data have been found. NPEs with 4 or 7 ethylene oxide units caused no mortality in concentrations up to 20 mg/l, indicating a low acute toxicity of NPE by inhalation.
Oral LD_{50} values for NP mostly in the range of 1200 - 2400 mg/kg have been reported indicating a low order of acute oral toxicity of NP. For various NPEs (number of ethylene oxide units 4-10, 12, 13, 15 or 20) oral LD_{50} values between 1000 and more than 5000 mg/kg have been reported. Acute oral toxicity seems to be independent of NPE ethylene oxide chain length.
A dermal LD_{50} of 2031 mg/kg NP in rabbits has been reported. The acute dermal toxicity of NPEs with 4, 5, 7, 9,10, 12, 13 and 40 ethylene oxide

units is low, as LD_{50} values varying between 2000 mg/kg and 5-10,000 mg/kg have been reported.

local effects

The sensory irritation potential of nonylphenol has been investigated in mice in a respiratory depression test. At 3636 mg/m3 a mean respiratory rate depression of about 25% was found during exposure. However, at 267 mg/m3 there were no changes in the respiratory rate. These results suggest that nonylphenol can cause mild sensory irritation to the respiratory tract at high exposure levels.
NP is corrosive on contact with skin and is a severe eye irritant. Exposure to the saturated vapour may lead to mild sensory irritation of the respiratory tract.

repeated exposure

In a 28-day study performed according to OECD guideline 407, rats received doses of 0, 25, 100 or 400 mg/kg b.w./day of NP in the diet. In a 90-day study performed according to EPA guidelines and of GLP quality, rats were administered NP in the diet at levels of 0, 15, 50 and 150 mg/kg b.w./day. In both studies reduced body weight, food consumption, and food utilisation was found; while relative kidney and liver weights were increased. In the 90-day study, females showed a slightly decreased ovary weight. In both studies, these biologically and statistically significant adverse effects were found at the highest dose level only. The NOAEL of the 28-day study is thus considered to be 100 mg/kg b.w./day by the rapporteur, while the NOAEL in the 90-day study is considered to be 50 mg/kg b.w./day by the rapporteur.
In a multigeneration study in rats increased incidence of renal tubular degeneration and/or dilatation were found in both sexes and across all generations. There was no dose level without effect. The lowest dose level, 15 mg/kg b.w./day is therefore a LOEL.

For NPEs, non-guideline quality studies performed between 1959 and 1965 indicate that toxicity depends on ethylene oxide chain length. A collection of 90-day feeding studies in rats with NPEs with 4-40 ethylene oxide units, shows NOAELs ranging between 40 mg and 5 g/kg/day. The lowest toxicity was found for NPEs with ethylene oxide chain lengths of 20 or more. Toxic effects included retarded growth and increased liver weight, for some compounds necrosis of liver cells.
In dogs, similar effects have been found. Dose-response relations seem comparable. However, in this species a specific toxic effect of certain NPEs on the heart has been found, related to ethoxylene oxide chain lengths of 15, 17.5, and 20 (but not for NPEs with chains outside this range). The cardiac effect is focal myocardial necrosis, sometimes lethal. A dose of 1 g/kg/day reliably induced cardiotoxicity. A dose of 40 mg/kg/day was also able to induce the lesion (microscopically detectable lesions only, table 6: NPE with 20 EO). The NOAEL for cardiotoxicity in the dog is not known, nor is the mechanism. Guinea pigs also seem to develop this type of lesion, while cats, rats, and rabbits do not.
NPEs with 4 or 9 ethoxylene oxide units have been administered orally to rats and dogs over periods of 2 years in studies of non-guideline standard. In the dog study, the group size was only 3 of each sex. In rats, reduced weight gain was observed after administration of NPE with 4 EO. In dogs, increased relative liver weight without accompanying histopatho-

logical findings, but with elevated serum alkaline phosphatase level was observed. In both rats and dogs, the NOAEL for NPE with 4 ethoxylene oxide units was 40 mg/kg/day. NPE with 9 ethoxylene oxide units did not cause any effects in rats in highest dose administered, 270 mg/kg/day. In dogs, the only effect was an increased relative liver weight without accompanying histopathological findings at the highest dose level, 88 mg/kg/day.

Reproductive and developmental effects
NP has been shown to mimic the effects of oestrogen via activation of the oestrogen receptor. NP has shown oestrogenic effect in fish, daphnids, and in human breast tumour cells. In uterotrophic assays NP has shown oestrogenic effect in immature Wistar rats, in immature Sprague-Dawley rats, and in ovariectomised Sprague-Dawley rats.
In 28-day and 90-day studies of NP, the latter study having special emphasis on reproductive organ function and morphology, sexual organ morphology, oestrous cycle pattern, and spermatogenesis were not found to be affected by treatment. Absolute, but not relative, ovary weight was slightly reduced in the highest dose group in the 90-day study.
A three-generation study has revealed effects on female and male reproductive parameters of NP, without effects on fertility. The NOAEL for reproductive effects in this study was 15 mg/kg/day.
Neither NP nor NPE (9 or 30 ethylene oxide units) induced malformations in rat foetuses exposed during organogenesis.

Genotoxicity
The existing mutagenicity studies of NP are not of sufficient quality to allow a proper evaluation of mutagenic potential. NPEs with 9 or 30 ethylene oxide units were negative in the Ames test.

Carcinogenicity
For NP, no data have been found.
NPEs with 4 or 9 ethylene oxide units have been administered in 2-year studies. However, because of an insufficient number of animals, the studies do not allow a proper evaluation of carcinogenic potential.

7 Evaluation

A study in humans involving two volunteers provides evidence that nonylphenol is rapidly absorbed from the gastrointestinal tract in humans. Also, the fact that only a small proportion of the dose was recovered in faeces within 56 hours suggests that almost complete absorption of a dose had occurred. Following oral administration, most of the nonylphenol was present in the blood as glucuronide or sulphate conjugates, in contrast to the findings for intravenous administration where similar proportions of unconjugated and conjugated nonylphenol were detected; these findings are indicative of extensive first pass metabolism. First pass metabolism does not occur when the route of exposure is inhalation. Therefore, an inhalatory dose of NP may be more toxic than the same dose administered orally.

No data have been found which describe the health effects of NP or NPEs in humans after oral ingestion or exposure via inhalation.

The systemic toxicity of NP and NPE by inhalation is unknown. Data from a mouse study suggest that NP can cause mild sensory irritation to the respiratory tract at high exposure levels. At a vapour concentration of 267 mg/m^3 there was no effect.

The acute oral toxicity of NP and NPE is low.

NP has not been tested for mutagenicity in a study of good quality. No data regarding the carcinogenicity of NP have been found. NPEs with 9 or 30 ethylene oxide units were negative in the Ames test. Two-year feeding studies showed no tumourigenic effects of NPEs with 4 or 9 ethylene oxide units, however, the studies did not include a sufficient number of test animals and are for this reason inconclusive.

Nonylphenol
A 28-day study NOAEL of 100 mg/kg b.w./day for NP, and a 90-day study NOAEL of 50 mg/kg b.w./day for NP have been determined in studies of good quality. The results of the 28-day study and the 90-day study are in agreement with each other. In a multigeneration study, also of good quality, increased incidence of renal tubular degeneration and/or dilatation were found. There was no dose level without effect. It is difficult to decide for certain whether or not the kidney effect was related to treatment because these changes were not seen in the 90-day study, which was conducted using the same strain of rats, and because a dose-dependent trend was not apparent in all generations/sexes. The lack of concordance between the studies cannot be explained on the basis of a slightly longer exposure period in the multigeneration study because kidney effects were seen in the F3 generation which were exposed for only 8 weeks, nor solely on the basis of in utero and neonatal exposure because the effect also occurred in the F0 generation. Giving special emphasis to the fact that the increased incidence occurred consistently across all four generations in the multigeneration study, it is considered that this cannot be dismissed as background variation. The F3 generation showed the

highest incidence of kidney changes, indicating that the effect may become more pronounced after exposure during several generations. Consequently, the conclusion has been drawn from this study that there is a LOEL for repeated exposure of 15 mg/kg/day, based on histopathological changes in the kidneys. Since renal tubular degeneration and/or dilatation are common findings in untreated rats, and as they were not accompanied by other related signs or symptoms in the affected rats, they are not considered signs of severe toxicity by the rapporteur.

Alkyl phenols, including NP, have been shown in laboratory studies to mimic the effects of oestrogen in vitro and in vivo.
NP has been found positive in the uterotrophic response assay in immature Wistar-derived rats, in immature Sprague-Dawley rats, and in ovariectomised Sprague-Dawley rats. Although the uterotrophic assay is a standard assay for oestrogenic effect, the significance to human health of oestrogenic effects in this assay has not been established.
In the 28-day study, and especially the 90-day study of NP, rather extensive examinations of sexual organs were performed. Sexual organ morphology, oestrous cycle pattern, and sperm quality were studied and were found to be unaffected by treatment. Absolute ovary weight was found to be slightly decreased in the highest dose group. The relative ovary weight was not reduced, and histopathological changes of the ovary were not found. Other targets which may be affected by oestrogen (haemoglobin, red blood cell count, pituitary gland, mammary gland, endometrium) were not affected by NP in this study. It is therefore concluded that, although NP may possess oestrogenic activity, it did not affect endpoints commonly associated with oestrogenic activity at the highest dose used in this study, which was high enough to cause general toxicity in the rats.

However, the results of the three-generation study indicate that effects on male and female reproductive parameters may occur at dose levels above 15 mg/kg/day. In females, accelerated sexual maturation, increased oestrous cycle length and reduced ovarian weights were found, while males exhibited a reduced number of spermatids. The effects were found in one or more of the three filial generations.

NOAEL for NP
In conclusion, for NP a LOAEL of 15 mg/kg/day is set, based on the reproductive/developmental effects seen in the oral three-generation study. This dose level is also a LOEL for the kidney effects also identified in this study.

Nonylphenol ethoxylate
For NPEs, a number of 90-day studies in rats and dogs exist. The studies are all rather old (reports dated 1959-1965) and probably do not fulfil present standards. Histopathology apparently has only been performed in the highest dose groups, and therefore it is not possible to evaluate the toxicological significance of increased organ weights of other dose groups. For this reason, a change in organ weight was regarded as an adverse effect in the absence of histopathological data. NOAELs ranging between 40 and 160 mg/kg/day in rats for NPEs with 4-15 ethylene oxide units have been found. In dogs, 90-day NOELs of 40 mg/kg/day were found for NPEs with 4, 6, 9, 15, and 20 ethylene oxide units. For NPEs with ethylene oxide chains of 20 or 30, NOAELs of 1000 ->5000

mg/kg/day were found in rats. In dogs, the NOAEL for NPE with 30 ethylene oxide units was >1000 mg/kg/day. NPE with 40 ethylene oxide units had a NOAEL of 300 mg/kg/day in rats. NPE effects included retarded growth and increased liver weight, for some compounds necrosis of liver cells.
In dogs, similar effects have been found. Dose-response relations seem comparable. However, in the dog a specific toxic effect of certain NPEs on the heart has been found, related to ethoxylene oxide chain lengths of 15, 17.5, and 20 (but not NPEs with chains outside this range). The cardiac effect is focal myocardial necrosis, sometimes lethal. A dose of 1000 mg/kg/day reliably induced cardiotoxicity. Microscopic changes in the myocardium were found even at a dose of 40 mg/kg/day for NPE with 20 ethylene oxide units. The NOAEL for cardiotoxicity in the dog is not known, nor is the mechanism. Guinea pigs also seem to develop this type of lesion, while cats, rats, and rabbits do not. It is not known whether humans are sensitive to the cardiotoxic effect of NPEs with ethoxylene oxide chain lengths of 15, 17.5, and 20.
NPEs with 4 or 9 ethoxylene oxide units have been administered orally to rats and dogs for periods of 2 years. Effects included reduced weight gain, and increased relative liver weight, while no increased frequency of tumours was reported. However, the studies were not properly designed to evaluate carcinogenic effects. In the dog studies, the group size was very small, and the 2-year dose period did not cover the whole lifetime for this species, which is at least 7-8 years. In the rat studies, the number of animals examined in detail for tumour occurrence was far too small to allow any conclusions. In rats and dogs, the 2-year chronic toxicity NOAEL for NPE with 4 ethoxylene oxide units was 40 mg/kg/day, while NPE with 9 ethoxylene oxide units did not cause any effects in rats in highest dose administered, 270 mg/kg/day. In dogs, the 2-year NOAEL for NPE with 9 ethoxylene oxide units was 88 mg/kg/day.

NOAEL for NPE

In conclusion, an oral NOAEL of 40 mg/kg/day for NPEs with ethylene oxide chain lengths shorter than 15 and between 21-40 can be set. This NOAEL covers the most toxic NPEs among the group tested (Table 6). For NPEs with ethylene chain lengths between 15 and 20 a NOAEL cannot be determined from the available data. The LOAEL for cardiotoxicity in the dog is 40 mg/kg
For the purpose of setting a limit value covering all NPEs a LOAEL of 40 mg/kg/day is set.

8 TDI, health based limit values

8.1 **TDI**

NP

$$TDI = \frac{LOAEL}{SF_I \times SF_{II} \times SF_{III}} = \frac{15 \text{ mg/kg b.w./day}}{10 \times 10 \times 30}$$

$$= 0.005 \text{ mg/kg b.w./day}$$

The safety factor SF_I is set to 10 assuming that humans are more sensitive than animals. The SF_{II} is set to 10 to protect the most sensitive individuals in the population. The SF_{III} is set to 30 since a LOAEL is used and because data for genotoxicity and carcinogenicity are lacking.

NPE

$$TDI = \frac{LOAEL}{SF_I \times SF_{II} \times SF_{III}} = \frac{40 \text{ mg/kg b.w./day}}{10 \times 10 \times 30}$$

$$= 0.013 \text{ mg/kg b.w./day}$$

The safety factor SF_I is set to 10 assuming that humans are more sensitive than animals. The SF_{II} is set to 10 to protect the most sensitive individuals in the population. The SF_{III} is set to 30 since a LOAEL is used and because data for genotoxicity and carcinogenicity are lacking.

Allocation
The sources of NP and NPE exposure for the general population are via consumer products and via the environment through food, drinking water, and air. The size of these exposures is unknown, although it is expected that exposure via air is negligible.
For the purpose of setting a limit value, only 10 % of the TDI is allocated to ingestion of soil and 10 % to drinking water.

8.2 **Limit value in soil**

NP
Based on the TDI of 0.005 mg/kg b.w. per day for NP, and 0.04 mg/kg b.w. per day for NPE, and assuming a daily ingestion of 0.2 g soil for a child weighing 10 kg (w_{child}), a limit value is calculated:

$$LV_{soil} = \frac{TDI \times X\% \times w_{child}}{ingestion_{soil}} = \frac{0.005 \text{ mg/kg day} \times 0.1 \times 10 \text{ kg}}{0.0002 \text{ kg/day}}$$

= 25 mg/kg soil

NPE
Based on the TDI of 0.013 mg/kg b.w. per day for NPE, and assuming a daily ingestion of 0.2 g soil for a child weighing 10 kg (w_{child}), a limit value is calculated:

$$LV_{soil} = \frac{TDI \times X\% \times w_{child}}{ingestion_{soil}} = \frac{0.013 \text{ mg/kg day} \times 0.1 \times 10 \text{ kg}}{0.0002 \text{ kg/day}}$$

= 65 mg/kg soil

8.3 Limit value in drinking water

NP and NPE
The existing limit value for phenols in drinking water of 0.5 µg/l offers adequate protection against adverse health effects induced by NP or NPE.

8.4 Limit value in air

NP

$$LV_{air} = \frac{TDI \times 70 \text{ kg}}{20 \text{ m}^3/\text{day}} = \frac{0.005 \text{ mg/kg/day} \times 70 \text{ kg}}{20 \text{ m}^3/\text{day}}$$

= 0.017 mg/m^3

NPE

$$LV_{air} = \frac{TDI \times 70 \text{ kg}}{20 \text{ m}^3/\text{day}} = \frac{0.013 \text{ mg/kg/day} \times 70 \text{ kg}}{20 \text{ m}^3/\text{day}}$$

= 0.05 mg/m^3

9 Quality criteria

9.1 **Quality criteria in soil**

NP
A limit value of 25 mg/kg has been calculated based on children's ingestion of soil. A quality criterion of 25 mg/kg soil is proposed.

Quality criteria
Quality criterion: 25 mg/kg soil

NPE
A limit value of 65 mg/kg has been calculated based on children's ingestion of soil. A quality criterion of 65 mg/kg soil is proposed.

Quality criteria
Quality criterion: 65 mg/kg soil

9.2 **Quality criteria in drinking water**

The existing limit value for phenols in drinking water of 0.5 µg/l offers adequate protection against adverse health effects induced by NP or NPE.

Quality criteria
Quality criterion: 0.5 µg/l.

9.3 **C-value**

NP
A limit value of 0.017 mg/m^3 has been calculated based on toxicological considerations in relation to repeated oral exposure. For substances having acute or subchronic effects, but for which activity over a certain period of time is necessary before the harmful effect occurs, the C-value is set at the limit value.
A C-value of 0.02 mg/m^3 and placing in Main Group 1 is proposed. Main Group 1 is justified because of concern for the environment due to the persistence of NP. This proposed C-value also protects against sensory irritation caused by NP.

C-value
0.02 mg/m^3, Main Group 1.

NPE
A limit value of 0.05 mg/m^3 have been calculated based on toxicological considerations in relation to repeated oral exposure. For substances having acute or subchronic effects, but for which activity over a certain period of time is necessary before the harmful effect occurs, the C-value

is set at the limit value. A C-value of 0.05 mg/m^3 and placing in Main Group 1 is proposed. Main Group 1 is justified because of concern for the environment due to the persistence of NP.

C-value
0.05 mg/m^3, Main Group 1

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