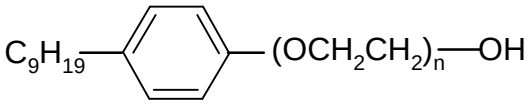
Alkylphenol ethoxylates

(Synonyms: Nonylphenol ethoxylate, Octylphenol ethoxylate, Nonoxynol-4. Polyethylene glycol nonylphenyl ether)

Nonylphenol ethoxylate
(CAS 9016-45-9)



1 Acute and 8-hr RELs

Nonylphenol ethoxylate Acute REL

Reference Exposure Level	**0.73 mg/m^3 (0.03 ppm) [Inhalation]**
Critical effects	Ocular and respiratory irritation
Hazard Index target	Eyes and respiratory system

There are very few data on the toxicity of the alkylphenol ethoxylates in non-aquatic media. No studies were located that could be used to derive an 8-hr REL for the ethoxylates.

2 Physical and Chemical Properties of Alkylphenol ethoxylate (n=9)

Description	Nearly colorless liquid
Molecular formula	$C_{15}H_{24}O[C_2H_4O]_9$
Molecular weight	617.6 g/mol
Specific gravity	1.057 @ 20°C
Boiling point	295-320ºC
Melting point	2.8 ºC
Vapor pressure	1 x 10^{-10} mm Hg @ 25ºC
Log Kow	3.59
Solubility	"soluble"
Atmospheric half-life	not found
Conversion factor	1 ppm = 25.2 mg/m^3

3 Metabolism and environmental fate of alkylphenol ethoxylates

The alkylphenol ethoxylates are non-ionic surfactants in wide use as wetting agents, emulsifiers, and dispersants in paints and coating, residential and commercial cleaning products, in pesticide formulations, and in textile and paper processing. Of the alkylphenol ethoxylates used in commerce, nonylphenol ethoxylate is the most common (80% vs 20% octyl phenol ethoxylates)(Cox, 1996), and will be treated here as representative of the entire group of alkylphenol ethoxylates. However, it is recognized that some of the effects of octylphenol,

notably related to its estrogenicity, appear to be more severe than those associated with nonylphenol.

Microbial degradation of the alkylphenol ethoxylates occurs under both aerobic and anerobic conditions. Under aerobic conditions, progressive cleavage of the carbon chains results in shorter chain nonylphenol ethoxylates and/or other alkylphenolic compounds. The ethoxyacetic acid is formed early in this process (Jonkers et al., 2001). Under aerobic conditions, further degradation to nonylphenol is thought not to occur. By contrast, under anaerobic conditions, such as those found in sewage treatment plants, and in river and lake sediment, microbial activity may shorten the ethoxylate chain to form nonylphenol while concurrent carboxylation reactions generate carboxylated alkyl phenol ethoxylates (Jonkers et al., 2001). While there is some evidence that the phenol ring may be opened and mineralized under aquatic conditions (Naylor et al., 2006), nonylphenol and the carboxylated metabolites tend to resist further degradation and to be more environmentally persistent. Because of its moderate volatility, nonylphenol may enter the air from treated waste water and from lakes and streams contaminated with NP or the parent ethoxylate. The very low volatility of the alkylphenol ethoxylates is expected to limit inhalation exposure to their vapors. However, inhalation of aerosols generated during spray application of ethoxylate-containing cleaners is possible.

4 Animal toxicity of alkylphenol ethoxylates

In a study of the effects of acute (4 hr) exposure of rats to aerosols of alkylphenol ethoxylates (tridecylhexaethoxylate, $C_{13}E_6$; tetradecylheptaethoxylate, $C_{14}E_7$) at 0.28, 0.63, 1.48, 3.65, and 9.28 g/m^3, Benke et al. (1977) reported labored breathing, rales, corneal opacities and decreased activity as the main treatment-related effects. Eyes and lungs were the primary target organs. Corneal opacity was seen in nearly all test animals but no indication of relative severity was reported. Vacuolation and hyperplasia of the corneal epithelium were present in about 50% of the test animals, but whether they were dose-related is not clear. Upon autopsy, the lungs of rats dying from the exposure were dark red and smaller than normal, while lung:body weight ratios were unchanged, indicating that decreased weight gain was also associated with exposure. These results clearly show that ocular and pulmonary toxicity was associated with concentrated ethoxylate aerosols; however, a no effect level (NOEL) was not observed. This study also reported an LC_{50} between1.5 and 3 g/m^3 but a precise value was not given since the death rate was either 0 or 100% in all but one or two groups.

Another study of the acute effects of aerosolized alkylphenol ethoxylate was conducted by Union Carbide (1991) with the detergent Tergitol NP9, whose principal component is nonylphenol ethoxylate. Sprague Dawley rats of both sexes received one whole-body exposure for four hours to aerosols of 0.50, 0.90 and 1.41 g/m^3. In all groups on the day of the exposure there were signs of ocular and respiratory irritation (blepharospasm, and periocular and perinasal wetness and encrustation), and hypoactivity. During the two-week post-exposure observation period, all groups showed weight loss or decreased weight gain, and perinasal encrustation. At the two higher concentrations, there were also signs of labored and audible breathing, unkempt fur and distended abdomens. An LC_{50} value of 1.60 g/m^3 was reported for both sexes combined. This study included no untreated controls, and a NOEL was not reported.

The NPEs appear to rapidly open tight junctions of epithelial cell membranes and to inhibit P-glycoproteins (P-gp), proteins involved in the transport of xenobiotics out of cells (Doo et al., 2005). The alkylphenol ethoxylates may thus enhance exposure to, and hinder clearance of, other toxicants.

The toxicity of the alkylphenol ethoxylates appears to be related in part to the inhibition of cytochrome P450 (CYP) enzymes. In rats injected with octylphenol (OP), OP monocarboxylate (OP1EC), or OP di-ethoxylate (OP2EO), the protein levels and catalytic activity of CYP2C11 were significantly decreased with a potency order of octylphenol > OP1EC ≥ OP2EO. By comparison the activity of CYP3A2 was significantly decreased only by octylphenol. Testosterone 2α-hydroxylase activity was also inhibited by these three compounds with the same potency order as for CYP2C11. Thus the ethoxylates also appear to have endocrine disrupting potential and an ability to interfere with intermediary metabolism but with a lower potency than octylphenol (Hanioka et al., 2000).

5 Derivation of Interim Acute REL for alkylphenol ethoxylates

Study	Benke et al., 1977
Study population	Rats
Exposure method	Chamber/whole body
Exposure continuity	Once
Exposure duration	4 hr
Critical effects	Ocular & nasal irritation
LOAEL	0.28 g/m^3
NOAEL	Not observed
Time-adjusted exposure	C^n*T n=3
Extrapolated concentration	0.44 g/m^3 $(0.28^3*4)^{1/3}$
Human concentration adjustment	0.44 g/m^3
LOAEL uncertainty factor	6
Subchronic uncertainty	1
Interspecies uncertainty factor	
Toxicokinetic (UF_{A-k})	√10
Toxicodynamic (UF_{A-d})	√10
Intraspecies uncertainty factor	
Toxicokinetic (UF_{H-k})	√10
Toxicodynamic (UF_{H-d})	√10
Cumulative uncertainty factor	600
Reference Exposure level	**0.73 mg/m^3**

The two studies of rats with 4-hour exposures to alkylphenol ethoxylate aerosols (Benke et al., 1977; Union Carbide, 1991) are consistent with one another with LOAELs of 0.28 and 0.50 g/m^3 for ocular and respiratory irritation, and LC_{50}s in the range of 1.5-3 g/m^3. The LOAEL of 0.28 g/m^3 for a 4-hour exposure was adjusted to a one hour exposure with the modified Haber's formula, C^n*T, where n=3. For time adjustment from longer periods to the one-hour period of the acute REL, 3 is the default value of 'n' except where chemical-specific data are available or

the effects are purely sensory irritation. In this instance the effects include both sensory irritation and irritation due to damage (corneal opacity, lung damage), as well as more systemic effects such as hypoactivity, corneal opacity, and lung damage. Since no NOAELs were observed in these studies and the effects were mild, a LOAEL uncertainty factor of 6 was employed. These studies were conducted in adult rats but the ocular and respiratory effects are not expected to be substantially different between species or across ages. For this reason the toxicokinetic and toxicodynamic UFs are assign values of √10 to account for both inter- and intraspecies variation. The cumulative UF is thus 600, resulting in an acute REL of 0.73 mg/m^3.

No suitable studies were located for the development of 8-hour RELs for the alkylphenol ethoxylates.

6 References

Benke GM, Brown NM, Walsh MJ and Drotman RB (1977). Safety testing of alkyl polyethoxylate nonionic surfactants. I. Acute effects. Food Cosmet Toxicol 15(4): 309-18.

Cox C (1996). Nonyl phenol and related chemicals. J. Pest. Reform 16(1): 15-20.

Doo MH, Li H, Jang HI, Song IS, Chung SJ and Shim CK (2005). Effect of nonylphenol ethoxylates (NPEs) on barrier functions of epithelial cell membranes: opening of tight junctions and competitive inhibition of P-gp-mediated efflux. Int J Pharm 302(1-2): 145-53.

Hanioka N, Tanaka-Kagawa T, Chung YS, Nishimura T, Jinno H and Ando M (2000). Changes in hepatic cytochrome P450 enzymes by biodegradation products of 4-tert-octylphenol polyethoxylate in rats. Bull Environ Contam Toxicol 64(6): 804-10.

Jonkers N, Knepper TP and de Voogt P (2001). Aerobic biodegradation studies of nonylphenol ethoxylates in river water using liquid chromatography-electrospray tandem mass spectrometry. Environ Sci Technol 35(2): 335-40.

Naylor CG, Staples CA, Klecka GM, Williams JB, Varineau PT and Cady C (2006). Biodegradation of [(14)C] ring-labeled nonylphenol ethoxylate. Arch Environ Contam Toxicol 51(1): 11-20.

Union_Carbide. (1991). Tergitol nonionic surfactant NP-9: acute aerosol inhalation toxicity test in rats. Bushy Run Research Center.