Environmental and human health concerns relating to diethyl phthalate (DEP), a common ingredient in cosmetics and other personal care products

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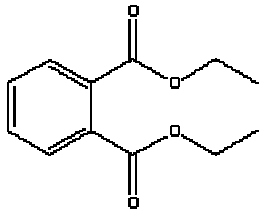
Greenpeace Research Laboratories Technical Note 06/2004

1. Introduction

Diethyl phthalate (DEP) belongs to a big family of phthalic acid diesters. It is a man-made, colourless, oily liquid with a slight aromatic odour and a bitter taste. Trade names include neantine, solvanol, estol 1550, palatinol A, phthalol, and placidol E.



Structure of diethyl phthalate

DEP is used in a diverse array of cosmetic and other personal care products, primarily as a solvent and vehicle for fragrances and other cosmetics ingredients and as an alcohol denaturant (SCCNFP 2003). Recently, the World Health Organisation (WHO 2003) has published a Concise International Chemical Assessment Document (CICAD) on diethyl phthalate. This document was developed based on publications available up to October 2001 and concludes that:-

- *As a result of its widespread use, human exposure to DEP is expected to be significant (albeit generally at doses substantially below those which induce the standard toxicological endpoints employed in most acute studies)*
- *DEP is likely to undergo biodegradation in the environment, and has a lower capacity to bind to sediments and to biomagnify through the food chain than many other phthalates*
- *Although DEP is hydrolysed to the monoester in the body and does not accumulate in tissues over time, it is clear that dermally applied DEP can penetrate the skin and become widely distributed around the body following each exposure*
- *DEP is a minimal to mild skin and eye irritant in animals and cases of both dermal irritation and dermal sensitisation, although rare, have been described in humans exposed to DEP*
- *Although changes in liver and kidney weights can occur following oral exposure, no adverse clinical or histopathological changes have been detected in most studies*
- *No carcinogenic effects were observed in rats following dermal exposure, though more equivocal results were obtained following dermal exposure in mice and in* in vitro *mutagenicity studies*

- *Perinatal exposure to DEP did not induce adverse effects in mothers or offspring, nor malformations of male reproductive organs, as have been observed for some other phthalates in laboratory animal studies*
- *However, in continuous breeding studies, decreased epididymal sperm concentration in the F_1 generation and decreased number of live F_2 pups per litter were observed in mice at higher doses. Ultrastructural changes in Leydig cells of rats have also been observed after only 2 days of oral dosage at 2000mg/kg*
- *No adverse immunological or neurological effects have been reported to date*
- *Although risks estimated for aquatic organisms are considered relatively low (using standard risk assessment methods), insufficient data are available to estimate risks to soil organisms or marine organisms*

A number of studies published since 2001 have raised additional concerns relating to phthalate esters, including DEP, in connection with human health and environmental effects due to their widespread distribution (WHO 2003, Blount *et al.* 2000) and lack of statistical information on toxicity of some phthalates.

2. Concerns regarding direct exposures for consumers

There are several significant routes of general population exposure to phthalates that have been more extensively reported recently, including inhalation (Adibi *et al.* 2003, Fromme *et al.* 2004), ingestion of food contaminated with phthalates (WHO 2003) or medication containing phthalates in enteric coatings (Hauser *et al*. 2004), and dermal absorption (Koo *et al.* 2002, WHO 2003). This last route is particularly important for products applied to skin. Inhalation and dermal absorption might be the primary routes of exposure to diethyl phthalate as this is chemical used in a variety of cosmetic products and toiletries and has moderate volatility.

People exposed to diethyl phthalate will excrete mono-ethyl phthalate in their urine. The amount of mono-ethyl phthalate is an indicator of how much contact with diethyl phthalate has occurred. It was reported (CDC 2003, Silva *et al.* 2004) that monoethyl phthalate (MEP), created in the body from diethyl phthalate, was present in the urine of adults aged 20 and older at nearly twice the concentration found in children aged 6-11. Levels in females were higher than levels in males. Non-Hispanic blacks had higher levels than non-Hispanic whites or Mexican Americans. It is currently unknown whether differences between ages, genders or races/ethnicities result from differences in exposure, body size relationships or metabolism.

Another study (Colon *et al.* 2000) reported that DEP was among other phthalates identified in the serum of Puerto Rican girls with premature breast development (thelarche). Puerto Rico has the highest known incidence of premature thelarche ever reported. DEP was detected in samples in concentrations of tens of parts per billion. Although this is a statistical association only, it is clearly worthy of further investigation.

Duty *et al.* (2003) investigated whether DNA integrity was associated with urinary concentrations of five phthalate monoesters including monoethyl phthalate (MEP), a metabolite of DEP, using neutral comet assay in human sperm. MEP was detected in 100% of subjects and had the highest concentration among other phthalate monoesters, ranging from 9.8 to 5396.2 ppb with a geometric mean of 186.8 ppb. The median MEP concentration ranged from 9- to 32-fold higher than any other phthalate metabolite. This study suggested that there was a statistically significant positive association between urinary MEP and increased DNA migration in the comet essay. Similar associations were not apparent for four other phthalates specifically quantified. However, as it was the first epidemiologic study on the subject and phthalate levels were based on a single urine

sample from a limited number of subjects (sample size for statistical analysis was 141 subjects), the authors suggested that the data must be interpreted cautiously and these results need to be duplicated in a larger study.

More recently still, Hoppin *et al.* (2004) studied the respiratory impact of phthalates in adults using urinary levels of phthalate monoesters and linked these to spirometry data collected the same day. The results suggested that two phthalate monoesters, monoethyl phthalate and monobutyl phthalate, might be associated with adverse pulmonary function among adult men.

3. Concerns regarding environmental exposures and ecotoxicity

Substantial usage and releases of DEP to the environment continue (Yuan *et al.* 2002, Hashizume *et al.* 2002) presenting concerns regarding its aquatic toxicity. The aquatic toxicity of DEP is quite well documented (WHO 2003). Fish were found to be more sensitive than algae while invertebrates spanned a wide range in toxicological responses (Parkenton & Konkel 2000). 10 day LC50 values (lethal concentration for 50% of the population), based on observed concentration-response relationship, were calculated for DEP (Call *et al.* 2001) for freshwater benthic species *H. azteca*, *C. tentans*, and *L. variegatus* as 4.21, 31.0, and 102 mg/L respectively. Ghorpade *et al.* (2002) showed in experiments with the freshwater fish *Cirrhina mrigala* that DEP at concentration in water above 75ppm caused 100% mortality within 24 hours. At lower concentrations (25 and 50ppm) mortality was dose-dependant. Enzyme assays carried out on liver, muscle, and brain samples of experimental fish showed that DEP is capable of interfering with the metabolic processes by altering enzyme activity of these vital organs. The long-term implications of such changes in enzyme activity are not known, though they could prove detrimental to survival.

In the study of the effect and toxicity of phthalates to hemocytes and the cellular defence functions of crustaceans, it was found that, in cultivated prawn *M. rosenbergii,* phthalates including DEP are able to inhibit cellular-immune responses (Sung *et al.* 2003). Hemocytes that are exposed to DEP for more than 10 minutes would primarily die through necrosis.

As noted above, once released into the environment, DEP is a subject to biodegradation by microorganisms (Chang *et al.* 2004, Yuan *et al.* 2002), that can lead to formation of degradation products such as the monoester (MEP) and phthalic acid (Jonsson & Baun 2003). It has been shown in tests with the bacterium *Vibrio fischeri*, the green alga *Pseudokirchneriella subcapitata* and the crustacean *Daphnia magna* that, additionally to the toxic effects of the DEP itself (EC50 ranged from 26.2 to 377 mg/L), its degradation products may also be toxic, though to a lesser extent than the parent compounds (Jonsson & Baun 2003).

4. Conclusions

In short, therefore, although evidence for adverse effects of DEP remains limited relative to that available for certain other phthalates, sufficient evidence does exist to give reasonable cause for concern regarding widespread environmental releases and human exposure through direct skin application. In our view this concern is sufficient to justify precautionary action, in particular to avoid the use of DEP in cosmetics and personal care products wherever less hazardous alternatives are available and to redouble efforts to identify such alternatives where they do not already exist.

In its updated opinion concerning diethyl phthalate, the EU Scientific Committee on Cosmetic Products and Non-Food Products intended for consumers (SCCNFP 2003) reviewed in particular the work of Duty *et al.* (2003) and arrived at a similarly cautious conclusion to that expressed in Section 2 above. For example, the Committee stressed that:-

"The results have to be considered with caution because of confoundings that belong to the representativity of the population exposed, the small number of selected people extracted from an andrology clinic and also, to limitations in term of interpretation regarding health effects. This study should therefore be considered as a pilot study that needs to be confirmed"

The advice of the SCCNFP that data should be considered with caution and that the results need to be confirmed is entirely reasonable. Nevertheless it is important to note that neither the Committee nor any other competent body has so far dismissed the work of Duty *et al.* (2003). Neither have the results been subsequently contradicted or refuted. Rather the findings stand to be confirmed or challenged through further research. Until such time, it can equally reasonably be argued that the results of this study raise significant additional cause for concern regarding potential health effects. Whether the remaining uncertainty is seen to provide sufficient reassurance to allow continued use of DEP (as the SCCNFP conclude) or sufficient concern, alongside other emerging evidence, on which to propose precautionary action to replace DEP with less hazardous alternatives depends merely on the philosophical and regulatory perspective from which the issue is approached. In this regard, it is important to note that the precautionary principle is now established as a fundamental tenet of much international law regarding environmental and health protection and the regulation of chemicals.

It should also be noted that although the original opinion expressed by the SCCNFP (2002) on DEP was based on a review of 117 references, only 2 of these had been published in the period from 2000 onwards. Of these two, one was subsequently discarded from consideration in formulating the final opinion of the Committee. The updated opinion of the SCCNFP (2003) was based on consideration of only two additional references, only one of which (Duty *et al.* 2003) was specific to DEP. In comparison, the synopsis provided above is based exclusively on literature published since 2000, including some reviews of previously published data but predominantly reflecting new research and emerging issues. It is important additionally, therefore, that our considered view that precautionary action is justified should not be seen as being in direct conflict with the SCCNFP since the body of literature reviewed is significantly different.

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