Social Europe

Recommendation from the Scientific Committee on Occupational Exposure Limits for commercial nonylphenol

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8-hour TWA	: insufficient data on which to base a recommendation
STEL (15 mins)	: insufficient data on which to base a recommendation
Additional classification	: -

Substance

"Commercial nonylphenol"

The term "nonylphenol" covers a large number of isomeric compounds of general formula $C_6 H_4$ (OH) C_9H_{19}. Nonylphenols vary in two ways: the substitution position of the nonyl group on the phenol molecule; and the degree of branching of the nonyl group. Commercially produced nonylphenols are predominantly 4-nonylphenol with a varied and undefined degree of branching in the alkyl group. Almost all of the toxicity studies available have used commercially produced nonylphenol; very rarely is the exact composition of the substance tested given and it is difficult to assess the extent (if any) to which variability in structure between various isomeric forms may influence the toxicological profile.

Identity and properties of the principal component:

Chemical name:	4-nonylphenol (branched)
CAS No:	84852-15-3
EINECS No:	284-325-5
Empirical formula:	$C_{15}H_{24}0$
Molecular mass:	220.3
Synonyms:	isononylphenol; para-nonylphenol; monoalkyl (C3-9) phenol
Melting point:	- 8°C
Boiling point:	290-300˚C
Conversion factor:	1 ppm = 9.2 mg/m^3

"Commercial nonylphenol" is a clear to pale yellow viscous liquid with a slight phenolic odour. It has an estimated vapour pressure of 0.3 Pa at 25°C and a water solubility of 6 mg/l at 20°C. It has a high octanol/water partition coefficient of about 4.5.

1. Occurrence and Use

Commercial nonylphenol is used in substantial quantities throughout the EU, with 70-80 000 tonnes being produced and consumed within the EU in 1997. Just over half of the total tonnage is used in the production of nonylphenol ethoxylate surfactants, which have a very wide range of uses across industry, e.g. in cleaning, textile processing and emulsion polymerisation of acrylate esters. Commercial nonylphenol is also used in the production of phenol/formaldehyde resins, plastics, stabilisers, tris(4-nonylphenyl) phosphite, as a catalyst in the curing of epoxy resins and in the production of phenolic oximes, used for the extraction and purification of copper from its ores. Its properties make it useful as a component of speciality paints.

Commercial nonylphenol is a viscous material of low volatility at ambient temperatures but is often heated to above 50°C to reduce the viscosity in handling. Apart from during its use in speciality paints, commercial nonylphenol is almost always processed in a closed plant. Exposure to commercial nonylphenol via skin contact and inhalation may occur during speciality paint manufacture and during charging of mixing vessels with nonylphenol. Exposure via inhalation and dermal contact with the vapour and aerosol may occur during spray application of speciality paints.

2. Health Effects

There are no studies in humans available for any aspect of nonylphenol toxicology.

Toxicokinetic studies in experimental animals with nonylphenol and the closely related substance octylphenol indicate that, following oral administration, absorption from the gastrointestinal tract is initially rapid and probably extensive. With oral administration there is evidence of extensive first-pass metabolism, primarily involving glucuronide and sulphate conjugation. Nonylphenol and its metabolites are distributed widely through the body, with the highest concentration in fat. The major routes of excretion are via the faeces and urine. The potential of nonylphenol to bioaccummulate is uncertain. There are no data on the toxicokinetics of nonylphenol following inhalation exposure, but it can be predicted that absorption from the respiratory tract would be significant and that first-pass metabolism would not be such an influence. There are no *in vivo* toxicokinetic studies involving dermal administration. *In vitro* data indicate that nonylphenol is poorly absorbed across the skin, although some limited skin penetration, especially into the stratum corneum, does occur.

As regards its acute toxicity, in experimental animals nonylphenol has moderate acute toxicity by the oral route, with LD_{50} values for the rat in the range of about 1 200 to 2 400 mg/kg (Berol Kemi AB, 1982; Hüls AG 1982; ICI, 1984). The acute toxicity of nonylphenol by the dermal route is similar, with an LD_{50} of 2 000 mg/kg in rabbits (Smyth et al 1969). No reliable data are available on the acute inhalation toxicity of nonylphenol, although its corrosive properties (see below) suggest that significant acute toxicity would be elicited following exposure by this route.

When applied to the skin or eyes, liquid nonylphenol can be severely irritating or even corrosive, although its potency appears to vary according to the source and exact composition of the material (Union Carbide 1902 a,b; Hüls, 1986a). On the basis of the skin effects it has been agreed to classify nonylphenol as "Corrosive" within the EU Classification & Labelling system. In an Alarie-type assay for respiratory irritation, a nominal concentration of 400 ppm produced some reduction in respiratory rate in mice; no such effect was seen at a nominal concentration of 30 ppm (ICI, 1995).

With regard to skin sensitisation, the results of several guinea pig maximisation tests suggest that nonylphenol does not have significant skin-sensitising potential (Hüls, 1986 c; ICI, 1980, 1979; Gaworski et al, 1979). No information on respiratory tract sensitisation is available, although it can be predicted from its low chemical reactivity and lack of skin-sensitising potential that nonylphenol is unlikely to be a respiratory allergen.

The repeated dose toxicity of nonylphenol has been explored in several studies in rats, although the results have been somewhat inconsistent. Only the oral route of administration has been used. In one investigation, groups of 30 male and 30 female rats were exposed to nonylphenol in the diet at doses equivalent to 0, 15, 50 or 160 mg/kg bodyweight/day in a three-generation study (NTP, 1997). The consequences of these dosing regimes for reproductive performance are discussed later. However, the other significant observation in this study was histopathological evidence of an increase, although often without a convincing dose-response relationship, in the incidence of renal tubular degeneration and/or dilation in adult males in all generations and all nonylphenol-treated groups; similar findings were also reported for adult females at 160 mg/kg per day in all three generations of offspring and additionally at 15 and 50 mg/kg/day in the F_3 generation. The findings were confirmed in a subsequent repeat examination of the kidney tissue samples by an independent pathologist not involved in the original investigation. It is difficult to be sure whether or not this increased incidence of renal tubular damage was related to treatment with nonylphenol, because the changes were not seen to the same extent in a 90-day study conducted using the same strain of rats (see below) and because a dose-dependent trend was not apparent in all generations/sexes in this multigeneration study. However, within this study the effect was seen with reasonable consistency across all four generations involved, suggesting that the finding cannot be dismissed as background variation. Consequently, it appears from this study that there was a LOAEL for repeated oral exposure of 15 mg/kg/day, based on these renal histopathological findings.

In a standard 90-day study in rats, 15 animals of each sex received dietary administration of 0, 15, 50 or 140 mg/kg/day nonylphenol (Chemical Manufacturers Association, 1997a; Cunny et al, 1997). There was a clear NOAEL of 50 mg/kg/day from this study. At the high dose of 140 mg/kg/day the mean bodyweights at the end of the study for both sexes were about 7% less than in the controls. Food consumption was also reduced in the high-dose animals and there was histopathological evidence of morpholical changes in the liver (slight or moderate individual hepatic cell necrosis) and the kidneys (male animals showing an increased incidence of deposits of intratubular mineralisation in the proximal tubule). A further study, involving dietary administration of nonylphenol at doses of 0, 25, 100 or 400 mg/kg/day for 28 days, has been reported (Hüls, 1989). This study produced a NOAEL of 100 mg/kg per day, with evidence of reduced bodyweight gain in both sexes and, in males, histopathological evidence of hyaline droplet accumulation in the renal proximal tubules and vacuolation of periportal hepatocytes in the liver at the top dose of 400 mg/kg/ day.

The repeated dose oral toxicity of nonylphenol in the rat appears to be enhanced when gavage dosing is used rather than dietary administration, with a dose-related increase in mortality being reported at 100 mg/kg/day (the lowest dose used) and above during a 10-week dosing period (de Jager et al, 1999a).

Nonylphenol has been reasonably well tested for its mutagenic potential. It was negative in well-conducted Ames and *in vitro* mammalian cell gene mutation tests (Hüls et al, 1984; Shimizu et al, 1985; Hüls, 1990). Two *in vivo* bone marrow micronucleus tests in mice, using

either oral gavage or intraperitoneal administration, both yielded negative results (Hüls, 1988; Hüls, 1999). These results indicate that nonylphenol is not mutagenic.

There are no carcinogenicity studies on nonylphenol.

The potential effects of nonylphenol on reproduction have been explored using both standard reproductive toxicity tests and also in assays exploring its oestrogenic activity, related to concerns that nonylphenol might express significant endocrine disruption/modulation activity. Nonylphenol has been shown to have oestrogenic activity in a number of *in vitro* and *in vivo* assays, the potency of this oestrogenic activity ranging from 3 to 6 orders of magnitude less than that of oestradiol (Routledge and Sumpter, 1997; Soto et al, 1991; White et al, 1994; ICI, 1996; Chemical Manufacturers Association, 1997b; Lee and Lee, 1996).

The effects of nonylphenol on fertility and reproductive performance have been investigated in a good-quality oral (diet) multigeneration study in the rat at doses 0, 15, 50 and 160 mg/kg/day (NTP, 1997). This study provided evidence that nonylphenol exposure over several generations can cause minor perturbations in the reproductive system of offspring, namely slight changes in the oestrous cycle length (15% at 160 mg/kg), the timing of vaginal opening (accelerated by 1.5 to 7 days at 50 mg/kg and 3 to 6 days at 160 mg/kg) and possibly also in ovarian weight and sperm/spermatid count, although functional changes in reproduction were not induced at the dose levels tested. The NOAEL for these changes was 15 mg/kg/day. The observed perturbations in offspring are compatible with the predictable or hypothesised effects of exogenous oestrogenic activity. Evidence of testicular toxicity, seen as seminiferous tubule vacuolation, cell necrosis and a reduction in tubule diameter, was reported at exposure levels which also caused mortality in a repeated dose gavage study in rats (de Jager, 1999a). The LOAEL for testicular toxicity was 100 mg/kg/day. No evidence that nonylphenol is a developmental toxicant was seen in a standard oral developmental toxicity study in rats dosed at 0, 75, 150, 300 and 600 mg/kg/day on gestation days 6-15 (Initiative Umweltrelevante Altstoffe, 1992). Maternal toxicity was manifested as macroscopic changes to the liver and spleen at 150 mg/kg and above and mortalities at 300 mg/kg. In contrast, in a gavage study involving *in utero*, lactational and direct post-weaning exposure at daily doses of 0, 100, 250 and 400 mg/kg, there was evidence of a reduction in sperm count (36%) at 250 mg/kg/day, although it is not possible to state whether this is a developmental effect or a result of direct exposure after weaning (de Jager et al, 1999b). No offspring were born from the mothers receiving 400 mg/kg/day; it is not clear from the report if this was because of maternal deaths or embryonic/foetal resorption. In an intraperitoneal study designed to investigate the effects of nonylphenol on male reproductive tract development of neonatal rats, evidence of impaired development was observed (Lee, 1998). However, this study was difficult to interpret and involved parenteral administration, so that these results carry little weight in the overall assessment of the available data. Overall, the observations of oestrogenic activity in the *in vitro* and *in vivo* assays, minor perturbations in the reproductive system of offspring in the multigeneration study and testicular changes in gavage studies collectively raise concerns about reproductive toxicity, possibly mediated through action on the oestrogen receptor.

Recommendation

In the opinion of the SCOEL a recommendation for a health-based limit for "commercial nonylphenol" cannot be made.

There are two major toxicological problems associated with the available database, created by the absence of any studies useful for the derivation of an occupational

exposure limit using the inhalation route of exposure. Firstly, given the irritating properties of nonylphenol, one would anticipate local effects in the respiratory tract on inhalation, with the potential for chronic inflammation on long-term repeated exposure. Unfortunately, there are no data available to explore this issue. Also, in relation to systemic toxicity, there are indications of substantial first-pass metabolism of nonylphenol in the liver when the substance is given orally (the dosing route used in all of the available repeated exposure studies). First-pass metabolism would not be such an influence on the toxicokinetics of nonylphenol following inhalation exposure. This gives rise to great uncertainty about the extrapolation of the systemic toxicity of nonylphenol from the oral to the inhalation route, and in particular, the quantitative aspects.

For these reasons, the SCOEL considered that it did not have sufficient information available from which to derive a health-based limit.

An additional problem is that currently there is no published and/or validated method available for sampling and measuring nonylphenol in air.

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