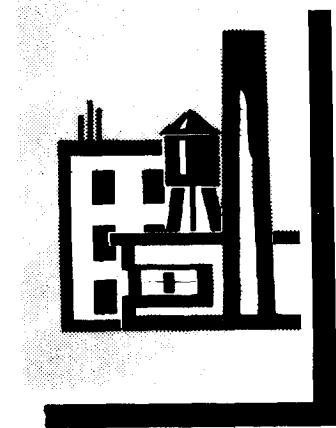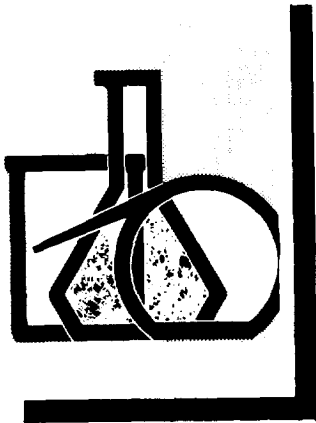# NIOSH

SPECIAL OCCUPATIONAL HAZARD REVIEW

ALTERNATIVES TO DI - 2 - ETHYLHEXYL PHTHALATE ("DOP") RESPIRATOR QUANTITATIVE FIT TESTING

SPECIAL OCCUPATIONAL
HAZARD REVIEW

ALTERNATIVES TO DI-2-ETHYLHEXYL PHTHALATE ("DOP")
IN
RESPIRATOR QUANTITATIVE FIT TESTING

DISCLAIMER

Mention of company names or products does not constitute endorsement by
the National Institute for Occupational Safety and Health.

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PREFACE

The Occupational Safety and Health Act of 1970 emphasizes the need for standards to protect the health and safety of workers exposed in the workplace. In order to fulfill its responsibilities under the Act, the National Institute for Occupational Safety and Health (NIOSH) established a program to evaluate the adverse health effects of widely used chemical and physical agents and make recommendations for preventing these adverse effects. This includes the development of documents which summarize any needed development of (or change in existing) standards. Such reports usually describe health effects including cancer, mutagenicity, teratogenicity or other effects on reproduction associated with occupational exposure to the agent or process, as well as recommending control measures, including work practices, to assist in protecting the health and well-being of workers.

This document evaluates recent information concerning di-2-ethylhexyl phthalate (DEHP) a substance widely used in the quantitative fit testing of respiratory protective devices. In 1982, the National Toxicology Program (NTP) reported positive results of tests of carcinogenicity in two species of rodents exposed to DEHP. As a result of that report, we (NIOSH) recommended several practices for reducing exposure to DEHP during the testing of respirators, and for the use of other materials in substitution for DEHP. The basis for these recommendations is provided on the following pages.

Contributions to this report by other Federal agencies or departments, external reviewers, reviewers selected by the American National Standards Institute, as well as the staff of NIOSH, are acknowledged and gratefully appreciated. The reviewers and the Federal agencies that received the report for review are listed on pages vii and viii. The conclusions and recommendations expressed in this report are those of the Director and staff of NIOSH, and not necessarily those of the reviewers or other Federal agencies. However, all comments, whether or not incorporated, have been carefully considered.

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SYNOPSIS

Di-2-ethylhexyl phthalate (DEHP; commonly known as "DOP") is examined for occupational carcinogenic potential and overall toxicity in respirator quantitative fit testing (QNFT). A DEHP aerosol is used in QNFT to measure faceseal leakage for the individual respirator wearer. Under present technology, the direct measurement of facial fit in QNFT is critical because only a limited number of respirator sizes and styles are marketed to accommodate an infinite array of human facial sizes and characteristics. NIOSH initiated this review of QNFT when the National Toxicology Program (NTP) reported that DEHP was carcinogenic in two rodent species under experimental conditions of the standard bioassay protocol. After evaluating all the information, NIOSH has concluded that a prudent course must now be followed in QNFT. Specific NIOSH recommendations for maintaining the important workplace practice of fitting respirators by QNFT are described in this report.

Although NIOSH estimates the carcinogenic risk to be minimal for the respirator wearer under normal conditions, at least the following two critical exposure factors must be considered in QNFT: (1) Exposures to the DEHP aerosol can vary for the respirator wearer being tested if QNFT is improperly conducted. (2) Field practitioners administering QNFT, especially those using portable testing equipment where aerosol ventilation is difficult to control, can be subjected to routine and varying exposures. Because such varying exposures can increase the attendant hazard, NIOSH advises that a substitute aerosol is required to replace DEHP in QNFT.

NIOSH tested several agents considered likely candidate substitutes to determine their suitability for use in existing QNFT equipment, originally made for the DEHP aerosol. The concentration and size distribution of the aerosol particles, critical factors in selecting a substitute, were determined for each candidate and compared to the aerosol characteristics of DEHP. Our experimental results indicated that (1) refined corn oil, (2) di-2-ethylhexyl sebacate (DEHS), and (3) dimethicone (Dow Corning 200 fluid, 50-centistoke) all exhibited polydisperse aerosol particle characteristics essentially equivalent to those generated with DEHP. These findings late- initiated direct applications of refined corn oil and DEHS aerosols in actual respirator fitting tests. Field test results at several different facilities showed that both refined corn oil and DEHS aerosols are highly suited for conducting QNFT.

After acceptable candidates were identified by their intrinsic aerosol properties, NIOSH also reviewed reports describing the toxicity and any associated health effects for each agent, as an aid in selecting the best option. Our review revealed that extensive laboratory tests have been conducted on refined corn oil in a variety of mammalian species. All the studies evaluated indicated a low toxicity for the compound. Furthermore, refined corn oil has demonstrated a lack of carcinogenic potential during

its extensive use as a control vehicle in carcinogen bioassays and other more direct experimental applications. Although the knowledge of the toxicity of any compound is seldom complete, the low toxicity of refined corn oil is well documented, in contrast to the other candidate agents. Review of the limited available reports on DEHS and dimethicone indicated little toxicity data that is relevant to a QNFT exposure. For the moment, unresolved questions about the metabolic fate of DEHS, thought to be similar to that of DEHP, also tend to preclude this candidate from further consideration.

NIOSH aerosol test results suggested that at least three substances are suitable for use in QNFT, while the toxicity assessment indicated that only one of these agents should be considered acceptable. Since toxicity is so critical in the final selection of a feasible substitute, NIOSH concludes, from the experimental evidence examined, that refined corn oil stands apart from the other agents. For these reasons, NIOSH recommends that a refined corn oil aerosol is the best option to replace DEHP in QNFT. The appropriate maintenance requirements for using a refined corn oil aerosol in QNFT are described in this report.

ACKNOWLEDGMENTS

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CONTENTS

I. INTRODUCTION

Respirator design and manufacturing specifications are most effective when the respirator facepiece properly fits the face of the wearer (Pritchard, 1976). The facepiece fit of a respirator may be measured either quantitatively or qualitatively. Quantitative fit testing (QNFT) actually measures respirator faceseal leakage and results in a numerical value. Qualitative tests do not directly measure facial fit, but instead rely on subjective responses of the wearer, such as odor identification of the vapor of a chemical agent like isoamyl acetate (banana oil). Positive or negative pressure tests and an irritant smoke test are other examples of common qualitative procedures. Selection of the appropriate test depends on the severity of the respiratory hazard for which the respirator is intended. QNFT is highly recommended when faceseal leakage must be minimized for occupations with exposures to highly toxic atmospheres, especially those immediately dangerous to life or health. Direct measurement of faceseal leakage by QNFT has become an integral part of health and safety programs designed to reduce workplace exposures to respiratory hazards.

Di-2-ethylhexyl phthalate (DEHP), used for many years to generate a polydisperse aerosol test atmosphere in QNFT, is the branched-chain isomer of di-n-octyl phthalate. Commonly known to respirator users and others as "DOP," DEHP has been considered to be well suited for QNFT because of its physical characteristics. A polydisperse aerosol consists of 'particles generated with a random size distribution over a narrow range, as opposed to a monodisperse aerosol, which has a uniform particle size distribution. Tests using the polydisperse DEHP aerosol have been demonstrated to be both accurate and meaningful in the evaluation of respirator fit (Hyatt et al, 1972). In QNFT, a human subject wearing a test respirator is placed in a chamber containing the DEHP challenge aerosol nebulized at a specific concentration. To determine faceseal leakage, the atmosphere inside the respirator is sampled through a probe inserted into the test respirator inlet covering, and the aerosol concentration is quantified by light-scattering photometry. Leakage is expressed as the ratio between the test concentration outside the respirator and that gaining entrance inside the facepiece.

The toxicity of the phthalate esters, including DEHP, has been reviewed by several authors (Lawrence et al, 1975; Lawrence, 1978; Thomas et al, 1978; Kolesar, 1980). Although different esters of phthalic acid have been reported to exhibit varying degrees of biologic effects in laboratory tests, DEHP has been considered to have a relatively low order of toxicity. Most reports have indicated that inordinately high doses of DEHP were required to elicit toxic effects in a wide variety of mammalian species. However, continued interest in the toxicity of several phthalate esters and their extensive commercial applications prompted the National Toxicology Program (NTP) to conduct chronic bioassay testing of DEHP for possible carcinogenicity (NTP Technical Report, 1982). Under the experimental conditions of the NTP test, DEHP elicited statistically significant

increases in the incidence of hepatocellular carcinomas in both sexes of B6C3F1 mice and in female Fischer 344 rats. The data further suggested that the incidence of these liver neoplasms was dose-related.

Because of its previously reported low order of toxicity, DEHP has been considered as an acceptable substance to generate a test atmosphere for QNFT. However, the NTP's recent finding that DEHP is carcinogenic to rodents raises questions about the carcinogenic potential and human risks to the QNFT aerosol. This NIOSH report reviews both the overall toxicity and the carcinogenic potential of DEHP, and describes NIOSH test results indicating that other agents may be substituted for the DEHP aerosol in QNFT. Substitute aerosols were generated with the same equipment originally made for DEHP use. The toxicity of each potential substitute is also examined.

The thermal generation of a monodisperse DEHP aerosol, used to test filter material efficiency in respirator cartridges or other air filtration systems, is not reviewed here. This use of DEHP is different from QNFT and should constitute a separate study. Filter tests with DEHP involve a different type of exposure, and the monodisperse aerosol is generated at such a high temperature that thermal breakdown products of DEHP can result. A QNFT protocol using a polydisperse sodium chloride aerosol is also not discussed here, since this protocol uses different equipment than that for the DEHP method.

II. TOXICITY OF DI-2-ETHYLHEXYL PHTHALATE (DEHP)

General Toxicity

The data reviewed below suggest that DEHP has a low order of acute toxicity. Table II-1 lists LD_{50} values in four animal species by intravenous (iv), intraperitoneal (ip), oral (per os or po), or dermal exposure routes, as adapted from Thomas et al (1978). Subacute and chronic toxic effects occurred only at relatively high doses. Rats administered 0.35% DEHP in the diet for 1 year exhibited lower body weights and increased liver and kidney weights (Nikonorow et al, 1973). No pathologic changes were found in the liver, kidneys, or spleen. At a daily oral dose of 0.2 g/kg to rats for 90 days, Shaffer et al (1945) reported no hematologic or pathologic alterations. Similar low toxicity has been reported for other phthalate plasticizers (Gaunt et al, 1968).

Lawrence et al (1975) studied cumulative effects of DEHP or di-n-octyl phthalate in male ICR mice. A series of doses of either phthalate ester was injected ip into groups of male mice 5 days/week, and an apparent LD_{50} was calculated at the end of each week. This procedure was followed until the apparent LD_{50} remained constant for 3 consecutive weeks, at which time it was assumed that the chronic toxicity value had been reached. Cumulative doses caused the calculated apparent LD_{50} values to decrease as the animals were treated. The initial LD_{50} values were 65,000 mg/kg (di-n-octyl phthlate) and 37,800 mg/kg (DEHP). At the end of 1 week, the calculated LD_{50} dropped to 25,000 mg/kg (di-n-octyl phthalate) and 6,400 mg/kg (DEHP). The toxic response stabilized by week 10 at 3,100 mg/kg (di-n-octyl phthalate) and 1,400 mg/kg (DEHP). The authors concluded that a cumulative effect resulted from repeated exposures to DEHP or di-n-octyl phthalate. Such dramatic increases in lethality over time were interpreted by Lawrence et al to indicate a need to reconsider the element of safety assumed from the relatively high LD_{50} values observed for these phthalate esters.

TABLE II-1

DEHP ACUTE LETHALITY

Species	Route	LD_{50} (g/kg)	Reference
Mouse	po	65.0*	Lawrence et al, 1975
"	ip	14.2	Calley et al, 1966
"	"	20	Mori et al, 1967
Rat	"	50*	Singh et al, 1972
"	po	26	Fassett, 1963
"	"	30.6	Shaffer et al, 1945
"	iv	13*	Miripol et al, 1975
Rabbit	po	33.9	Shaffer et al, 1945
"	iv	31	Harris et al, 1956
Guinea pig	Dermal	10*	Fassett, 1963

*LD_{50} given in ml/kg

Adapted from Thomas et al, 1978

Metabolism and Excretion

DEHP was rapidly excreted within 24 hours after either po or iv administration to male rats (Tanaka et al, 1975). Similar findings for DEHP in rats were reported by Lake et al (1975) following po administration. Daniel and Bratt (1974) examined excretion patterns following a single po administration of ^{14}C-labeled DEHP (1.8 mCi; 2.9 mg/kg) in male and female Wistar rats. Rats excreted 42% of the dose in the urine and 57% in the feces within 7 days. In biliary-canulated rats, 14% of the dose wa excreted in 4 days. Animals fed 1,000 ppm of DEHP in the diet for 7 dayь before administration of ^{14}C-labeled DEHP had 57% of the radioactive label in the urine and 38% in the feces in 4 days. Biliary-canulated rats excreted 9% of the dose in 4 days. When fed continuously at concentrations of 1,000 ppm or 5,000 ppm, DEHP concentrations in the liver attained a steady state in 9-14 days. No further DEHP accumulation was observed when equilibrium was achieved. After rats were returned to a normal diet, the half-life of radioactivity declined in the liver (1-2 days) and fat (3-5 days).

Ikeda et al (1979) evaluated species differences in DEHP excretion patterns. DEHP (50 mg/kg) was administered in the diet to male Sprague-Dawley rats, beagle dogs, and miniature Hormel strain pigs for 21-28 days before a single dose of ^{14}C-labeled DEHP (9.74 mCi/mmol; 50 mg/kg).

Animals were killed at various times, and the distribution of radioactivity was analyzed in specific organs and tissues. The authors observed that approximately 84% of the labeled material was excreted in the urine and feces of rats during the first 24 hours. Excretion during this time was 67% of the labeled DEHP in dogs and 37% in pigs. For all three species, DEHP excretion was virtually complete within 4 days. Amounts of radioactivity detected in muscle and fat of both dogs and pigs did not decrease as rapidly as those in liver or lung tissue. The authors emphasized that the greater amounts of fat and muscle tissue in the dog and pig were probably responsible for the slower depletion of labeled material. In addition, these investigators noted four radioactive labeled substances in rat urine, three in dog urine, and five in pig urine. No more than a trace of unmetabolized DEHP could be detected in the urine of each species. In 1981, Albro et al reported evidence of species variations in rodents, African green monkeys, and humans. The investigators observed that primates excrete glucuronide conjugates of mono(2-ethylhexyl)phthalate (MEHP), and rats excrete alkyl diacids. Thus, the mechanisms for the elimination of DEHP in primates and rodents appear to differ.

Limited pharmacokinetic investigations of DEHP have been reported. Daniel and Bratt (1974) observed that DEHP was extensively metabolized following po administration to male and female Wistar rats. In rodents, DEHP is initially hydrolyzed to 2-ethylhexanol and MEHP (Albro et al, 1973; Daniel and Bratt, 1974). The remaining alkyl chain of the monoester may then be oxidized to form acids, alcohols, and ketones. Although hydrolysis of DEHP may occur in the liver or small intestine, Daniel and Bratt (1974) observed that DEHP was more rapidly hydrolyzed in vitro when incubated with pancreatic lipase than with rat liver homogenate.

Carcinogenic Effects in Animals

Positive evidence of DEHP carcinogenicity resulted when the NTP tested the compound under the experimental conditions of the chronic bioassay protocol (NTP Technical Report, 1982). Testing results indicated that DEHP elicited treatment-related increases in the incidence of liver carcinomas in two rodent species. Groups of 50 male and 50 female Fischer 344 rats received either 12,000 ppm (the maximum tolerated dose) or 6,000 ppm of DEHP in their diets daily for 103 weeks. Mice, 50 males and 50 females of the B6C3F1 strain, were also fed diets containing DEHP at either 6,000 (maximum tolerated dose) or 3,000 ppm for 103 weeks. Results were compared with those of matched control animals, 50 untreated rats and 50 untreated mice, of both sexes. Statistical analysis of the data incorporated the one-tailed Fisher exact test to compare the tumor incidence observed in controls with that in dosed animals at each level.

Male rats exhibited an increased incidence of hepatocellular carcinomas or neoplastic nodules in a statistically significant positive relation (p = 0.01 at the high dose when compared with untreated controls (Table II-2). In female rats, significant increase (p = 0.012 in the low-dose

group and p < 0.001 in the high-dose group) in the incidence of hepatocellular carcinomas or neoplastic nodules was reported. A significant increase (p = 0.003) in hepatocellular carcinomas was found in female rats only at the high dose (a 16% final incidence of liver carcinomas, compared with 0% in controls). The incidence of hepatocellular carcinomas alone was significantly increased only in the female rats receiving the high dose. Neoplastic liver nodules, observed in both male and female rats, are thought by NTP to be precursors in a progression to hepatocellular carcinomas.

Histopathologic examination revealed that both male and female B6C3F1 mice exhibited significant increases in the incidence of hepatocellular carcinomas. Male mice had incidences of 29% (low dose) and 38% (high dose), compared with 18% in untreated matched controls; only the incidence of the high-dose group was significantly increased (p = 0.002). Females had a 14% (low dose) and a 34% (high dose) incidence of hepatocellular carcinomas, compared with an absence of such carcinomas in matched controls (Table II-2). The incidence of liver carcinomas was significantly increased for females in both the low-dose (p = 0.006) and high-dose (p < 0.001) groups. Hepatocellular adenomas also resulted in mice of both sexes at incidences higher than matched controls in males (at both doses) and in females (at the low dose), although these differences were not reported to be statistically significant. However, hepatocellular carcinomas or adenomas of the liver in both sexes of mice were observed in a statistically positive relation when compared with controls. High-dose male mice exhibited a significant incidence (p = 0.002) of hepatocellular carcinomas or adenomas; in the low-dose group, significant incidence (p = 0.013) was observed. Females had a significant incidence (p = 0.001) of hepatocellular carcinomas or adenomas at either dose.

A statistically significant positive dose-related trend of carcinogenicity was also reported for DEHP-treated rats and mice by the Cochran – Armitage test for linearity. Under this statistical test, the direction of a significant trend indicates a positive dose relationship to the carcinogenic response. Male rats exhibited hepatocellular carcinomas or neoplastic nodules with a linear trend statistically significant in the positive direction (p = 0.007). The Cochran-Armitage test for female rats was also significant in the positive direction (p < 0.001) for hepatocellular carcinomas and neoplastic nodules. In mice, hepatocellular carcinomas or adenomas of the liver showed a significant positive relation to dose (p = 0.002 for linear trend in males and p < 0.001 for females).

NTP concluded that DEHP was carcinogenic in the two species of rodents under the experimental conditions of the standard bioassay. A statistically significant increase in the incidence of hepatocellular carcinomas resulted in DEHP-treated male and female B6C3F1 mice and female Fischer 344 rats when compared with controls. This response was attributed to DEHP administration. Survival rates of the mice and rats exposed to DEHP did not differ from those of controls, according to the report. No statistically significant trends in mortality were associated with administration of DEHP.

TABLE II-2

INCIDENCE OF LIVER NEOPLASMS IN FISCHER 344 RATS
AND B6C3F1 MICE AFTER A 2-YEAR
DIET CONTAINING DEHP

Fischer 344 Rats	Untreated Matched Controls	Low Dose (6,000 ppm)	High Dose (12,000 ppm)
Males			
Liver			
Neoplastic nodules	2/50(4%)	5/49(10%)	7/50(14%)
Hepatocellular carcinomas	1/50(2%)	1/49(2%)	5/50(10%)
Females			
Liver			
Neoplastic nodules	0/50(0%)	4/49(8%)	5/50(10%)
Hepatocellular carcinomas	0/50(0%)	2/49(4%)	8/50(16%)*

B6C3F1 Mice	Untreated Matched Controls	Low Dose (3,000 ppm)	High Dose (6,000 ppm)
Males			
Liver			
Hepatocellular adenomas	6/50(12%)	11/48(23%)	10/50(20%)
Hepatocellular carcinomas	9/50(18%)	14/48(29%)	19/50(38%)*
Females			
Liver			
Hepatocellular adenomas	1/50(2%)	5/50(10%)	1/50(2%)
Hepatocellular carcinomas	0/50(0%)	7/50(14%)*	17/50(34%)*

*Significantly higher incidence of hepatocellular carcinomas in treated animals when compared with untreated matched controls (as determined by the one-tailed Fisher exact test).

Data excerpted from NTP Technical Report, 1982.

Mutagenic Effects

No definitive evidence of mutagenicity has been reported for DEHP, although a variety of tests have been performed in bacteria and mammalian cell cultures. For example, in the Salmonella in vitro test for mutagenicity using a thousandfold range of concentrations up to 22,500 µg/plate (full-strength DEHP), no excesses (greater than 2 times that of control values) of revertants occurred either with or without liver microsomal (S-9) activation (Hanson, 1979). Similar results were reported with DEHP and its principal metabolite, mono-ethylhexyl phthalate (MEHP), at concentrations up to 1,000 µg/plate (Rubin et al, 1979). One report described excess revertants in Salmonella strain TA 100 with 5,000 µg DEHP plus S-9 (Tomita and Nakamura, 1978). However, no other concentrations or dose-response relationships were given by the authors. NIOSH recently conducted Salmonella mutagenicity testing of DEHP to assess the mutagenic response of test strains TA 98, TA 100, TA 1535, and TA 1537 (Ong, 1981). No mutagenic activity was evident in any of the strains, either with or without S-9 activation.

DEHP at 50 µg/disc yielded negative results in the B subtilis Rec-assay for DNA damage (Tomita and Nakamura, 1978). No increases in chromosomal aberrations were reported following in vitro exposures of up to 60 µg DEHP/ml in cultured human leukocytes or human fetal lung cells (Stenchever et al, 1976) or in Chinese hamster cells (Ishidate and Odashima, 1977).

Teratogenic/Reproductive Effects

A single po dose of DEHP (1.0 ml/kg), administered on day 7 of gestation to a random mouse strain (ddY-Stc female x CBA male), elicited skeletal abnormalities in 18.4% of 38 live fetuses; untreated controls exhibited no adverse effects (Nakamura et al, 1979). Skeletal abnormalities included elongated and fused ribs, absence of tail bones, abnormal or incomplete skull bones, and incomplete or missing leg bones. In addition, the incidence of late fetal deaths was 58.5% as compared with 1.3% in untreated controls. When a higher dose of DEHP, 2.5 ml/kg, was given on day 7, an even greater incidence of skeletal malformations and early fetal deaths resulted. At doses of 5.0 or 10.0 ml/kg, an increase in the incidence of early fetal deaths was observed above that found in mice receiving 1.0 ml/kg. However, when DEHP was administered on earlier or later days of gestation, these effects were either reduced or absent. Fetuses from animals treated on day 7 with lower doses of DEHP (0.05 or 0.1 ml/kg) did not exhibit gross or skeletal malformations, and there was no evidence of an increase in the incidence of induced early fetal deaths. Because there was a linear relationship between fetal death and the dose of DEHP, the authors calculated the noneffective maximum dose in the mouse to be 0.065 ml/kg (64 mg/kg). Although a linear relationship was observed between dose and other fetotoxic effects, the authors concluded that exact values of the noneffective maximum dose for gross and skeletal abnormalities must await further study.

Maternal and fetal effects in rats exposed to DEHP over a wide range of doses have also been studied. Pregnant Wistar rats fed DEHP at doses ranging from 200 to 1,700 mg/kg/day during gestation had litters with reduced fetal body weights and increased resorptions only when maternal doses were 340 mg/kg or greater (Nikonorow et al, 1973; Onda et al, 1976). Furthermore, no adverse effect on fetal skeletal development could be related to doses ranging from 340 to 1,700 mg/kg (Nikonorow et al, 1973). DEHP (340 and 1,700 mg/kg/day) was also administered by gavage for 3 months prior to mating female Wistar rats, but not during gestation. While these doses produced a significant increase in mean maternal liver weights, no adverse embryo-fetotoxic effects were observed.

Embryo-fetotoxic effects observed in other rodent studies resulted only when DEHP was administered at exceedingly high doses. For example, groups of five pregnant female Sprague-Dawley rats, weighing 200-250 g, were given a single ip injection of either DEHP and/or di-n-octyl phthalate on day 5, 10, or 15 of gestation (Singh et al, 1972). Animals were injected with either 5,000 or 10,000 mg/kg, based on an acute LD_{50} determination of over 50,000 mg/kg for both phthalate esters. Control animals received either normal saline (10,000 mg/kg) or cottonseed oil (10,000 or 5,000 mg/kg), or were not treated. Animals were monitored for resorptions, fetal deaths, gross malformations, and skeletal abnormalities. Twisted hind limbs appeared in 15/55 (27.3%) of the fetuses given the high dose of di-n-octyl phthalate and in 8/51 (15.7%) given the low dose. Hemangiomas of the limbs occurred in 9/41 (22%) fetuses following the high DEHP dose; one fetus also developed twisted hind limbs. No gross malformations were observed in the low-dose DEHP treatment group, and no skeletal abnormalities were seen with either phthalate ester.

Singh et al (1974) found a significantly (p < 0.01) depleted number of embryonic implants and reductions in litter sizes following single ip injections of DEHP to male Harlan/ICR mice at 12,500, 18,800, or 25,000 mg/kg. Each male was mated sequentially with two virgin females each week for 12 weeks following DEHP exposure. Four of ten males that received the high dose died within 2 weeks of this single injection exposure, and a fifth male died within 10 weeks. Females mated with males given the high dose had fewer implants per pregnancy during the first 3 weeks than controls. No statistically significant dose-related differences were observed for implants per pregnancy, early fetal deaths, or litter sizes except during the first 3 weeks in the high-dose group. The authors interpreted their results to indicate reduced fertility and possible genotoxicity. However, both the liver and the testes of male rodents can be damaged at these toxic dose levels (Shaffer et al, 1945; Lake et al, 1976), making it difficult to assess potential genetic effects. Singh et al (1975) measured the distribution of radioactivity after ip injections of ^{14}C-labeled DEHP at 5 ml/kg in pregnant rats on day 5 or 10 of gestation. Even at these high doses, the maximum amounts of radioactivity detected were 0.016% in the amniotic fluid and 0.033% in fetal tissue. These data indicated to the authors that a low level of DEHP and/or its metabolites crossed the rat placenta on critical days during gestation.

Human Health Effects

A morbidity study was conducted by Thiess et al (1978) on 101 workers at a German plant that manufactures DEHP. These workers were potentially exposed to DEHP over an average of 12 years (range: 0.3-35 years). Atmospheric concentrations of DEHP in the workplace, as determined by this study, ranged from 0.0006 to 0.01 ppm (approximately 0.01-0.16 mg/m^3). The authors concluded that there were no significant differences in laboratory findings, illnesses, or injury rates in DEHP-exposed workers when compared with control workers from other areas of the same plant. In fact, the amounts of DEHP measured in the blood and urine of six DEHP-exposed workers (0.5-7.0 mg/l plasma; 0.2-7.5 mg/l urine) could not be distinguished from amounts in three medical department controls not directly exposed (0.5-10 mg/l plasma; 0.2-1.5 mg/l urine). This finding indicates the ubiquitous nature of DEHP in the total environment (Lawrence, 1978; Thomas et al, 1978). Thiess et al (1978) also reported no evidence for an increased rate of miscarriages or infant deformities among female workers or wives of male workers at the plant in Germany. Furthermore, no evidence of an increased rate of chromosomal aberrations was detected in leukocyte cultures taken from a group of 10 employees working with DEHP for 10-30 years (Thiess and Flieg, 1978).

Characterization of DEHP Exposure

The exposure of workers to DEHP during respirator QNFT has been reported to be low (Kolesar, 1980). The challenge aerosol concentration of DEHP for most tests is 25 mg/m^3, although some test chamber models can be adapted to challenge concentrations as high as 100 mg/m^3. Maximum uptake of DEHP during fit testing can be calculated for a human test subject assuming a respiration rate of 20 1/min and total absorption of inhaled particles during a full 30-minute test period. An average facepiece leakage of 1% in a 25-mg/m^3 test atmosphere would result in uptake of 150 µg of DEHP. It should be emphasized that QNFT is usually performed only once or twice yearly, or in the initial selection of a respirator. Even in cases where the test might be performed more frequently, DEHP uptake would appear to be minimal under normal conditions. However, the DEHP exposure could vary if QNFT is improperly administered. The exposure to individuals administering the test could also be elevated, especially where portable equipment is used in the field. Exposures of field testers to DEHP may vary considerably because of differences in (1) the duration or frequency of the test and (2) the workplace environment and ventilation characteristics where the test is conducted.

NIOSH has evaluated health hazards in several plants using phthalate plasticizers in thermoplastic molding materials and in a screen printing operation (Health Hazard Evaluations, 1976; 1977; 1978). Based on analytical methods sensitive to 1 ppm, investigators were unable, with one exception, to detect DEHP in either personal or workplace general air samples. In the vicinity of a curing oven, 4 ppm of DEHP was measured in the screen printing plant (Health Hazard Evaluation, 1977). Health effects in workers were not investigated in these studies.

Conclusions

After examining the data from the NTP study, NIOSH concludes that DEHP was carcinogenic to rodents under the experimental conditions of the standard bioassay protocol. This positive response indicates that DEHP should be considered as having a carcinogenic potential. No evidence of DEHP carcinogenicity in humans has been reported, but the scarcity of exposure data seriously limits conclusions that can be drawn.

Albro et al (1981) reported that the metabolism of DEHP in the rat may differ conspicuously from that observed in humans and African green monkeys. The authors found that primates excrete mainly glucuronides of mono(2-ethylhexyl)phthalate, while rats excrete unconjugated diacids. But until more definitive evidence resolves questions about (1) pharmacokinetic distinctions between rodents and humans and (2) the proximate agent that elicited the liver tumors in the NTP test animals, the relevance of these metabolic differences to DEHP carcinogenicity remains uncertain. It should also be emphasized that possible differences between rat and human metabolism of DEHP may or may not relate to the carcinogenic mechanism expressed under the conditions of rodent exposures in the NTP bioassay. Furthermore, the relevance of this species distinction between humans and rats for carcinogenesis awaits determinations of a probable mechanism of tumorigenic action for DEHP. Whether or not mice, which are susceptible to DEHP carcinogenicity, also metabolize DEHP under similar patterns reported for rats and humans is unresolved.

NIOSH, after reviewing all other available information, concludes that DEHP has exhibited negative results in several tests for mutagenicity including the Salmonella in vitro mutagenicity assay. Such negative results may suggest that DEHP is not a genotoxic carcinogen, although direct evidence of tumorigenic promoter activity for the compound is presently lacking. NIOSH also concludes that results of reproductive toxicity testing are inconclusive and that definitive evidence of teratogenicity is lacking. Additional teratogenicity testing is probably warranted from the positive results observed in several mammalian species, although any new experimental protocol should incorporate lower doses than those used in the widely reported studies.

The NTP report of DEHP carcinogenicity in rodents prompted NIOSH to examine the potential human health risks from this phthalate ester in QNFT. Although the available evidence indicates that DEHP exposure in QNFT would be low for the respirator wearer, the possibility for variations in conducting the test are noted by NIOSH. Exposures to the DEHP aerosol could vary if QNFT is improperly conducted in the field, especially where appropriate supervision in administering the procedure is lacking. Furthermore, when mobile portable equipment is used, there is also an increased risk to field practitioners administering QNFT, owing to difficulty in controlling the ventilation of the aerosol. For all these reasons, NIOSH concludes that an alternative QNFT aerosol must be found to reduce the potential health risk. Once identified, the alternative substance should be substituted for DEHP when conducting QNFT.