00148515

SPECIAL
HAZARD REVIEW

OF

DI-2-ETHYLHEXYL PHTHALATE
AND
ALTERNATE TEST AGENTS
IN
RESPIRATOR QUANTITATIVE FIT TESTING

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service
Centers for Disease Control
National Institute for Occupational Safety and Health

SEPTEMBER 1981

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DHHS(NIOSH) Publication No.

SUMMARY

This Special Hazard Review evaluates the toxicity of di-2-ethylhexyl phthalate (DEHP) as used in respirator quantitative fit testing (QNFT). A polydisperse DEHP aerosol test atmosphere is generated in QNFT to assess respirator faceseal leakage. Review of DEHP toxicity was initiated following a recent National Toxicology Program (NTP) test for possible carcinogenicity. Under the standard bioassay test protocol, DEHP was carcinogenic in female Fischer 344 rats and B6C3F1 mice of both sexes. The mechanism for this carcinogenic response is presently unknown. While DEHP's overall toxicity is widely reported to be low, the bioassay test data suggest a human carcinogenic potential. NIOSH estimates that although the carcinogenic risk to DEHP would be minimal under normal respirator test conditions, the exposure in QNFT could vary for the wearer if the procedure is conducted improperly. Persons who administer QNFT are also subject to varying exposures that must be considered, especially where portable equipment is used in the field. After weighing all the information, NIOSH concludes that an alternative test agent for QNFT is required. The present report identifies and recommends specific agents that are suitable as substitutes for QNFT employing the same oil-mist aerosol generating equipment made for DEHP.

Generation of polydisperse aerosols with (1) refined corn oil, (2) di-2-ethylhexyl sebacate (DEHS), and (3) dimethicone (Dow Corning 200 fluid, 50 centistoke) was examined by NIOSH using existing QNFT equipment. Each of these agents had particle characteristics essentially equivalent to those generated with DEHP. The findings of other laboratories indicating successful applications of polyethylene glycols to QNFT is also discussed. The toxicity of all the agents was evaluated and found to be low, further indicating that each could be a candidate for interim use in QNFT. Little toxicity information, however, has been reported for DEHS or dimethicone that is relevant to QNFT. A QNFT protocol that uses a sodium chloride aerosol is not discussed here because it requires different equipment than the DEHP protocol.

Although knowledge of the toxicity of any substance, including refined corn oil, is seldom complete, the low toxicity of this vegetable oil is well documented. Refined corn oil aerosols also have been successfully applied in QNFT at many different facilities under field test conditions. This report describes these findings and the appropriate maintenance requirements for using refined corn oil aerosols as a test atmosphere in QNFT. For these reasons, NIOSH has concluded that refined corn oil is well suited for interim use in conducting QNFT and stands apart from the other agents considered.

ACKNOWLEDGMENTS

The Division of Standards Development and Technology Transfer, Priorities and Research Analysis Branch, was responsible for the development of this Special Hazard Review. Primary NIOSH personnel responsible for this review were Paul Schad and Rhoda Yarkin.

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I. INTRODUCTION

Respirator design and manufacturing specifications can yield maximum effectiveness when a proper match is initially established and subsequently maintained between the respirator facepiece and the face of the wearer (Pritchard, 1976). Facepiece fit tests may involve either qualitative or quantitative procedures. Quantitative fit testing (QNFT) actually measures respirator leakage and results in a numerical value for face seal fit. Qualitative fit tests make no direct measurement but rely instead 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 extent and severity of the respiratory hazard for which a particular type of respirator is intended. QNFT is highly recommended when face seal leakage must be minimized for occupations involving exposures to highly toxic atmospheres, especially those immediately dangerous to life or health. Accordingly, direct measurement of face seal leakage by QNFT has become an integral part of respiratory protection.

Di-2-ethylhexyl phthalate (DEHP) has been used for many years to generate a polydisperse aerosol that is incorporated as a challange test atmosphere in QNFT. This phthalate ester is the branched-chain isomer of di-n-octyl phthalate. DEHP, commonly known to respirator users and others as "DOP," has been considered to be well-suited for this test because of its physical characteristics. Tests using the DEHP aerosol have been demonstrated to be both accurate and meaningful to evaluate respirator fit (Hyatt et al, 1972).

The QNFT procedure involves placing a human subject wearing a test respirator into a controlled atmosphere of a DEHP challenge aerosol generated at a specific concentration. The atmosphere inside the respirator is sampled during the procedure through a probe inserted into the test respirator inlet covering so that face seal leakage may be determined (DEHP aerosol is quantified by light scattering photometry). Leakage is expressed as the ratio between the test concentration outside the respirator and that concentration 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. The majority of reported evidence reviewed has indicated that inordinately high doses of DEHP were required to elicit toxic effects in a variety of animal species. Interest in the toxicity of several phthalate esters and their extensive commercial applications recently prompted the National Toxicology Program (NTP) to conduct chronic bioassay testing of DEHP for possible carcinogenicity (NTP Technical Report, draft, 1980). Histopathologic findings indicated that, under the experimental conditions of the 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 indicated that the incidence of these liver neoplasms was dose related. On October 15, 1980, a draft NTP report describing these test results received peer review and approval by the Technical Reports Review Subcommittee of the NTP Board of Scientific Counselors. The technical report describing these findings will be published later by NTP.

Because of its previously reported low order of toxicity, DEHP has been considered as an acceptable substance to generate a test atmosphere for QNFT. NTP's recent findings that DEHP was carcinogenic to rodents has raised the question of human risk in QNFT. This NIOSH report reviews and evaluates reported toxicologic responses for DEHP and also the results of the NTP carcinogen bioassay test. In addition, this report describes NIOSH test results and those of a Harvard study, both indicating that other agents may be substituted to generate a QNFT polydisperse aerosol test atmosphere. Aerosols generated with a variety of suitable candidate materials have yielded particles with characteristics essentially equivalent to those of DEHP. These aerosols were generated with the same equipment used for DEHP. NIOSH, in the present review, also examines the toxicity of each candidate in terms of exposure during QNFT.

The thermal generation of a monodisperse DEHP aerosol, used to test filter material in respirator cartridges or other air-filtration systems, is not reviewed in this report. NIOSH believes that this application of DEHP is different from that in QNFT and requires additional study. Filter tests with DEHP involve a different type of exposure, and the monodisperse aerosol is generated at a high temperature that can lead to thermal breakdown products of DEHP.

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

The data reviewed below suggest that DEHP has a low order of acute toxicity. Table 1 lists LD_{50} values in four animal species by either intravenous (iv), intraperitoneal (ip), oral (per os or po), or dermal exposure routes, as adapted from Thomas (1978). Subacute and chronic toxic effects occurred only at relatively high doses. The lowest doses known to elicit toxic effects in rodents were 40-200 mg/kg administered daily for 13-104 weeks (Gaunt et al, 1973; Nikonorow et al, 1973). Lowered body weights and increased liver and kidney weights resulted.

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, when it was assumed that the chronic toxicity value had been reached. Cumulative doses caused the calculated apparent LD_{50} values to lessen as the animals were treated. The initial LD_{50}s 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 the 10th week at 3,100 mg/kg (di-n-octyl phthalate) and 1,400 mg/kg (DEHP). The authors concluded from these findings that a cumulative effect resulted following repeated exposures to DEHP or di-n-octyl phthalate. Such dramatic increases in lethality over time were further interpreted by the authors to indicate a need to reconsider the element of safety assumed from the relatively high LD_{50} values observed for these phthalate esters.

TABLE 1

DEHP ACUTE LETHALITY

Species	Route	LD_{50} (g/kg)	Reference
Mouse	po	65.0*	Lawrence et al, 1975
Mouse	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, 1978

Metabolism and Excretion

DEHP is rapidly excreted within 24 hours following either oral or iv routes of administration to male rats (Tanaka et al, 1975). Similar findings in rats were reported by Lake et al (1975) following the oral administration of DEHP. Daniel and Bratt (1974) examined excretion patterns following a single oral administration of ^{14}C-DEHP (1.8 µCi; 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 was excreted in 4 days. Animals fed 1,000 ppm of DEHP in the diet for 7 days before ^{14}C-DEHP administration exhibited 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 dietary concentrations of 1,000 ppm or 5,000 ppm, the amount of DEHP in the liver attained a steady-state concentration within 9-14 days. No further DEHP accumulation was observed when equilibrium was achieved. After rats were returned to a normal diet, the radioactivity in the liver declined with a half-life of 1-2 days; the half-life in the fat at 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 prior to a single dose of ^{14}C-DEHP (9.74 mCi/mmole; 50 mg/kg). Animals were killed at various times and then analyses were made for distribution of radioactivity 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 that monitored 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. More recently, Albro et al (1981) 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. Accordingly, the mechanism for the elimination of DEHP in primates and rodents appears to differ.

Limited pharmacokinetic investigations of DEHP have been reported. Daniel and Bratt (1974) observed that DEHP was extensively metabolized following oral 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.While 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

The NTP recently completed a chronic bioassay test of DEHP for possible carcinogenicity in two rodent species (NTP Technical Report No. (NIH)81-1773, 1980 draft). Groups of 50 Fischer 344 male and 50 female rats received in the diet either a maximally-tolerated dose (12,000 ppm) or half that level (6,000 ppm) of DEHP daily for 103 weeks. Mice, 50 male and 50 female of the B6C3F1 strain, were also fed diets containing DEHP at either 6,000 (maximally-tolerated dose) or 3,000 ppm for 103 weeks. Results were compared to those of matched control animals, 50 untreated rats and 50 untreated mice, of both sexes.

Histopathologic examination of liver tissue indicated that DEHP treatment elicited increased incidences of hepatocellular carcinomas in both rodent species above the incidence in untreated matched control animals (Table 2). The NTP report also described a statistical conclusion that the incidences of hepatocellular carcinomas in mice of both sexes were in a positive relation to the administration of DEHP. Statistical analysis of the data was performed using the one-tailed Fisher exact test to compare the tumor incidence observed in a control group with that found in a group of dosed animals at each level.

A significant ($p = 0.003$) increase in hepatocellular carcinomas resulted in female rats only at the high dose. Female rats fed diets containing the high dosage yielded a 16% final incidence of liver carcinomas, when compared with a total absence of liver carcinomas in control animals. Male rats had an elevated (but not statistically significant) increase in hepatocellular carcinomas. NTP interpreted this as suggestive evidence of carcinogenicity. An increase in the incidence of neoplastic nodules was also reported for male and female rats. These nodules in the liver are thought to progress to the stage of hepatocellular carcinomas.

Male and female B6C3F1 mice both exhibited significant increases in the incidence of hepatocellular carcinomas. Female mice had a 14% (low dose) and a 34% (high dose) incidence of hepatocellular carcinomas, compared with an absence of such carcinomas in matched controls. The incidence of liver carcinomas was significantly increased for females in both the low ($p = 0.006$) and high ($p < 0.001$) dose treatment groups. Male mice had an incidence of 29% (low dose) and 38% (high dose) compared with the 18% incidence in untreated matched control animals. The incidence of hepatocellular carcinomas for males was significantly increased ($p = 0.002$) only in the high dose group. 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). However, differences in the incidence of adenomas were not reported to be statistically significant.

The NTP concluded that the observed incidences of hepatocellular carcinomas in mice and in female rats were related to DEHP treatment. The NTP draft report further indicated that the concentrations of DEHP used in the bioassay did not alter the survival rate of experimental rats and mice. No statistically significant trends in mortality associated with DEHP administration were observed at the doses given in the test.

TABLE 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%)*
Metastatic osteosarcomas	1/50(2%)	0/48(0%)	0/50(0%)
Females			
Liver			
Hepatocellular adenomas	1/50(2%)	5/50(10%)	1/50(2%)
Hepatocellular carcinomas	0/50(0%)	7/50(14%)*	17/50(34%)*
Metastatic osteosarcomas	0/50(0%)	1/50(2%)	0/50(0%)

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

Data excerpted from the NTP Draft Technical Report on the Carcinogenesis Bioassay of Di(2-ethylhexyl)phthalate, 1980 (draft).

Mutagenic Effects

No definitive evidence of mutagenicity has been reported for DEHP, although a variety of different tests for mutagenic response have been performed in bacteria and mammalian cell cultures. For example, in the Salmonella in vitro test for mutagenicity using a thousand-fold range of concentrations up to 22,500 µg/plate (full-strength DEHP), no excesses (greater than 2x 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, 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 ug/disc has also been observed by Tomita and Nakamura (1978) to yield negative results in the B subtilis Rec-assay for DNA damage. No increases in chromosomal aberrations were reported following in vitro exposures of up to 60 µg/ml DEHP 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 oral dose of DEHP (1.0 mg/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. Since a linear relationship occurred 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 non-effective maximum dose for gross and skeletal abnormalities must await further study.

Maternal and fetal effects of DEHP exposure over a wide range of doses have been studied in rats. Pregnant Wistar rats fed DEHP at doses ranging

from 200-1,700 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 by gavage) was also administered 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 the 5th, 10th, or 15th day of gestation (Singh et al, 1972). Animals were administered 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 higher dose of di-n-octyl phthalate and in 8/51 (15.7%) given the lower dose. Hemangiomas of the limbs occurred in 9/41 (22%) fetuses following the higher DEHP dose; one fetus also developed twisted hind limbs. No gross malformations were observed in the lower 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 highest dose died within 2 weeks of this single injection exposure; a fifth male died within 10 weeks. Females mated with males given the highest dose had fewer implants/pregnancy during the first 3 weeks than controls. No significant dose-related differences were observed for implants/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 (Lake et al, 1976), making it difficult to assess potential genetic effects. Singh et al (1975) measured the distribution of radioactivity from ^{14}C-DEHP ip injections of 5 ml/kg administered topregnant 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 employed at a German plant that manufactures DEHP. In this investigation, the average length of work with potential exposure to DEHP was 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 (or approximately 0.01 to 0.16 mg/m^3). The authors concluded that no significant differences in laboratory findings, illnesses, or injury rates occurred 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/liter plasma, 0.2- 7.5 mg/liter urine) could not be distinguished from the amounts detected in three medical department personnel controls (0.5-10 mg/liter plasma, 0.2-1.5 mg/liter urine), a finding that indicates the ubiquitous occurrence of DEHP in the total environment (Lawrence, 1978; Thomas et al, 1978). Theiss et al (1978) have 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 liters/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 exposure to DEHP 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. A considerable variation in exposures to DEHP for fieldtesters may occur because of differences in (1) the duration or frequency of administering the test and (2) the workplace environment and ventilation characteristics where the test is conducted.

NIOSH has conducted several health hazard evaluations in plants that use phthalate plasticizers in thermoplastic molding materials and in a screen printing operation (NIOSH 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 (NIOSH Health Hazard Evaluation, 1977). Health effects in workers were not investigated in these studies.

Conclusions about DEHP Toxicity

In the past, the generation of a polydisperse DEHP aerosol for use as a test atmosphere in QNFT was widely accepted because of the reported low order of toxicity for this phthalate ester. Definitive evidence of mutagenicity has not been reported even following several independent investigations that included the Salmonella in vitro mutagenicity assay. Furthermore, high doses (frequently in the g/kg range) have been necessary to elicit adverse biologic effects in laboratory test animals. For example, teratogenic and reproductive effects have been cited in several studies, but the high doses required to elicit these responses make it questionable whether these data are relevant for considerations of human exposure.

Any assessment of DEHP carcinogenicity must be based largely on the NTP findings in rodents. The available evidence reviewed here indicates that DEHP should be considered as having a potential for carcinogenicity. At this time, however, no evidence has been reported to indicate DEHP carcinogenicity in humans. The epidemiologic study, previously described, at a German plant manufacturing DEHP did not find an increased prevalence of cancer in exposed workers, although enough time may not have elapsed to detect the disease. Hence, this study may not be a complete characterization of occupational exposure to DEHP from which conclusions may be drawn. The apparent lack of representative human exposure data to this ubiquitous phthalate ester also seriously limits the conclusions about cancer that can be made about its relative potential hazards.

Albro et al (1981) reported that the metabolism of DEHP in the rat may differ conspicuously from that observed in humans and monkeys. The authors found that primates excrete mainly glucuronides of mono(2-ethylhexyl)phthalate, and 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 NTP test animals, the question of 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 test. Although the available evidence indicates that DEHP exposure in QNFT would be low forthe respirator wearer, the possibility for variations in conducting the test are also noted. Improperly administered tests or variations of exposure for individuals conducting the procedure must also be considered in the overall assessment of DEHP exposure. Based on all the information reviewed, NIOSH has concluded that a search for alternate substances to replace DEHP in QNFT is warranted.

III. ALTERNATE TEST AGENTS FOR RESPIRATOR QUANTITATIVE FIT TESTING (QNFT)

NIOSH has experimented with other substances to determine their suitability for generating a polydisperse aerosol test atmosphere in oil-mist aerosol QNFT systems designed for DEHP (Smith et al, 1980). Based on criteria such as density, vapor pressure, flash point, information about use in aerosol research, and available toxicologic data, four substances were selected for study (Table 3). These agents included di-2-ethylhexyl sebacate (DEHS) and linoleic acid, which have been used in the past to generate aerosol particles of controlled size for lung deposition studies. Dimethicone, a silicone oil, and refined corn oil were also selected for study. The dimethicone used was Dow Corning 200 fluid (50 centistokes).

These four substances and DEHP were aerosolized in a Laskin-type nebulizer, common in QNFT systems. The concentration and size distribution of the aerosol particles were determined. In addition, the response of a forward light scattering photometer, also used in QNFT systems in detection of these aerosols, was checked.

All the oils tested exhibited particle size characteristics similar to those of DEHP (Table 4). In addition, they could all be detected as concentrations at or below 1/10,000th of the challenge aerosol concentration, which gives sufficient sensitivity for QNFT. Linoleic acid, however, reacted with brass fittings on the nebulizer. For this reason, and for the toxicologic implications of free fatty acids discussed later, the use of linoleic or similar acids is not advised. The NIOSH study noted that refined corn oil appeared to become thicker and cloudy after prolonged use, and it recommended periodic replacement of unsaturated hydrocarbon oils to prevent problems due to oxidation of the oil. A Harvard University study (Hinds et al, 1981) also concluded that, from the standpoint of aerosol generation, a suitable polydisperse test atmosphere for QNFT may be generated with mineral oil and polyethylene glycols as well as DEHP, DEHS, and refined corn oil.

Several different laboratories that conduct QNFT have investigated direct applications with either DEHS or refined corn oil aerosols in conducting fitting tests on respirator wearers. The Department of Energy, Richland, Washington, (Larry Musen, verbal communication to NIOSH, June 1981) and the OSHA Training Center, Des Plaines, Illinois (Lee Saltsgaver, personal communication to NIOSH, February 1981) both indicated their success in the use of refined corn oil aerosols in QNFT equipment. The NIOSH laboratory in Morgantown, West Virginia, also generated refined corn oil aerosols in mannequin respirator tests and concluded that, under the conditions of the tests, this vegetable oil performed as well as DEHP (Myers, 1980). Askin (1980) also reported a recommendation for using corn oil aerosols in QNFT. The Los Alamos National Laboratory (LANL) has indicated its successful application of DEHS aerosols to QNFT in a report by Fairchild and Talley (1981).

Refined corn oil has an odor which is characteristic of vegetable oils in general. This odor is variously described as ranging from unobjectionable to "rancid," often depending upon past impressions of

TABLE 3

PHYSICAL PROPERTIES OF COMPOUNDS TESTED BY NIOSH

SUBSTANCE	PHYSICAL STATE (room temp.)	DENSITY (dyne/cm^2)	MOLECULAR WEIGHT	REFRACTIVE INDEX	COLOR	FLASH POINT (°C)	BOILING POINT (°C)	VISCOSITY (centistoke)
Di-2-ethylhexyl phthlate (DEHP)	liquid	0.9861 (20°C)	390.6	1.4836	colorless	220.6	230.0	(25°C) 57.4
Di-ethylhexyl sebacate (DEHS)	liquid	0.913 (25°C)	426.0	1.447	colorless	215.0	248.0	(25°C) 27.4
Linoleic acid (9,12-octadecalienoic acid)	liquid	0.903 (10°C)	208.4	1.4699	colorless	188.9	230.0	(38°C) 28.0
Dimethicone (dimethyl polysiloxane)	liquid	0.960	____	(25°C) 1.401	colorless	285.0	250.0	(25°C) 50.0
Refined corn oil	liquid	0.922 (15°C)	____	1.4734	light yellow	____	____	____

Adapted from Smith et al, 1980

TABLE 4

AEROSOL CHARACTERISTICS OF COMPOUNDS TESTED BY NIOSH

SUBSTANCE	MASS MEDIAN AERODYNAMIC DIAMETER	GEOMETRIC STANDARD DEVIATION	MASS OUTPUT (mg/m^3)	AEROSOL VOLUME CONCENTRATION ($(u)m^3/cc$)
DEHP	0.53	1.83	134.0	$.169 \times 10^5$
DEHS	0.63	1.94	159.1	$.169 \times 10^5$
Linoleic acid	.56	1.96	----	$.357 \times 10^5$
Dimethicone	.57	1.84	121.0	$.456 \times 10^4$
Refined corn oil	.53	1.85	118.1	$.130 \times 10^5$

Adapted from Smith et al, 1980

Compounds were tested using a 2-jet generator at a pressure of 5.0 psi.

individuals in experiencing odors where commercial fryers are used. The degree to which the odor is objectionable frequently depends upon the extent to which the oil is reused. Concern about an undesirable odor from corn oil use in QNFT has prompted NIOSH to make inquiries among practioners using this vegetable oil under field test conditions. Users have indicated to NIOSH that applications of refined corn oil aerosols to QNFT have not resulted in objectionable odor or prohibitive maintenance problems (Written communications to NIOSH: Marshall H. Marcus, Jr., Industrial Hygiene Consultant, May 1981; Daniel P. Askin, President, Energy Saving and Clean Air Technologies, May 1981; Lee Saltsgaver, Occupational Safety and Health Administration Training Institute, February 1981. Verbal communication to NIOSH: Larry Musen, Department of Energy, June 1981). Collectively, these field practioners have conducted over a thousand individual fittings utilizing corn oil aerosols in QNFT.

Corn oil, being a vegetable oil, requires cleanup procedures that are different than those needed for DEHP. Slightly more maintenance seems to be needed for corn oil in QNFT than for DEHP. However, the maintenance required for corn oil would be less than that required by another QNFT system that utilized sodium chloride to generate an aerosol test atmosphere. By performing proper routine maintenance when using fresh refined corn oil in QNFT, any potential for an objectionable odor problem should be negligible. For example, the generator may need routine daily cleanup, and the test chamber or plastic shroud may require cleaning if an oil buildup becomes noticeable.

A question has also arisen as to whether fungal growth may be a problem with corn oil use. In one QNFT laboratory, mold formation was observed on an exhaust filter following several weeks of corn oil use (Truman Williams, verbal communication, November 1980). No fungal growth was observed elsewhere on the equipment, including the test chamber. Examination of the filter in question by the Mycology Division, Centers for Disease Control (CDC), revealed a minimal presence of four common molds: Alternaria species, Ulocladium, species, and Aureo basidium (pullulans), and Aspergillus fumigatus (Dr. Libero Ajello, Written communication, September 1981). The first three organisms are not considered to be pathogenic; however, Aspergillus fumigatus is a ubiquitous pathogen of low infectivity. CDC indicated that there was no visible sign of any fungal growth on the filter they received. Colonies of molds cultured from the filter were also low in number. The organisms identified from the cultures could have originated from the filter or sources other than from the use of corn oil in QNFT, especially since all the molds cultured are common. CDC also advised NIOSH that corn oil would not likely provide a good growth medium for fungi because of its viscosity and immiscibility with water. Furthermore, while known to be associated directly with corn, the possibility of aflatoxin contamination directly from corn oil is not likely, since an alkali step in the refiningof corn oil would eliminate any potential for this occurrence (Bennett and Anderson, 1978). A more detailed discussion of processing procedures for corn oil is presented in the Appendix of this report.

IV. TOXICITY OF AGENTS FOUND TO BE SUITED FOR QNFT

1. Dimethicone (dimethyl polysiloxane), a silicone oil consisting of dimethylsiloxane polymers and purified for pharmaceutical use, has been used extensively as a vehicle for topical drug applications and as a skin protectant (Windholz et al, 1976). Also, because of its antifoaming properties, dimethicone may be added to cooking oils for deep-fat frying. In veterinary practice, it is used to prevent bloat in cattle. The polydimethylsiloxanes occur in a wide range of molecular weights and viscosities and are noted for their water repellency. This has led to a wide variety of cosmetic, medical, and industrial applications.

The toxicity of the polydimethylsiloxane compounds examined has been of a low order, as reviewed by Calandra et al (1979). Kennedy et al (1976) studied the potential for mutagenic, reproductive, or teratogenic effects with selected polydimethylsiloxanes in rats and rabbits. Testing results indicated that Dow Corning (DC) 700 vapor booster pump fluid, 7 centistoke (cs), was not teratogenic in rats at oral doses as high as 1,000 mg/kg and was not mutagenic at ip doses of 5 and 10 g/kg. DC 225 fluid (10 cs) was also not observed to be teratogenic in rabbits at a dermal application of 200 mg/kg. In other experiments by the same investigators, DC 360 medical grade fluid (350 cs) was administered sc to pregnant rats on days 6 to 11 of gestation at doses of either 200 or 1,000 mg/kg. The authors reported an increase of incompletely developed sternebrae in fetuses derived from dams at the high dose. This response was not concluded by the investigators to be significant. The only signficant effect found was an apparent dose-related incidence of in utero mortality at both dose levels of the DC 360 fluid. However, no evidence of fetotoxicity was observed by the authors in a second study performed on rats at the same doses.

No detailed studies were found describing the direct inhalation toxicity testing of Dow Corning 200 fluid, the siloxane considered by NIOSH as a candidate QNFT substitute. Calandra et al (1976) have reported a low order of inhalation toxicity to an aerosol of mixed cyclic siloxanes. However, a subchronic 90-day inhalation toxicity test of a polyethylsiloxane aerosol at concentrations of 0.2, 2, and 10 mg/m^3 to rats was observed to produce both localized pulmonary irritation and other generalized toxic effects (Tikhonova and Bizin, 1976). Tracheal inflammation and lung lesions were also noted. Furthermore, pathologic cellular changes were found in cardiac muscle and in the liver for animals exposed at the higher concentration. No pathologic changes were reported in animals exposed at 0.2 mg/m^3.

2. Di-2-ethylhexyl sebacate (DEHS) has properties that make it suitable for generating a polydisperse test aerosol in QNFT. It is currently used to generate an aerosol for tests that evaluate human pulmonary deposition (Swift, 1967). No adverse health effects have been indicated from this human application. Although DEHS has been used extensively for this purpose, its pulmonary toxicity does not appear to have been studied. Since data describing inhalation effects of DEHS are lacking, toxicity testing of this potential QNFT test agent by the

inhalation route of exposure is warranted. NIOSH is presently conducting both acute and subchronic inhalation toxicity testing of DEHS.

In an earlier inhalation study using a limited number of test animals, no fatalities were reported among cats, guinea pigs, rabbits, or rats exposed to a mist of DEHS at 400 mg/m^3, for 7 hours/day over a 10-day period (Treon et al, 1955). However, 2/4 rabbits, 3/4 rats, and 0/2 guinea pigs died within 7 hours when exposed to a DEHS mist at 940 mg/m^3, generated at high temperature (371°C). An oral LD_{50} value has been reported for DEHS in the rat and mouse to be 12.8-25.6 g/kg (Sandmeyer and Kirwin, 1981). An ip LD_{50} of greater than 25.0 g/kg has also been reported for the rat and mouse. These rather limited data indicate a low order of toxicity for DEHS.

Like DEHP, DEHS is a 2-ethylhexyl ester, but of sebacic acid rather than phthalic acid. A metabolite, 2-ethylhexanol, is currently considered to be suspect by NTP as the proximate carcinogen in their bioassay test for DEHP. NTP is considering a chronic bioassay study of 2-ethylhexanol, since bioassays of two esters containing a 2-ethylhexanol moiety (DEHP and di-2-ethylhexyl adipate) have both yielded positive test results of carcinogenicity (NTP Chemical Selection Working Group Meeting Agenda, 1980). At the present time, the mechanism of DEHP carcinogenicity remains unknown. It is also not clear whether DEHP was carcinogenic in the NTP study because it contains a 2-ethylhexyl moiety. Until more data are available concerning the metabolism of DEHP or DEHS and the potential carcinogenic mechanisms of 2-ethylhexanol, questions about this chemical moiety of both DEHP and DEHS are unresolved. In addition, another metabolite of DEHP, mono(2-ethylhexyl)phthalate, is suspected by the NTP as the proximate carcinogen.

Moody and Reddy (1978) fed either di-2-ethylhexyl adipate, DEHP, or DEHS to male Fisher 344 rats at a dietary concentration of 2% for 3 weeks. Hepatic peroxisome proliferation, increases in liver size and activities of peroxisome-associated enzymes, and hypolipidemia were observed in animals fed each of the above esters. The same results occurred when animals were fed 2-ethylhexanol, a finding that indicated to the investigators that the alcohol may be the active portion of the molecule responsible for the observed peroxisome changes in all three esters.

3. Corn Oil. An LD_{50} for corn oil in rats has been obtained following a protocol of intragastric administration daily for 5 days (Boyd et al, 1969). No single gastric dose of corn oil could be retained sufficiently to induce death in rats. The LD_{50} was achieved after 5 days when a cumulative dose totaling 279 ± 31 ml/kg (256 ± 28 g/kg) was administered. This dosage is approximately equivalent to one-quarter of the animal's body weight, indicating a very low order of acute toxicity for corn oil. Corn oil has been studied using a chamber-scarification test for assessing skin irritancy of topically applied substances (Frosch, 1977). Test results were compared with other oily materials frequently used in cosmetics. Corn oil was rated as only a "slight" irritant when

applied for 72 hours on scarified human skin. An erythema developed along scratch lines of the test patch. Under the conditions of this test, corn oil was ranked as more irritating than lanolin, but less irritating than mineral oil.

Corn oil has been used extensively without incident as a vehicle to administer test chemicals by gavage to rodents in a variety of experimental laboratory procedures, including carcinogen bioassays conducted by the National Cancer Institute (NCI). For example, as part of tests involving potential carcinogenicity of bis(2-chloro-1-methylethyl) ether (NCI Report No. 191, 1979), histopathologic examination of both untreated control Fischer 344 rats and rats administered the corn oil vehicle only showed no essential difference for observed neoplasms. In this test, the corn oil vehicle was administered at a dose of 1 ml/kg body weight by gavage 5 days/week for 103 weeks. Similar observations have resulted from numerous other studies (NCI Report Nos. 68, 73, and 110, 1978). It is emphasized that such data do not reflect results of standard test conditions for a direct bioassay of corn oil, because the agent was not the prime material under test, and predetermined maximally tolerated doses were not administered to the test animals. However, the negative findings for corn oil in literally thousands of applications to rodents by the NCI would suggest overall that there is no suspicion of carcinogenicity for this vegetable oil.

When administered for prolonged periods as a major component of the diet, either 5% or 20% of the feed, corn oil has been reported to enhance colon carcinogenesis induced by 1,2-dimethylhydrazine (DMH) in Fischer 344 rats (Reddy et al, 1976). Such a response to a steady diet of corn oil at these high dietary levels has been related to mechanisms of carcinogenesis for known carcinogens in test animals having a high fat intake. For example, Reddy et al (1977) showed that a high fat diet of corn oil resulted in the excretion of elevated amounts of bile acids. These authors emphasized that it was the elevated levels of bile acids caused by a high fat diet, and not the corn oil itself, which acted as colon tumor promoters during DMH carcinogenesis. The same response was observed by these investigators when animals were on a diet high in animal fat.

Results of another dietary study have indicated that refined corn oil was negative in a test for carcinogenicity. Mice of the T.M. strain given refined corn oil in the diet, 200 mg given in a dish/mouse daily for up to 540 days, exhibited essentially no difference in the appearance of forestomach tumors when compared with untreated control mice (Szepsenwol, 1978). But if either (1) free fatty acids (up to 1.5%) added to refined corn oil or (2) crude corn oil (containing free fatty acids) was administered, a high incidence of forestomach tumors resulted. The authors attributed the free fatty acids, either added to the refined oil or present in crude corn oil, to have elicited the forestomach tumors observed. Furthermore, the investigators concluded that refined corn oil was not carcinogenic under these experimental conditions. The authors concluded that forestomach tumors in refined corn oil-treated mice were absent because free fatty acids are eliminated in the refining process.

O'Gara et al (1969) studied the effects of corn oil, as a 10% mixture in the diet, in NIH black rats. When corn oil, either heated at 200°C for 6-8 hours or used repeatedly for deep-fat frying, was administered to rats for 17 months, a higher incidence of alimentary tract tumors resulted compared to those of untreated or fresh corn oil-treated rats. The authors concluded that the heating or extensive reuse (in frying) of corn oil, which can cause changes in corn oil chemical composition, led to the tumors observed. Furthermore, these investigators advised against the excessive reuse of cooking fats in the preparation of food for human consumption.

Little information is currently available concerning mutagenic or teratogenic effects. Corn oil, administered orally at a dose of 10 mg/kg to CD-1 mice, was one of several negative control substances used in a test of the sensitivity and reproducibility of a dominant lethal assay system (Anderson et al, 1977). Responses to corn oil in terms of pregnancy frequency, implantations, and early deaths were similar to those of three other control substances, including water. The results were markedly different from those of substances that elicited mutagenic effects.

A comparison of the distribution, effects, and fate of corn oil and petroleum-derived oil aerosol particles in the lungs of mice were studied by Shoshkes et al (1950). Mice were exposed to 12.6 g/m^3 of corn oil aerosols having a mass median particle diameter of 2.6 um. Lungs, examined immediately following a 6-hour exposure, showed that oil droplets were limited to the terminal bronchiolar areas, and they impinged on the walls of alveolar ducts opposite the air stream. There was an immediate and active phagocytosis by macrophages, and the lungs were essentially cleared within 48 hours. This macrophage response in the lungs occurred following only a single 2-hour exposure, or at longer exposures of 4-8 hours/day, 5 days/week. With longer exposures to the corn oil aerosol, an increase in the number of lung macrophages resulted. In contrast, petroleum-derived oils under the same experimental conditions were not enzymatically degraded and were only slowly removed from the lungs through the lymphatic drainage system. Patches of acute inflammatory changes, consistent with a diagnosis of lipoid pneumonia, were observed in mice exposed to the petroleum-derived oil. Corn oil and other edible oils, on the other hand, were lipolyzed rapidly by lung macrophages. In addition, corn oil did not irritate the upper respiratory tract, and effects such as reflex apnea or bronchoconstriction were not observed.

Review of clinical cases of lipoid pneumonia, which frequently results from oil droplets in the lung, showed an increase in phagocytic cells in the lung (Keshishian et al, 1969). Vegetable oils were found to be metabolized and removed from the lung, whereas oils of mineral origin tended to remain in the lung tissue. Mineral oil does not undergo metabolic changes and, thus, remains and can cause the formation of a paraffinoma. Adenocarcinoma of the lung has also been reported clinically in a patient with chronic mineral oil pneumonia (Bryan and Boitnott,1968). The tumor was thought to have resulted from the induction of pulmonary fibrosis elicited directly by the exposure to the mineral oil.

Cases of localized lipoid pneumonia, due to exogenous oil in lung alveoli, have been correlated clinically with the prolonged treatment of nasal sinusitis with mineral oil-based nose drops (Borrie and Gwynne, 1973). These studies of lipoid pneumonia have indicated that the disease can result from large dosage exposures to mineral oil over extended periods of time.

Although limited, more toxicity information is available concerning corn oil than for dimethicone or DEHS. Overall, the data reviewed here suggests that refined corn oil has a relatively low order of toxicity. Attempts to determine LD_{50}s for corn oil in animals has required inordinately large quantities of the oil to be given over 5 days. Toxic responses to corn oil occurred only when the oil was treated in such a way as to alter its chemical composition, as in heating to high temperatures or in reuse as in the frying of foods. A brief summary of the composition and characterization of corn oil is included in the Appendix.

Although the inhalation toxicology of corn oil and other oils has been described here, much is lacking regarding the characterization of corn oil use in QNFT. Acute and subchronic inhalation toxicity testing, aimed at corn oil use in QNFT, is underway by NIOSH. For the present, however, corn oil is a strong candidate as an interim QNFT test agent.

4. Other Substances. Mineral oil and the polyethylene glycols, as indicated earlier in this report, have been proposed by some laboratories as having physical and chemical properties that may render them suitable for generating a QNFT aerosol test atmosphere. The observation that mineral oil tends to remain in the lung for prolonged periods, and reports of clinical cases exhibiting adverse reactions to this oil, tend to preclude further consideration of its use in QNFT. The glycols, on the other hand, could be considered to be potential interim test agents provided that consistent and reproducible data of their suitability for QNFT become available. The low order of toxicity of many of the lower molecular weight polyethylene glycols is well documented (Smyth et al, 1950; 1955), although the pharmacodynamics of these materials warrant study. The United States Army has informed NIOSH of its successful applications of PEG-400, a low molecular weight polyethylene glycol, to QNFT (Bernard Gerber, written communication, January 1981). The Army is now conducting inhalation toxicity testing of these glycols in addition to reviewing the overall toxicity of these agents.

Administration of a low molecular weight polyethylene glycol (PEG 200) to Cynomolgus monkeys, daily by gastric intubation at a dose of 2-4 ml/kg for 13 weeks, elicited intratubular deposition of oxalate crystals in the renal cortex (Prentice and Majeed, 1978). It was indicated by the investigators that ethylene glycol, a probable metabolite of PEG 200, could have induced the renal changes observed. The authors concluded that polyethylene glycols are not devoid of toxic manifestations following oral administration, and that they should be used with caution. However, thisresponse appears to be at variance with those suggested by other reports (Smyth et al, 1950; 1955). In addition, the monkeys examined were treated at such a high dose that comparison to QNFT would be questionable. Results of the Army's toxicity testing of these agents may better resolve the biologic properties of the polyethylene glycols for QNFT.

V. CONCLUSIONS

Data that describe the biologic effects resulting from exposure to DEHP indicate a relatively low order of general toxicity. DEHP has been shown to be toxic only when administered to laboratory test animals at high dose levels. This review has noted that inordinately high doses (often in the g/kg range) have been required to elicit adverse reproductive or teratogenic effects in several species. Such adverse biologic effects resulting from high doses are difficult to interpret and can only serve to warrant additional laboratory testing under different experimental protocols. At present, the evidence does not indicate that DEHP should be viewed as a teratogen. Furthermore, definitive evidence of mutagenicity has not been ascertained for DEHP, even though it has been subjected to a variety of testing protocols including the Salmonella in vitro mutagenic assay, as conducted by several independent laboratories.

This report has also reviewed the findings of an NTP chronic bioassay test of DEHP in rodents. Histopathologic examination of liver tissues indicated that, under the conditions of the study in male and female B6C3F1 mice and in female Fischer 344 rats, a treatment-related increased incidence of hepatocellular carcinomas resulted. NTP concluded that DEHP was carcinogenic to the two rodent species examined. Although differences in metabolism between the rat and primates, including humans, have been described, the evidence is not yet sufficient to suggest that this difference relates to carcinogenicity, or even to toxicity. The mechanisms are still unknown by which DEHP elicited liver neoplasms under the test conditions of the bioassay. Based on the available data, NIOSH has concluded that DEHP should be considered as having a human carcinogenic potential. Therefore, where alternative substances can be feasibly substituted for DEHP, they should be used in QNFT.

Several alternative substances have been tested to determine their suitability for generating a polydisperse QNFT aerosol test atmosphere. Refined corn oil and DEHS adapt well to existing QNFT equipment designed for DEHP use. Aerosols of refined corn oil and DEHS exhibit particle characteristics essentially equivalent to those generated with DEHP. In addition, these substances appear to have a low order of toxicity, although more information is known about refined corn oil than for DEHS. The polyethylene glycols also are widely known to exhibit a low order of toxicity, although the data are sparse on the metabolic fate of these polymers. Mineral oil has been shown to accumulate in the lungs, a fact which discourages consideration for its use in QNFT. NIOSH recently tested corn oil, DEHS, and polyethylene glycol 400 for mutagenic activity in the Salmonella mutagenicity assay using tester strains TA98, TA100, TA1535, and TA1537. No mutagenic activity was observed with or without S-9 activation in any of the strains studied. NIOSH also evaluated the mutagenic potential for 2-ethylhexanol, a possible metabolite of DEHS and DEHP. This alcohol was observed to be toxic, but not mutagenic, up to 1.0 mg/plate for all tester strains (Ong, 1981).

Based on the type and extent of exposure in QNFT and the toxicologic data reviewed herein, refined corn oil, DEHS, the polyethylene glycols

(PEG-400), and dimethicone (Dow Corning 200 fluid) may all be considered as candidates that should receive serious consideration in QNFT. Of the three substances that NIOSH found to be suitable for use in QNFT, refined corn oil has a very low order of toxicity and stands out from all other agents reviewed, especially because of the extensive negative data on carcinogenic potential. The remaining candidates warrant more thorough evaluations of their toxicities, especially after further experimental investigations are available. The US Army's toxicity testing of the polyethylene glycols may provide greater insight about these potential QNFT agents. In conducting this review, NIOSH has learned that many QNFT field practitioners are already using corn oil aerosols as a test atmosphere. Field testers have indicated that, although some increased maintenance has been required with its use, corn oil is acceptable as an alternative test agent to DEHP in respirator fitting tests.

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VII. APPENDIX

PROPERTIES AND PROCESSING PROCEDURES FOR CORN OIL

Corn oil is a clear, light yellow, oily liquid with a faint characteristic odor and taste (Windholz et al, 1976). It is obtained from the embryo of Zea mays, Gramineae (L.) as a byproduct of milling during the manufacture of corn starch, corn syrup, glucose, dextrins, etc.

Corn oil has widespread use as a nutritive substance as a common component of the diet. During crop year 1975-1976, 514 million pounds (92% of the total crop yield) were used in edible products such as cooking oil, salad dressing, and margarine (Reiners, 1978; Sonntag, 1979). As a food, corn oil yields 8.9 calories/gram (Mazola Data Sheet, 1979).

Refined corn oil is composed almost entirely (99%) of triglycerides, which are the primary forms of fats in the body. These triglycerides contain a mixture of saturated and unsaturated fatty acids which include linoleic acid, a polyunsaturated fatty acid comprising 34-62% of corn oil, one of the "essential fatty acids." Corn oil is known as a "semi-drying" oil (Windholz et al, 1976) because it contains traces of fatty acid fractions which readily oxidize and lead to a drying (hardening) of the oil.

Refined cooking grade corn oil generally meets the US Pharmacopeial (USP) standard for corn oil as a pharmaceutical aid. The USP standard specifies an iodine value between 102-130; a saponification value between 187-193; and not more than 1.5% unsaponifiable matter. Iodine number is a measure of the degree of unsaturation among fatty acid components, while the saponification value indicates the mean molecular weight of the fatty acid constituents. Unsaponifiable matter consists of water insoluble compounds.

The unsaponifiable fraction of crude corn oil is partially removed during alkali refining (Sonntag, 1979), with less than 1.5% remaining in the refined product. Most of the remainder (0.6-1.2%) are sterols which are relatively inert and may occur in the free form or as wax-like esters. In the diet, these sterols may enter into the biosynthesis of Vitamin D or steroid hormones.

Other major components of the unsaponifiable fraction are the tocopherols. These are a group of closely related fat soluble compounds collectively known as Vitamin E. Traces of triterpene alcohols, less than 0.1%, may also be present in the unsaponifiable fraction of which nine components have been identified in corn oil (Sonntag, 1979). Small (0.02%) amounts of ubiquinone, an electron carrier known as coenzyme Q found in chloroplasts, have also been identified in the unsaponifiable fraction (Mazola Data Sheet, 1979).

The refining process removes free fatty acids and most nonglycerides, such as phosphatides, carbohydrates, carbohydrate derivatives, protein fragments, and trace resinous and mucilaginous materials (Sonntag, 1979).

These substances give a water-holding ability to the crude corn oil. After they have been removed, the refined oil is almost anhydrous (0.1% water).

The alkali refining step removes any aflatoxins or pesticide residues that may be present. Waxes, colored carotinoid compounds, and volatile materials are removed during other refining steps (Sonntag, 1979; Reiners, 1978). The resulting product is a light, bland oil with a smoke point of about 238°C.

Corn Oil Additives

Silicones or polydimethysiloxanes, which are antifoaming agents and also considered as QNFT aerosols, may be added (0.1-1.0 ppm) to oils for deep-fat frying (Formo, 1979). Any such additive must be listed on the label according to FDA requirements (21 CFR 101.6).

While corn oil contains natural antioxidants, chiefly tocopherols, which confer a greater resistance to oxidative deterioration than found in pure triglycerides, manufacturers have also added other antioxidants, particularly for deep-fat frying. Two of the most common antioxidants are butylated hydroxyanisol (BHA) and butylate hydroxytoluene (BHT). The total concentration of antioxidants, singly or in combination, may not exceed 200 ppm (0.02%) (21 CFR 182.3173).

Oxidative Deterioration

Oxidative deterioration does occur, especially at elevated temperatures during deep frying (Sonntag, 1979; Chang et al, 1978). A total of 95 (30 acidic, 65 nonacidic) volatile decomposition products in small amounts have been isolated from corn oil heated at 185° C for 30 hours (Krishnamurty et al, 1967). Oxidation polymers impart disagreeable tastes and odors to the oil (Chang et al, 1978). In general, corn oil darkens and increases in viscosity as the composition of the oil changes with prolonged heating.

The unsaturated fatty acids of corn oil can also oxidize (autoxidation) during prolonged exposure to air (Sonntag, 1979). The initial uptake of oxygen is at a relatively slow and uniform rate; color and odor changes coincide with rapid oxygen uptake. Natural antioxidants in corn oil increase the resistance to oxidation and also the amount of oxygen required to cause deterioration in flavor and odor (rancidity). Unhydrogenated corn oil can absorb up to 150% oxygen by volume before becoming rancid. Linoleic acid is the primary polyunsaturated component in oxidative rancidity. The first step is a conjugation of monohydroperoxides at double bonds in linolates. This reaction proceeds by a free radical mechanism to further yield hydroperoxides anddecomposition products. Such products include low and medium weight (C_3-C_{11}) saturated and unsaturated aldehydes, ketones, and acids which have strong, unpleasant odors. Rancidity occurs when less than 0.1% of the fat is decomposed. Polymers are produced under more prolonged

conditions of autoxidation. The rate of oxygen uptake, leading to oxidative rancidity, is accelerated by heat, ultraviolet, and near-ultraviolet (Sonntag, 1979). Metals, particularly copper, act as pro-oxidants.

Since corn oil aerosol in QNFT is generated at room temperature and is not reused, much less oxidation would occur than with deep-frying conditions. Nevertheless, to minimize the possibility of autoxidation in QNFT, it is advisable to remove any unused oil at the end of each test session.