8 CARCINOGENICITY

In a carcinogenicity study (47, 62) groups of 50 male and female Fischer 344 rats and male and female $B6C3F_1$ mice were fed diets containing 6000 or 12000 (rats) or 3000 or 6000 (mice) mg DEHP/kg for 103 consecutive weeks. Concurrent controls (50 of each sex and species) were fed diet without the addition of DEHP. All of the animals were given control diet for 1-2 weeks after 103 weeks of treatment and were then killed and examined both grossly and microscopically. Food and water were supplied ad libitum. The administered concentrations of DEHP were estimated to be half maximally tolerated doses and maximally tolerated doses.

Table I. Carcinogenic effect of DEHP on the liver (from ref 62)

	Control	Low dose	High dose
Hepatocellular carcinoma			
Male rats	1/50	1/49	5/49
Female rats	0/50	2/49	8/50
Male mice	9/50	14/48	19/50
Female mice	0/50	7/50	17/50
Neoplastic nodules			
Male rats	2/50	5/49	7/49
Female rats	0/50	4/49	5/50
Hepatocellular adenoma			
Male mice	6/50	11/48	10/50
Female mice	1/50	5/50	1/50

Under these conditions, DEHP caused an increased incidence in female rats and male and female mice of hepatocellular carcinomas, and an increased incidence in male rats of either hepatocellular carcinomas or neoplastic nodules. (See Table I.) Twenty of the 57 hepatocellular carcinomas in the DEHP-treated mice (sexes and doses combined) had metastasized to the lung. The 9 hepatocellular carcinomas in control male mice are said to be within a normal range (62).

The reported decreased incidence of tumors of the thyroid, pituitary, and testis could be related to an increased endocrine activity of the pituitary gland (62).

The carcinogenicity of DEHP was supported by the results of another chronic study (78) even though the group sizes were small in that study.

IARC (45) has made the evaluation that there is sufficient evidence for the carcinogenicity of DEHP phthalate in mice and rats, based on a significantly increased incidence of liver cell tumors in animals of both species, and an observed dose-response relationship.

Two other long-term studies have been performed (21, 44), but due to the small numbers of animals used, the studies are inadequate to assess the carcinogenic potential of DEHP.

9 SPECIAL STUDIES

Since DEHP in most test systems lacks genotoxic activity it has been hypothetized that the carcinogenic effect is exerted during the promotion phase of hepatocarcinogenicity. DEHP has therefore been tested in several initiation/promotion experiments in rats and mice where the end point has been the number and/or volume of foci of altered liver cells. As expected, DEHP lacks initiating activity in these experiments (78, 120). DEHP is a probable promoter of such foci in the mouse liver and accordingly a possible tumor promoter in the mouse (120). In the rat, however, DEHP does not promote altered foci during two years of feeding (78) and even seems to accelerate the regression or inhibit the appearance of some kinds of such

foci (28, 29). The reasons for this, as well as for the divergent responses in rats and mice, are unclear.

Extrapolation from mouse data to humans is considered impossible since the mechanism of altered foci promotion in mice is unknown.

10 EFFECTS ON MAN

Two adult subjects who were given 5 or 10 g of DEHP experienced no untoward effects apart from mild gastric disturbances and moderate catharsis at the 10 g dose (95). Three cases of non-specific hepatitis were described among 27 hemodialysis patients with terminal renal failure. The PVC blood tubings used released DEHP in an amount of 10-20 mg/l perfusate. The symptoms and signs of hepatitis disappeared rapidly when the use of tubings not containing DEHP was resumed (63).

There are very few data on effects on man of specific DEHP occupational exposure on man.

Two studies report symptoms and signs of polyneuropathy among 47 out of 147 and 12 out of 23 workers examined in a Russian PVC-processing plant and an Italian plant for phthalate production. The workers were exposed to mixed phthalates and DEHP was a minor exposure, at least in the Russian plant. The total phthalate air concentrations recorded varied between 1.7 and 66 mg/m^3 and 1 and 60 mg/m^3 respectively (36, 59).

In a study from a Swedish PVC-processing factory the presence of symptoms and signs from the peripheral nervous system were examined among 54 male workers exposed mainly to DEHP, diisodecylphthalate and some butylbenzylphthalate. The workers were divided into three groups of equal size with mean phthalate exposures 0.1, 0.2 and 0.7 mg/m^3, respectively. None of the outcome variables studied showed a significant association with exposure (64). No subject reported work related obstructive lung disease and conventional lung function tests showed no association with exposure.

Several biochemical parameters showed significant associations with exposure. There was a slight decrease of the hemoglobin level with time of

employment as well as exposure in the last year. Alpha-1-antitrypsin in serum increased slightly with time of employment and immunoglobulin A in serum rose with rising exposure during the last year (64).

One case of occupational asthma due to DEHP has been reported in a PVC-processing worker (17). When the patient was exposed to DEHP in an inhalation chamber an asthmatic reaction was elicited. The action was inhibited by prior administration of sodium chromoglycate.

A study of blood lipids, serum activities of liver enzymes and routine hematological tests was carried out among workers in a German plant for DEHP production. The study was negative and uninformative due to lack of a control group and very low exposures, below 0.16 mg/m^3 (112).

Thiess & Flieg (110) investigated the frequency of chromosome aberrations in 10 workers engaged in DEHP production in the same plant from 10-30 years. There was no increase in chromosome aberrations compared to control groups but air exposure levels were very low, 0.09-0.16 mg/m^3.

A mortality study of 221 workers exposed to DEHP in the same plant was also conducted in which there were only 8 deaths. The study is uninformative due to small cohort size, short follow-up and low exposures (111).

IARC (45) concluded that no adequate data were available to assess the carcinogenicity of DEHP to humans.

11 CONCLUSIONS

Data on occupational exposure concentrations are limited. Concentrations of DEHP up to about 5 mg/m^3 have been reported but usually the industrial levels of DEHP are below 1 mg/m^3. In some cases the total phthalate exposure concentrations have been recorded to be between 0.1 and 60 mg/m^3.

Dose dependent kinetics of DEHP or its metabolites have been indicated in several studies as well as marked animal species differences in metabolism. Induction phenomena have also been described. These facts complicate

extrapolation from animal studies to man and also extrapolations from high doses to low doses.

Data on effects of DEHP on humans are scarce and do not permit any conclusions on dose-effect or dose-response relationships.

There are no data on health effects from DEHP exposure outside the occupational environment. A few studies of workers exposed to phthalate mixtures have been published. However, no consistent findings are reported.

One case-report suggests that DEHP could cause asthma.

In animals few inhalation studies have been performed. The oral and intraperitoneal LD_{50} values exceed 25 g/kg, which indicate that DEHP has low acute toxicity. Prolonged dosing of DEHP produces hepatomegaly and proliferation of peroxisomes. In the rat the no-effect level for feeding studies appears to be about 0.01% in the diet. The no-effect level in the rat for testicular atrophy fed DEHP is about 0.3-0.5% in the diet, and is more pronounced in young animals. Hamsters and mice appears to be more resistant to the testicular effects of DEHP.

In rats 2% DEHP in the diet throughout gestation produced an increased incidence of resorptions but not of malformations. In the mouse, however, 0.1% throughout pregnancy increased the incidence of embryolethality and abnormalities. Days 7-9 of gestation were most sensitive. The dose, 0.05 g/kg, to mice which induced fetotoxicity, is not expected to induce maternal toxicity. Contradictory results are obtained in fertility studies with DEHP.

Results from several different genotoxicity tests indicate that DEHP and its major metabolites do not exhibit any direct genotoxic effect in either bacteria, fungi or mammalian cells in vitro. This has also been confirmed in binding studies with DEHP, which indicated that DEHP and its metabolites do not interact covalently with DNA. However, it has been established that DEHP has the potential of inducing aneuploidi in fungi, as well as in mammalian cells in vitro. These results, together with several positive results obtained in different cell transformation assays, indicate that DEHP can effect the cellular genome in vitro.

DEHP acts as a tumor promoter in mouse liver but not in rat liver in established in vivo test systems.

High doses (12000 mg/kg in rats; 6000 mg/kg in mice) of DEHP in a feeding study resulted in increased incidences of hepatocellular carcinoma.

Based on animal data it can be concluded that DEHP is carcinogenic and teratogenic. Due to a lack of human data the degree of risk to humans can not be evaluated, but DEHP should be considered as potentially carcinogenic and teratogenic to humans.

12 SUMMARY

12.1 Summary in English

P. Garberg, J. Högberg, I. Lundberg, P. Lundberg. NIOH and NIOSH basis for an occupational health standard: Di(2-ethylhexyl)phthalate. Arbete och Hälsa 1989:25, pp 1-53.

The document is a survey of the literature with regard to health effects of exposure to DEHP. Data on occupational exposure levels and effects on humans are limited. DEHP is hydrolized to MEHP and further oxidized. No accumulation has been observed.

DEHP has a low acute toxicity. Long-term exposure to rats causes testicular atrophy. DEHP is carcinogenic and teratogenic in rodents. Most genotoxicity tests have been negative. However, certain tests have indicated that DEHP may affect the genome in vitro.

Key words: DEHP, testicular atrophy, teratogenicity, carcinogenicity, genotoxicity

12.2 Sammanfattning på svenska

P. Garberg, J. Högberg, I. Lundberg, P. Lundberg. NIOH and NIOSH basis for an occupational health standard: Di(2-ethylhexyl)phthalate. Arbete och Hälsa 1989:25, s 1-53.

Dokumentet utgör en sammanställning av litteraturuppgifter beträffande hälsoeffekter vid exponering för DEHP. Data på exponeringsnivåer i arbetsmiljö och effekter på människa är begränsade. DEHP hydrolyseras till MEHP som oxideras vidare. Någon accumulering har inte observerats.

DEHP har låg akuttoxicitet. Långtidsexponering av råtta orsakar testikelatrofi. DEHP är carcinogen och teratogen för gnagare. De flesta genotoxicitetstest har givit negativa resultat. Vissa test antyder att DEHP dock kan påverka genomet in vitro.

Nyckelord: DEHP, testikelatrofi, teratogenicitet, carcinogenicitet, genotoxicitet

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Sent for publication October 5, 1989.