ALKYLPHENOLS BULLETIN

An Update from the Alkylphenols & Ethoxylates Research Council June 20, 2007

The Alkylphenols Bulletin periodically notifies manufacturers and users of alkylphenols and their derivatives of national and international developments of interest. For further information, please contact the APE Research Council at the address below.

HUMAN SAFETY OF NPE

The results of numerous mammalian toxicity studies conducted on nonylphenol (NP) and nonylphenol ethoxylates (NPE) along with an understanding of their occupational and consumer use practices[i] support the conclusion that human safety should not be a concern for these compounds.

This view was confirmed in a 2001 risk assessment[ii] conducted jointly by the governmental agencies Health Canada (HC) and Environment Canada (EC) that concluded NP and NPE "are not considered a priority for investigation of options to reduce human exposure." The Canadian assessment emphasized that worst case assumptions about exposure to these compounds via skin contact were used in their assessment. It was assumed that NP and NPE "absorbed across the skin to the same extent as via the gastrointestinal tract," which greatly overestimates absorption through the skin. A study published in 2003 determined that the skin absorption of NP and NPE is less than 1% and was "even lower than previous estimates"[iii] indicating that the Canadian assessment was very conservative.

The Canadian assessment also considered the potential for these chemicals to demonstrate estrogenic activity. It concluded NPE of longer chain lengths (NPE4, NPE9 and NPE12), which are the NPE of commercial interest, were not estrogenic in *in vivo* (conducted on living animals) studies and in a sensitive *in vitro* (laboratory) test.[iv] These longer chain NPE are the ingredients found in the products that workers and consumers use.

The Canadian Assessment also concluded "NP was estrogenic only at relatively high doses." In fact, those studies that have shown NP to have any estrogenic activity have shown only very weak activity - ten thousand to one million times less potent than the natural estrogen found in the human body. It is also note-worthy that "estrogenic activity" is a term considered by many scientists to be a mechanism of action rather than a toxicological endpoint - or effect - in and of itself.

Traditional toxicological studies in rats that measure chronic effects (due to long-term exposure) and/or monitor effects in parents and offspring over multiple generations often include an evaluation of reproductive and developmental effects that are indicative of an

endocrine mode of action. Numerous studies - some conducted over two or three generations - have evaluated whether the alleged weak estrogenic activity of NP affected reproductive or developmental end points in rats.[v,vi,vii,viii, ix,x] These studies uniformly concluded that there are no effects on reproductive function or performance from NP at any of the doses tested. These findings are consistent with and support the results of a multi-generation rat study conducted by the US National Institute of Environmental Health Sciences, which concluded that "NP was not a selective reproductive or developmental toxicant."[xi] Another recently published study determined that there were no adverse effects on sperm following three generations of exposure in rats.[xii]

Research has also confirmed that ingested NP is rapidly broken down into compounds that are not estrogenic and are eliminated within 24 hours.[xiii] This study, conducted on rats, also confirmed that no significant accumulation of NP occurs in any body organ or tissues following dosing at levels exceeding real-world exposure estimates. More recent assessments conducted by Environment Canada[xiv] and the State of Washington[xv] have also confirmed that NP and NPE do not bioaccumulate, meaning they do not build up in the body or in the food chain.

In conclusion, the weight-of-evidence provided by numerous existing studies on NP and NPE supports the human safety of these products in their current uses.

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[i] NPEs are surfactants used in a wide variety of applications including detergents, cleaning products and paper and textile manufacture. NP is used solely in industrial settings for the manufacture of NPE and other compounds. It is also a minor intermediate formed during the anaerobic (lacking oxygen) biodegradation of NPE in the environment.

[ii] Environment Canada and Health Canada. (2001). Priority Substances List Assessment Report - Nonylphenol and its Ethoxylates.

[iii] Monteiro-Rivere, N.A., Van Miller, J.P., Simon, G.S., Joiner, R.L., Brooks, J., and Riviere, J.E. (2003). In Vitro Percutaneous Absorption of Nonylpheonl (NP) and Nonylphenol Ethoxylates (NPE-4 and NPE-9) in Isolated Perfused Skin. Journal of Toxicology: Cutaneous and Ocular Toxicology, 22 (1&2), 1-11.

[iv] Environment Canada and Health Canada. (2001).

[v] Latendresse, J.R., Weis, C.C., Mellick, P.W., Newbold, R.R., and Delclos, K.B. (2004). A Five Generation Reproductive Toxicity Assessment of *p*-Nonylphenol (NP) In CD Sprague-Dawley Rats. Toxicologist, 1066, 219.

[vi] Nagao, T., Wada, K., Marumo, H., Yoshimura, S., and Ono, H. (2001). Reproductive Effects of Nonylphenol in Rats after Gavage Administration: A Two-Generation Study. Reproductive Toxicology, 15, 293-315.

[vii] Odum, J., and Ashby, J. (2000). Neonatal Exposure of Male Rats to Nonylphenol Has No Effect on the Reproductive Tract. Toxicological Sciences, 56, 400-404.

[viii] Odum, J., Pyrah, I.T.G., Soames, A.R., Foster, J.R., Van Miller, J.P., Joiner, R.L., and Ashby, J. (1999). Effects of p-Nonylphenol (NP) and Diethylstilboestrol (DES) on the Alderley Park (Alpk) Rat: Comparison of Mammary Gland and Uterus Sensitivity Following Oral Gavage or Implanted Mini-pumps. Journal of Applied Toxicology, 19, 367-378.

[ix] Cunny, H.C., Mayes, B.A., Rosica, K.A., Trutter, J.A., and Van Miller, J.P. (1997). Subchronic Toxicity (90-Day) Study with *para*-Nonylphenol in Rats. Regulatory Toxicology and Pharmacology, 26, 172-178.

[x] Tyl, R., Myers, C.B., Marr, M.C., Castillo, N.P., Seely, J.C., Sloan, C.S., Veselica, M.M., Joiner, R.J., Van Miller, J.P., and Simon, G.S. (2006). Three-Generation Evaluation of Dietary para-Nonylphenol in CD (Sprague-Dawley) Rats. Toxicological Sciences, 92, 295-310.

[xi] Chapin, R.E., Delaney, J., Wang, Y., Lanning, L., Davis, B., Collins, B., Mintz, N., and Wolfe, G. (1999). The Effects of 4-Nonylphenol in Rats: A Multigeneration Reproduction Study. Toxicological Sciences, 52, 80-91.

[xii] Tyl. (2006).

[xiii] Green, T., Swain, C., Van Miller, J.P., and Joiner, R.L. (2003). Absorption, Bioavailability, and Metabolism of para-Nonylphenol in the Rat. Regulatory Toxicology and Pharmacology, 38, 43-51.

[xiv] Environment Canada. (2005). Decision on Categorization of Nonylphenol, Octylphenol and their Ethoxylates. http://www.aperc.org/docs/environmentcanadadecision112105.pdf

[xv] Department of Ecology. (2006). Washington State PBT Rule (Chapter 173-333 WAC). http://www.ecy.wa.gov/programs/eap/pbt/rule/.