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 III-1). 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 studied. The dimethicone used was Dow Corning 200 fluid (50-centistoke).

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 III-2). In addition, they could all be detected at concentrations at or below 1/10,000 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. NIOSH recommends periodic replacement of unsaturated hydrocarbon oils when necessary 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 the polyethylene glycols as well as DEHP, DEHS, and refined corn oil. The Harvard report did not indicate testing of dimethicone.

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 (Musen, verbal communication to NIOSH, June 1981), and the OSHA Training Center, Des Plaines, Illinois (Saltsgaver, personal communication to NIOSH, February 1981), both indicated their success in the use of refined corn oil aerosols in QNFT equipment. NIOSH also generated refined corn oil aerosols in mannequin respirator tests and concluded that it performed as well as DEHP under test conditions (Myers, 1980). Askin (1980) reported a recommendation for using corn oil aerosols in QNFT. Fairchild and Talley reported in 1981 that the Los Alamos National Laboratory successfully used DEHS aerosols in QNFT.

TABLE III-1

PHYSICAL PROPERTIES OF COMPOUNDS TESTED BY NIOSH

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

Adapted from Smith et al, 1980

TABLE III-2

AEROSOL CHARACTERISTICS OF COMPOUNDS TESTED BY NIOSH

SUBSTANCE	MASS MEDIAN AERODYNAMIC DIAMETER	GEOMETRIC STANDARD DEVIATION	MASS OUTPUT (mg/m^3)	AEROSOL VOLUME CONCENTRATION ($\mu m^3/cc$)
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 lb/in^2.

Refined corn oil has an odor characteristic of vegetable oils in general. This odor is variously described as ranging from unobjectionable to "rancid," often depending on past experiences where commercial fryers are used. The degree to which the odor is objectionable frequently depends on the extent to which the oil is reused. Concern about undesirable odor prompted NIOSH to ask practitioners who were using corn oil in QNFT in the field. The users indicated that refined corn oil aerosols had not resulted in objectionable odor or prohibitive maintenance problems (written communications from: M. H. Marcus, Jr., Industrial Hygiene Consultant, May 1981; D. P. Askin, Energy Saving and Clean Air Technologies, May 1981; and L. Saltsgaver, OSHA Training Institute, February 1981; verbal communication from L. Musen, Department of Energy, June 1981). Collectively, these field practitioners have conducted over a thousand individual fittings using a corn oil aerosol in QNFT.

Being a vegetable oil, corn oil requires cleanup procedures that are different from those needed for DEHP. Slightly more maintenance seems to be needed for corn oil than for DEHP. However, the maintenance required for corn oil would be less than that required by another QNFT system that uses sodium chloride to generate an aerosol test atmosphere. If proper routine maintenance is performed when using fresh refined corn oil in QNFT, objectionable odors 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.

NIOSH investigated whether fungal growth could be a potential problem with corn oil use in QNFT. In one testing site, mold formation was observed on an exhaust filter after several weeks of corn oil use (T. 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, Aureo basidium (pullulans), and Aspergillus fumigatus (L. 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. Only a few colonies of molds could be cultured from the filter. 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 be a good growth medium for fungi because of its viscosity and immiscibility with water. Furthermore, although associated directly with corn, aflatoxin contamination directly from corn oil is not likely, since any possibility of it would be eliminated by an alkali step in the refining of corn oil (Bennett and Anderson, 1978). The Appendix discusses more details of processing procedures for corn oil.

IV. TOXICITY OF OTHER AGENTS SUITABLE FOR QNFT

Dimethicone (Dimethyl Polysiloxane)

A silicone oil consisting of dimethylsiloxane polymers and purified for pharmaceutical use, dimethicone 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 (Calandra et al, 1976). Kennedy et al (1976) studied the potential for mutagenic, reproductive, or teratogenic effects with selected polydimethylsiloxanes in rats and rabbits. Test results indicated that Dow Corning (DC) 700 vapor booster pump fluid, 7 centistokes (cs), was not teratogenic in rats at po doses as high as 1 g/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 significant 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 DC 200 fluid, the siloxane considered by NIOSH as a candidate QNFT substitute. In 1976, Calandra et al 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 produced 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 highest concentration. No pathologic changes were reported in animals exposed at 0.2 mg/m^3.

Di-2-Ethylhexyl Sebacate (DEHS)

A monodisperse DEHS aerosol is used extensively to evaluate human pulmonary deposition (Swift, 1967). Although no adverse human health effects have been indicated from this application, a characterization of

the inhalation effects for DEHS is lacking. If this agent is to be used in QNFT, the inhalation toxicity of the compound must be examined.

Limited data from previous studies have indicated a low toxicity for DEHS. Treon et al (1955), using small numbers of test animals, reported no fatalities in 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. However, 2/4 rabbits, 3/4 rats, and 0/2 guinea pigs died within 7 hours after inhaling a DEHS mist at 940 mg/m^3, generated at high temperature (371°C). A po LD_{50} for DEHS in the rat and mouse was reported to be 12.8-25.6 g/kg (Sandmeyer and Kirwin, 1981). An ip LD_{50} greater than 25.0 g/kg was also reported for the rat and mouse.

Like DEHP, DEHS is a 2-ethylhexyl ester, but of sebacic rather than phthalic acid. A metabolite of DEHS, 2-ethylhexanol, is currently suspected by the NTP of being the proximate carcinogen in its bioassay of DEHP. The NTP may conduct a chronic bioassay study of 2-ethylhexanol, because two esters with a 2-ethylhexanol moiety (DEHP and di-2-ethylhexyl adipate) were both found to be carcinogenic in previous bioassays (NTP Chemical Selection Working Group, 1980). The mechanism of DEHP's carcinogenicity remains unknown, and it is not clear whether DEHP was carcinogenic in the NTP study because it contains a 2-ethylhexyl moiety. Until more data are available on the metabolism of DEHP or DEHS and the potential carcinogenic mechanisms of 2-ethylhexanol, questions about this chemical moiety of both DEHP and DEHS will remain unresolved.

Moody and Reddy (1978) fed either di-2-ethylhexyl adipate, DEHP, or DEHS to male Fischer 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 these esters. The same results with 2-ethylhexanol in the diet 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.

Corn Oil

An LD_{50} for corn oil (refined, U.S.P. XVII) in rats was obtained when daily intragastric doses were administered over 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 finally achieved after 5 days by administering a cumulative dose totaling 279 ± 31 ml/kg (256 ± 28 g/kg), a dosage approximately equivalent to one-quarter of the animal's body weight. The dosage and time required to attain the LD_{50} indicate a very low order of acute toxicity for refined corn oil. The Appendix discusses the components of corn oil and describes its refining and processing procedures.

A chamber-scarification test for assessing skin irritancy of topically applied substances was used to evaluate irritancy properties of corn oil (Frosch, 1977). The author did not specify whether the corn oil was

refined. 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, the 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, histopathologic examination of Fischer 344 rats administered refined corn oil vehicle only and untreated controls showed no essential difference for observed neoplasms in the NCI test of bis(2-chloro-1-methylethyl) ether (NCI Report No. 191, 1979). The refined corn oil vehicle was administered at 1 ml/kg body weight by gavage 5 days/week for 103 weeks. Similar observations resulted from other NCI studies (NCI Report Nos. 68, 73, and 110, 1978). NIOSH emphasizes that such data do not reflect results of standard test conditions for a direct bioassay of refined corn oil, which was not the prime material under test, and that predetermined maximum tolerated doses were not given. However, NCI's negative findings in literally thousands of applications to rodents suggest that there is no suspicion of carcinogenicity for refined corn oil.

When administered for prolonged periods as a major component of the diet, either 5% or 20% of the feed, corn oil was reported to enhance colon carcinogenesis induced by 1,2-dimethylhydrazine (DMH) in Fischer 344 rats (Reddy et al, 1976). The authors did not specify whether the corn oil was refined. The study's observations have 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 unstripped corn oil resulted in the excretion of elevated amounts of bile acids. They emphasized that it was the elevated levels of bile acids caused by a high fat diet, and not the corn oil itself, that 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.

The results of a dietary study of refined corn oil was negative in a test for carcinogenicity (Szepsenwol, 1978). Mice of the T.M. strain, each fed 200 mg of refined corn oil in a dish daily up to 540 days, exhibited essentially no difference in the incidence of forestomach tumors when compared with untreated control mice. However, treatment with either (1) free fatty acids (up to 1.5%) added to refined corn oil or (2) crude corn oil (containing free fatty acids) elicited a high incidence of forestomach tumors. The authors attributed this carcinogenic response to free fatty acids, either added to the refined oil or present in crude corn oil. They also concluded that refined corn oil was not carcinogenic under these experimental conditions because free fatty acids are eliminated in the refining process.

O'Gara et al (1969) studied the effects of commercial (cooking) corn oil as a 10% mixture in the diet in NIH black rats. When corn oil either (1)

heated at 200°C for 6-8 hours, or (2) used repeatedly for deep-fat frying, was given to rats for 17 months, a higher incidence of alimentary tract tumors resulted compared with those of untreated or fresh corn oil-treated rats. The authors concluded that heating or extensive reuse (in frying) of the corn oil, which can change the oil's chemical composition, led to the tumors. The investigators advised against excessive reuse of cooking fats in the preparation of food for human consumption.

Little information is available on mutagenic or teratogenic effects. Refined 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 refined corn oil in terms of pregnancy frequency, implantations, and early deaths were similar to those of three other control substances, including water. The results differed markedly from those of substances eliciting mutagenic effects.

Shoshkes et al (1950) compared the inhalation toxicity of refined corn oil and petroleum-derived oil aerosols. Mice were exposed to 12.6 g/m^3 of corn oil aerosols with a mass median particle diameter of 2.6 μm. Lungs examined immediately after 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 only after 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, the number of lung macrophages increased. 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. Refined corn oil and other edible oils, on the other hand, were lipolyzed rapidly by lung macrophages. In addition, refined 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 lungs, showed an increase in phagocytic cells in the lungs (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; thus, it 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 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 exposures to mineral oil over extended periods of time.

Other Substances

Mineral oil and the polyethylene glycols, in addition to refined corn oil and DEHS, have been proposed by other laboratories as having physical and chemical properties that may render them suitable for generating a QNFT aerosol test atmosphere (Hinds et al, 1981). The observation that mineral oil tends to remain in the lung for prolonged periods, and reports of clinical cases exhibiting adverse reactions to the oil, preclude further consideration of its use in QNFT. The glycols, on the other hand, could 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 polyethylene glycol of low molecular weight, to QNFT (Gerber, written communication, January 1981). The Army is now testing the inhalation toxicity of these glycols in addition to reviewing reports of biologic effects.

Low molecular weight polyethylene glycol (PEG 200) given to Cynomolgus monkeys by gastric intubation at 2-4 ml/kg daily for 13 weeks, elicited intratubular deposition of oxalate crystals in the renal cortex (Prentice and Majeed, 1978). The investigators indicated that ethylene glycol, a probable metabolite of PEG 200, could have induced the renal changes. The authors concluded that polyethylene glycols are not devoid of toxic manifestations following po administration, and that they should be used with caution. However, this response appears to vary with those suggested by other reports (Smyth et al, 1950; 1955). In addition, the monkeys examined were treated at such a high dose that relevance 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.

Conclusions

Although limited, more toxicity information is available on corn oil than on dimethicone or DEHS. Overall, the data reviewed here indicate that refined corn oil has a relatively low order of toxicity. Attempts to determine LD_{50}'s for refined 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 its chemical composition was altered, as in heating to high temperatures, or in reuse, as in the frying of foods. Corn oil's chemical composition and physical properties are summarized in the Appendix.

NIOSH recently tested refined corn oil and DEHS 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 both DEHS and DEHP. The metabolite was observed to be toxic, but not mutagenic, up to 1.0 mg/plate for all tester strains (Ong, 1981).

Inhalation testing of refined corn oil in rodents indicated a low toxicity for the compound, although NIOSH recognizes that much is unknown about the use of a corn oil aerosol in QNFT. Data describing the inhalation toxicity of DEHS and dimethicone are even more limited than that of corn oil. To resolve these deficiencies, NIOSH is presently conducting both acute and subchronic inhalation toxicity tests in rodents at the Johns Hopkins University. The two leading QNFT candidates, refined corn oil and DEHS, are being examined using an experimental protocol specifically designed to expose the test animals to polydisperse aerosols as human test subjects would be in QNFT. This study is scheduled for completion in April, 1983. For the present, however, refined corn oil is the stronger candidate as an interim QNFT test agent.

V. EVALUATION AND RECOMMENDATIONS

QNFT is performed to assure that a proper facial fit is established for the individual respirator wearer. Since only a limited number of respirator sizes and styles are marketed, QNFT is critical in the fitting process because of the infinite number of human facial size variations and characteristics. Hence, DEHP has become an integral component of sound occupational safety and health programs designed to reduce worker exposure to respiratory hazards. DEHP has been widely accepted in QNFT for years because of its suitable physical properties for nebulizing a polydisperse aerosol test atmosphere. This acceptance of the DEHP aerosol in QNFT was also encouraged by reports of low toxicity for the compound. However, after examining the data in the NTP study, NIOSH concludes that DEHP must be considered to have a carcinogenic potential. NIOSH believes that a prudent future course is necessary in conducting QNFT and recommends that DEHP be discontinued in the procedure. Because QNFT is indispensable in establishing proper respirator fit, NIOSH recommends that an alternate aerosol test agent replace DEHP. NIOSH tested several candidate agents to determine their adaptability to QNFT and reviewed the toxicity of each compound. Results of these studies have led NIOSH to conclude that there are several agents presently available for use in existing QNFT equipment, originally made for the DEHP aerosol. After reviewing the toxicity of the candidate agents, NIOSH recommends that refined corn oil is the best option as a DEHP substitute in QNFT.

NIOSH testing results show that several compounds have properties that make them suitable for use in QNFT. The results demonstrate the ease with which other compounds may be substituted for DEHP in the procedure. Refined corn oil, DEHS, and dimethicone all adapted well to existing QNFT equipment. Aerosols of these candidate agents exhibited particle characteristics essentially equivalent to those generated with DEHP. Furthermore, these substances appear to have a low order of toxicity, although information on dimethicone that is relevant to QNFT is sparse. Refined corn oil and DEHS appear to be the stronger candidates to replace DEHP in the procedure. A substantial amount of data on biologic effects reviewed here indicate that refined corn oil has a low overall toxicity. Furthermore, inhalation testing of refined corn oil suggested a low toxicity in the rodent lung (Shoshkes et al, 1950). Limited data on DEHS reviewed here also suggest a low toxicity for this candidate. DEHS has been used for years in pulmonary physiology to assess human lung deposition without reports of adverse health effects. However, the inhalation toxicity of this compound does not appear to have been characterized, leaving questions about the potential risks of using the compound in QNFT. NIOSH anticipates that its recently initiated inhalation toxicity testing of refined corn oil and DEHS will resolve these critical questions. Results of these NIOSH experiments, presently underway at the Johns Hopkins University, are expected in April, 1983. For the present, NIOSH concludes from the available information that refined corn oil is the best option for use as a DEHP substitute in QNFT.

A study at Harvard University also indicated successful generation of polydisperse aerosols suitable for QNFT with refined corn oil, DEHS, polyethylene glycol (PEG 400), and mineral oil (Hinds et al, 1981). The polyethylene glycols are widely known to exhibit a low order of toxicity, but the data are sparse on the metabolic fate of these polymers. On the other hand, mineral oil has been shown to accumulate in the lungs, a fact that discourages its consideration for use in QNFT.

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 U.S. 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, refined corn oil is acceptable as an alternative test agent to DEHP in respirator fitting tests.

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VII. APPENDIX

PROPERTIES OF 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 in the diet. During crop year 1975-1976, 257 x 10^9 g (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 cal/g (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 that 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 that readily oxidize and lead to a drying (hardening) of the oil.

Iodine Number A measures the degree of unsaturation among fatty acid components, and 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 that 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. This group of closely related fat soluble compounds is collectively known as Vitamin E. Traces of triterpene alcohols, less than 0.1%, may also be present in the unsaponifiable fraction; nine components have been identified in corn oil (Sonntag, 1979). Small amounts of ubiquinone (0.02%), 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 polydimethylsiloxanes, 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). 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. Oxidation polymers impart disagreeable tastes and odors to the oil. In general, corn oil darkens and increases in viscosity as the composition of the oil changes with prolonged heating.

Unsaturated fatty acids of corn oil can also oxidize (autoxidation) during prolonged exposure to air (Sonntag, 1979). The initial uptake of oxygen is relatively slow and uniform; 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 linoleic components. This reaction proceeds by a free radical mechanism to further yield hydroperoxides and decomposition products. Such products include low- and medium-weight (C_3-C_{11}) saturated and unsaturated aldehydes, ketones, and acids with 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 light, and near-ultraviolet light (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.

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