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Federal Register

FRIDAY, JUNE 23, 1978
PART V

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

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ETHYLENE OXIDE, ETHYLENE CHLOROHYDRIN, AND ETHYLENE GLYCOL

Proposed Maximum Residue Limits and Maximum Levels of Exposure

[4110-03]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Parts 211 and 821]

[Docket No. 77N-0424]

ETHYLENE OXIDE, ETHYLENE CHLOROHYDRIN, AND ETHYLENE GLYCOL

Proposed Maximum Residue Limits and Maximum Levels of Exposure

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: This proposal would impose restrictions on the continued use of ethylene oxide as a sterilant for certain drug products and medical devices for human use, by: (1) Establishing maximum residue limits for ethylene oxide and its two major reaction products, ethylene chlorohydrin (2-chloroethanol) and ethylene glycol, in drug products for human and veterinary use, including biological products for human use, and in medical devices for human use and (2) establishing maximum daily levels of exposure for drug products for ethylene oxide and its two major reaction products. This action is being taken because residues of ethylene oxide and its two major reaction products in drug products and devices for which ethylene oxide is used as a sterilant may produce toxic reactions in patients, and because of the potential risk of mutagenicity from exposure to these residues.

DATES: Comments by August 22, 1978. The Commissioner proposes that the final regulation based on this proposal be effective 60 days after publication of the final regulation in the FEDERAL REGISTER.

ADDRESS: Written comments (four copies, indentified with Docket No. 77N-0424) to the Hearing Clerk (HFC-20), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Marilyn L. Watson, Bureau of Drugs (HFD-30), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, (301-443-3640).

SUPPLEMENTARY INFORMATION: Ethylene oxide has been used for a number of years as a sterilant for human drugs (e.g., certain ophthalmic and parenteral drug products), veterinary drugs (e.g., ophthalmic ointments for small animals and certain intramammary infusion products), biological products for human use (e.g., tuberculin test preparations and inactivation of some vaccines), medical devices for human use containing heat sensitive plastic components (e.g., heart pacemakers, kidney dialysis machines, and heart lung machines) as well as for other devices such as surgical sutures, intraocular lenses, and surgical scrub sponges. Ethylene oxide also has been used as a sterilant for the individual ingredients of drug products and for containers, container closures, and delivery systems of drugs and medical devices for human use. Because some drugs, medical devices for human use, and other articles cannot be sterilized by heat, filtration, radiation, or liquid chemical agents without degradation or other damage, gaseous sterilization must be used. Possible substitutes for ethylene oxide are formaldehyde or glutaraldehyde. Of these, there is no literature on tests for the long-term toxicity of gluteraldehyde. Formaldehyde has, however, been shown to be mutagenic (Ref. 1).

Ethylene oxide is an alkylating agent which reacts primarily with nucleophilic groups—amines, alcohols, phenols, organic and inorganic acids, and water. Its biochemical reactions include those with the ring nitrogens of purine and pyrimidine bases and the amino and carboxy groups of amino acids and proteins. Ethylene oxide reacts with the chloride ion to form ethylene chlorohydrin or with water to form ethylene glycol.

In response to questions raised regarding the safety and effectiveness of ethylene oxide as a sterilant for drugs and medical devices for human use and because of reports of serious adverse reactions associated with the use of products sterilized with ethylene oxide, a notice was published in the FEDERAL REGISTER of September 12, 1973 (38 FR 25213) inviting the submission of published and unpublished data concerning the use, performance, and toxicity of ethylene oxide and its reaction products, or any other date having a bearing on the safety and effectiveness of ethylene oxide.

An internal Food and Drug Administration (FDA) Ethylene oxide Review Committee evaluated the data submitted in response to this notice, other data contained in new drug applications and petitions, data submitted by the Association for the Advancement of Medical Instrumentation (AAMI) Ethylene oxide (Z-79) Subcommittee, and data from other sources. The FDA committee submitted recommendations to the Commissioner of Food and Drugs on May 30, 1975 (Ref. 2). One of the actions recommended by the FDA committee and approved by the Commissioner was the eventual publication of maximum residue limits for ethylene oxide and for its two major reaction products, ethylene chlorohydrin and ethylene glycol.

In January 1977, the Department of Health, Education, and Welfare's (HEW) Committee to Coordinate Toxicology and Related Programs chartered a subcommittee to provide the Assistant Secretary for Health with a comprehensive analysis of the benefits and risks of ethylene oxide. The HEW subcommittee concluded in a report of April 1, 1977 (Ref. 1) that "ethylene oxide is an extremely useful chemical which, unfortunately, possesses mutagenic properties." The report further stated that "there is little evidence that it is also carcinogenic to experimental animals, although adequate testing has yet to be conducted."

The Environmental Protection Agency (EPA) reviewed the report of the HEW subcommittee and other literature available on the toxicity of ethylene oxide and its two major reaction products and issued in the FEDERAL REGISTER of January 27, 1978 (43 FR 3801) a "Notice of Rebuttable Presumption Against Registration and Continued Registration of Pesticide Products Containing Ethylene Oxide," based on reports of mutagenicity and reproductive effects. This is the first step in EPA's regulatory procedures that could result in cancellation of the registration as a pesticide of ethylene oxide.

The EPA action and this proposal should be viewed as compatible efforts to reduce the risks presented by ethylene oxide to levels which are considered safe. At present, there are several memoranda of understanding between FDA and EPA under which the two agencies have agreed to share regulatory responsibility for actions which arise under the various statutes they administer. The existing memoranda do not discuss the particular regulatory problems associated with ethylene oxide, however, and the precise details regarding the relationship between this action and the notice of rebuttable presumption against registration issued by EPA must await each agency's final action.

In addition to its use as a sterilant in the manufacture of drugs and devices, uses with which this proposal is concerned, ethylene oxide is also listed in FDA's food additive regulations as a fumigant for the control of microorganisms and insect infestation in ground spices and other natural seasoning materials. A separate proposal concerning the food additive uses of ethylene oxide will be published in the FEDERAL REGISTER in the future.

The Commissioner has no information showing that ethylene oxide is an essential sterilant for cosmetics; therefore no requirements that permit its continued use as such are proposed herein. Nonetheless, the Commissioner invites the submission of data or other information regarding the use of ethylene oxide as a sterilant for cosmetics. The FDA is particularly inter-

ested in information on the types and frequency of use of ethylene oxide, on methods of determining residual amounts of ethylene oxide, ethylene chlorohydrin, and ethylene glycol in cosmetics, and on procedures that might be followed to reduce residual levels to the lowest concentrations obtainable under current technological constraints.

I. Toxicity Review

The following information summarizes the toxicity data on ethylene oxide, ethylene chlorohydrin, and ethylene glycol as contained in the HEW subcommittee report as well as additional toxicity data received by the agency since the HEW subcommittee report.

ETHYLENE OXIDE

A. *Human Acute Toxicity*

Ethylene oxide is an eye and respiratory tract irritant and a skin vesicant (blistering agent). Nausea, dizziness, and signs of mental disturbance have been observed in humans accidentally exposed to high concentrations of the compound (Ref. 1).

b. *Animal Acute Toxicity*

1. *Lethal dose from oral and parenteral administration.*—The LD_{50} of ethylene oxide (administered in aqueous solution to rats, mice, and rabbits) from oral and parenteral exposure (studies by Woodard and Woodard, Ref. 4) has been summarized by Bruch (Ref. 3). The doses ranged from 127 milligrams per kilogram (mg/kg) by the subcutaneous route in the rat to 631 mg/kg by the oral route in rabbits. In most cases, deaths occurred within 24 hours. Signs of pharmacological action included ataxia, prostration, labored respiration, and an occasional tonic convulsion.

2. *Irritation to eye and tissues.*—Woodard and Woodard (Ref. 4) in a study designed to determine the acute eye and tissue irritant properties of ethylene oxide (in aqueous solution) reported no effect at solution concentrations ranging from 0.1 percent (5 mg total dose) by subcutaneous administration to guinea pigs to 2.1 percent (2 mg total dose) by ocular instillation in rabbits.

In a study by McDonald et al. (Ref. 6), the acute eye irritant properties of ethylene oxide (in a balances salt solution) were investigated in rabbits. The study showed that the maximum nondamaging concentrations (highest concentration that produced no treatment-related damage to the eye) of ethylene oxide for ocular tissues after a 6-hour acute topical ocular instillation varied from 0.1 percent in the conjunctiva to greater than 20 percent for the lens and retina. After a single anterior chamber injection, the maximum nondamaging concentration of ethylene oxide ranged from 0.1 percent for the anterior chamber, iris, and lens to 1 percent for the cornea and conjunctiva.

3. *Inhalation.*—Hine and Rowe (Ref. 8) compiled data on inhalation exposure from studies of Jacobson et al. (Ref. 9), Hollingsworth et al. (Ref. 10), Waite et al. (Ref. 11), and Flury and Zernik (Ref. 12). The data illustrate the variable lethal response by species, concentration, and duration of exposure for guinea pigs, cats, dogs, and rabbits. In general, no deaths were reported at ethylene oxide exposure levels of 250 to 280 parts per million (ppm) for these animals.

C. *Animal Subchronic Toxicity* (repeated doses for a period not exceeding 1 year)

1. *Oral and parenteral administration.*—Ethylene oxide was administered to rats orally by gavage five times a week (Ref. 10). At the high dosage level (100 mg/kg, 15 doses were administered in 21 days) a marked loss of body weight, gastric irritation, and slight liver damage were found. Repeated oral doses of 30 mg/kg given daily, 5 days a week, for a period of 30 days produced no toxic effect in rats.

In another study (Ref. 4), ethylene oxide was administered to rats and dogs by daily subcutaneous injection for 30 days at 3 dosage levels (6, 18, and 54 mg/kg). In the dog study, the high dosage level was reduced to 36 mg/kg on day 7 due to severe pharmacologic and toxicilogic effects and continued at that dosage for the remainder of the study. The no-effect level for the rat was 18 mg/kg. A no-effect level was not established for dog; however, the lowes dosage administered was 6 mg/kg. All rats survived the duration of the study but experienced inflammation and occasional hemorrhage and necrosis at the injection sites. Male rats at the high dosage level showed a mean body weight of 92 percent of that achieved by control rats.

Dogs on the high level dosage 54(36) mg/kg showed extensive and sometimes necrotic inflammatory changes, whereas dogs at a lower level dosage (18 mg/kg and 6 mg/kg) showed marked local inflammatory changes. The study also showed increased mortality at the high level dosage (54(36) mg/kg), and reduced hemoglobin and hematocrit values at all dosage levels. Hematological changes of dose-related severity attributed to sever local tissue injury at the injection sites were reported. Hepatic changes such as increased liver weights at each dose, and cholestasis at the high dose (54(36) mg/kg) in each dog and at the mid dose (18 mg/kg) in one of four dogs, were observed. Increased ectopic hematopoiesis was observed in two of four dogs at all dosage levels. Other pharmacologic effects observed were muscular hypertonicity, lowered body temperature, prostration (at the 54-mg/kg dosage) and ataxia, sluggish behavior, tremors, loss of skin elasticity, lacrimation, and conjunctival congestion (at the 36-mg/kg dosage).

2. *Inhalation.*—Hollingsworth et al. (Ref. 10) and Jacobson et al. (Ref. 9) conducted studies in which a variety of animal species (rats, rabbits, monkeys, mice, guinea pigs) were repeatedly exposed to ethylene oxide vapors at concentrations that ranged from 100 to 841 ppm. The results of these studies are summarized by Hine and Rowe (Ref. 8). Pathological findings included growth depression, anemia, impairment of nervous system function including posterior paresis and transient paraplegia, severe lung injury and, in guinea pigs, degeneration of the tubules of the testes.

D. *Hemolytic Effects.*

Hemolysis has been reported with ethylene oxide sterilized devices used for blood perfusion, and with devices used for intravenous administration in patients (Refs. 85-87). Anemia of dose-related severity was reported (Ref. 4) to have developed in dogs injected subcutaneously (6 to 36 mg/kg ethylene oxide in saline solution for 30 days). However, a later study by FDA was unable to confirm the finding of anemia. In this FDA study, three beagle dogs were dosed intravenously with ethylene oxide glucose solution daily for 3 weeks. Doses were increased from 3 to 60 mg/kg at intervals. Three controls received the vehicle. No evidence of anemia was detected (Balazs, Ref. 13).

E. *Allergenic Response*

Sensitization-allergic-type reactions have been reported in workers drenched with ethylene oxide solution (Sexton and Henson, Ref. 14) and patients exposed to improperly degassed dressings (Hanifin, Ref. 15). Ethylene oxide (1 percent solution) was not a contact sensitizer in the occlusive patch test in guinea pigs nor did a 0.1 percent ethylene oxide solution produce sensitization by the intracutaneous injection method in this species (Woodard and Woodard, Ref. 4).

In a report (Ref. 78) of recent skin irritation studies by Shupak, sponsored by AAMI Ethylene Oxide (Z-79) Subcommittee, delayed sensitization in human subjects was observed in response to ethylene oxide contained in polyvinylchloride blocks and films and in petrolatum. This finding supports an earlier report of anaphylaxis from reaction products of ethylene oxide gas used in the sterilization of renal dialysis equipment (Poothullil et al., Ref. 16).

F. *Mutagenicity*

Evidence from a variety of prokaryotic (bacterial) and eukaryotic (animals and higher plants) systems indicate that ethylene oxide causes mutations. The test organisms include *Drosophilia melanogaster* (Rapoport, Ref. 17; Bird, Ref. 18; Nakao and Auerbach, Ref. 19), *Neurospora crassa* (Kolmark and Kilbey, Ref. 20), barley (Ehrenberg and Gustafsson, Ref. 21; Sulovska et al., Ref. 22), *Aspergillus* (Morpurgo, Ref. 23), and *Salmonella typhimurium* (Rannug, Ref. 79). The studies by Embree and Hine (Ref. 24) and Rannug et al. (Ref. 79) indicate that ethylene oxide can induce base-pair substitutions (a type of gene mutation). This is consistent with the action of monofunctional alkylating agents. In addition, ethylene oxide has been shown to induce chromosome aberrations in maize (Faberge, Ref. 25), barley (Moutschen-Dahmen et al., Ref. 26), Vicia faba (Loveless, Ref. 27), *Tradescantia* (Smith and Lotfy, Ref. 28), *Drosophila* (Nakao and Auerbach, Ref. 19), and rats (Strekalova, Ref. 29, Embree and Hine, Ref. 24).

Embree (Ph.D. dissertation, Ref. 30) employed three different assays for mutagenicity in the rat. In a direct cytogenetic assay of bone marrow samples from rats exposed to 250 ppm of ethylene oxide in air for 7 hrs/day for 3 days, the frequency of chromosome aberrations increased from .05 (controls) to .84 (treated). In a rat dominant lethal assay conducted with males exposed to 1,000 ppm ethylene oxide in air for 4 hours, increases in post-implantation loss were found in weeks 1, 2, 3, and 5 after exposure indicating genetic damage in post-meiotic and meiotic sperm cells. In the third test, a micronucleus test which measures the appearance of micronuclei in polychromatic erythrocytes, rats in groups of five were exposed for 4 hours to doses of 10, 25, 50, 250, and 1,000 ppm of ethylene oxide in air. A linear increase in micronuclei was seen with doses up to 50 ppm (only 50 ppm and above were statistically higher than controls). The effect of 250 ppm was only slightly greater than at 50 ppm, but the effect of 1,000 ppm was more than three times greater than at 250 ppm. Although, the micronucleus test is an indirect test for chromosomal damage, studies (Refs. 76 and 77) have shown that it correlates with some direct methods.

In another study by Strekalova, E. E., et al., (Ref., 31) of the mutagenic effect in rats of ethylene oxide on mammalian somatic and reproductive cells, cytogenic analysis of the bone marrow and analysis of the male reproductive cells were carried out by the method of dominant lethal mutations. Cytogenic analysis of the bone marrow showed an increased incidence of chromosome reorganizations in experimental male animals compared to controls. In animals exposed to the action of high concentrations of ethylene oxide, chromosome abrerrations were detected in 9.4±0.9 percent; in animals exposed to the action of low concentrations, 7.6±0.1 percent; in the control, 2.6±0.3, ($p<0.001$).

ETHYLENE CHLOROHYDRIN

A. *Human Acute Toxicity*

Serious systemic toxic effects have been reported from exposure to ethylene chlorohydrin. Inhalation of ethylene chlorohydrin vapor may result in nausea, dizziness, vomiting, circulatory failure, stupification, and death. Poisoning occurs from inhalation of 18 ppm. Ethylene chlorohydrin irritates mucous membranes and causes kidney and liver degeneration. The effects may be cumulative (Ref. 1).

B. *Animal Acute Toxicity*

1. *Lethal dose from oral and parenteral administration.*—The acute toxicity (LD_{50}) values have been determined for ethylene chlorohydrin in mice, rats, rabbits, and dogs (Refs. 4, 43, 82–84). The results of these studies point to LD_{50} values in a range of 56 mg/kg by the parenteral route in rats to 178 mg/kg by the oral route in mice (Ref. 3). Ethylene chlorohydrin was shown to be somewhat more toxic acutely than ethylene oxide. The route of administration appeared to have little influence on the acute toxicity values. The animals showed signs of central nervous system effects such as depression and labored respiration and usually died within 24 hours without specific organ pathology.

In another study (Friedman et al., Ref. 38), a single oral dose of ethylene chlorohydrin (10 to 50 mg/kg) caused a dose-related decrease of liver protein synthesis and glutathione level in rats.

2. *Irritation to eye and tissues.*—The results of studies to determine the acute effect of ethylene chlorohydrin on eye and other tissues have been summnarized by Bruch (Ref. 3). Maximal no-effect concentrations ranged from 0.5 percent (0.25 mg total dose) administered subcutaneously in guinea pigs to 20 percent (40 mg total dose) by dermal application in the rabbit. In the eye and tissue studies by Woodard and Woodard (Ref. 4), ethylene chlorohydrin solution produced induration and ecchymoses (small hemorrhages) in one of five animals tested following subcutaneous injection (0.5 percent) in the guinea pig, minimal irritation after dermal administration in the rabbit, and lacrimation and conjunctival erythema, corenal opacity, iritis, and conjunctival irritation following ocular administration in the rabbit.

The acute eye irritant properties of ethylene chlorohydrin (in a balanced salt solution) were investigated in the rabbit by McDonald et al., (Ref. 6). The maximal nondamaging concentrations of ethylene oxide ranged from 2 percent for the conjunctiva to greater than 40 percent for the lens after a 6-hour acute topical ocular instillation. After a single anterior chamber instillation, 0.5 percent and 5 percent were the maximum nondamaging concentrations of ethylene chlorohydrin for the iris and conjunctiva, respectively.

C. *Animal Subchronic Toxicity* (Repeated doses for a period not exceeding 1 year)

Ethylene chlorohydrin has been administered subchronically by the oral route, both by gavage and in the diet, to the rat, dog, and monkey, parenterally to the dog and rat; and by inhalation to rats (Refs. 4, 32, 41–44). Effects include depressed weight gain and increased mortality, subacute myocarditis, and changes in organ weights. Data from the 30-day subcutaneous dosing (27 mg/kg) of ethylene chlorohydrin to dogs indicated hepatocellular degenerative changes and increased serum alkaline phosphatase and bilirubin levels. One dog died. No hepatic effects were seen with significantly lower doses (9 mg or 3 mg/kg). Seminiferous tubular degeneration was detected at the 27 and 9 mg/kg dose levels.

In another study (Feuer, G. et al., Ref. 39), subcutaneous daily dosing of rats (20 mg/kg of ethylene chlorohydrin for 7 days) caused a reduction in the activities of hepatic drug-metabolizing enzymes and of glucose 6-phosphatase. A trend of reduction was seen also at 3 or 10 mg/kg in male rats.

A 21-day ocular irritation study has been performed in rabbits with solutions of ethylene chlorohydrin, ethylene glycol, and combinations of ethylene chlorohydrin and ethylene glycol (Ref. 7). The concentrations of the ethylene chlorohydrin solutions ranged from 0.1 to 40 percent; of the ethylene glycol solutions, from 0.5 to 80 percent; and of the combination solution of ethylene chlorohydrin and ethylene glycol, from 0.1 percent/0.5 percent to 30 percent/70 percent. Maximal conjunctival congestion and discharge, moderate swelling, increasing corneal cloudiness, damage as evidenced by fluorescein staining, and pannus were observed with solutions of 40 percent ethylene chlorohydrin; moderate conjunctival congestion, minimal discharge and minimal swelling with solutions of 80 percent ethylene glycol; and moderate conjunctival congestion, moderate discharge, minimal swelling, flare, iritis, corneal cloudiness, damage as evidenced by fluorescein staining, and moderate pannus with solutions of 30 percent/70 percent ethylene chlorohydrin/ethylene glycol.

D. *Animal Chronic Toxicity* (Repeated doses for period exceeding 1 year)

The results of oral and parenteral administration of ethylene chlorohy-

drin in chronic toxicity studies are summarized in references 40 and 44-47. No chronic systemic toxic effects or carcinogenic effects were detected in mice and rats.

E. *Mutagenicity*

Two studies have been reported in which increases in chromosome aberrations in rat bone marrow cells were induced after exposure to ethylene chlorohydrin (Isakova, G. K., et al., Ref. 32 and Semenova, V. N., et al., Ref. 33). Rosenkranz and Wlodkowski (Ref. 34) found a dose-related increase in mutation rate in strains TA1530 and TA1535 of *Salmonella*, but no increase in strain TA1538, which indicates that ethylene chlorohydrin induces base-pair substitutions, but not frameshift mutations. Data from studies by Rannug et al. (Ref. 79) show ethylene chlorohydrin to be a weaker mutagen than ethylene oxide in causing mutations in *Salmonella* TA1535.

F. *Teratogenicity and Fetotoxicity*

Verrett (Ref. 80) tested ethylene chlorohydrin for teratogenic and fetotoxic effects in the developing chick embryo by injecting 5, 12.5, 25, and 50 mg/kg in the air sac of 4-day old embryos. This resulted in a dose-related increase in defective embryos. A later study (Courtney and Andrews, Ref. 81) in CD-1 mice failed to produce malformations when ethylene chlorohydrin was administered orally or by inhalation.

ETHYLENE GLYCOL

A. *Human Acute Toxicity*

The single oral lethal dose of ethylene glycol for a human has been estimated at 1.4 mg/kg or about 100 milliliters for an average adult (Rowe, Ref. 37). This estimate indicates that the compound is more acutely toxic for humans than for the animal species for which LD_{50} ranges have been determined.

B. *Animal Acute Toxicity*

1. *Lethal dose from oral and parenteral administration.*—The most recent study of the acute and parenteral toxicity of ethylene glycol by four routes of administration in mice, rats, and rabbits is summarized by Bruch (Ref. 3). The LD_{50}'s ranged from 2.4 gram/kg by the intraperitoneal route of administration in female mice to 17 gram/kg by the oral route in rats. Although there is some variation from earlier findings (Browning, Ref. 35; Lang et al., Ref. 36), the variation does not appear to be due to dose concentrations or sex. Unlike ethylene oxide and ethylene chlorohydrin, which generally produced death within 24 hours, ethylene glycol produced a number of delayed deaths which were associated with kidney lesions accompanied by the deposition of oxalate crystals in the kidney.

2. *Irritation to eye and tissues.*—The results of studies (Ref. 4) to determine the acute eye and tissue irritant properties of ethylene glycol (in aqueous solution and in undiluted form) have been summarized by Bruch (Ref. 3). The highest no-effect concentration of ethylene glycol ranged from 1 percent (0.5 mg total dose) by subcutaneous administration to 10 percent by ocular (10 mg total dose) and intramuscular (50 mg total dose) administration. Both ethylene glycol solutions and undiluted compound produced some mild irritation by the intradermal route, transient lacrimation and erythema from ocular administration, and minimal irritation following dermal application.

The acute eye irritant properties of ethylene glycol (in a balanced salt solution) were investigated by McDonald et al. (Ref. 6). The maximum nondamaging concentrations of ethylene glycol 6 hours after topical ocular instillation ranged from 4 percent for the conjunctiva to greater than 80 percent for the lens. After a single anterior chamber injection of ethylene glycol, the nondamaging concentrations ranged from 2 percent for the iris to from 20 percent to 80 percent for the cornea, lens, and retina.

B. *Animal Subchronic Toxicity* (Repeated doses for a period not exceeding 1 year)

1. *Oral, parenteral, and inhalation administration.*—In a subchronic oral study in the monkey (Ref. 48), ethylene glycol was administered in the drinking water from 13 to 157 days. The no-effect level was 1 milliliter per kilogram (ml/kg) total dose. From 1 ml/kg to 15 ml/kg, mild glomerular damage with azotemia was noted. Total doses of 15 ml/kg and above produced deposition of calcium oxalate crystals in the proximal renal tubules and associated tubular degeneration. In other subchronic studies (Ref. 49), monkeys were exposed to ethylene glycol by inhalation at a concentration of 600 milligrams per cubic meter (mg/m^3), continuously for 5 to 7 months. At 5 months, liver mitochonria showed respiration and uncoupled oxidative phosphorylation. Mitochondria from monkeys exposed for 6 and 7 months had normal phosphate/oxygen (P/O) ratios and respiration that was returning to normal. Rats and mice exposed by the inhalation route to 300 mg/m^3, 8 hrs/day, for 16 weeks, showed no effects (Ref. 50). In rats and dogs treated by the subcutaneous route for 30 days, 50 mg/kg was a no-effect dose for the rat; a no-effect dose was not established for the dog (Ref. 4). Both species showed an increased number of white cells.

2. *Ocular.*—See discussion of ocular irritation study in paragraph C. under "Ethylene Chlorohydrin" above.

C. *Animal Chronic Toxicity* (Repeated doses for periods exceeding 1 year)

A number of oral chronic studies have been performed with ethylene glycol, but a no-effect level has not been clearly established. In two rat studies (Refs. 52 and 53), dietary levels of 0.5 percent and higher depressed growth and produced oxalate calculi and deposition of crystals in the kidneys. In one of these studies, the no-effect level appeared to be approximately 0.2 percent. In another study (Ref. 51), three monkeys were fed ethylene glycol for 3 years, one monkey at a level of 0.2 percent and 2 monkeys at a level of 0.5 percent. No effects were seen. In still another study (Ref. 47), ethylene glycol showed no carcinogenic effect when administered subcutaneously at a dose of 1,000 mg/kg twice a week to rats for 1 year followed by an additional 6 months with no treatment.

D. *Mutagenicity*

The Food and Drug Administration is aware of one report (Rapoport, Ref. 17) which suggests that ethylene glycol at high concentrations may cause mutations in *Drosophilia*. To FDA's knowledge, this has not been confirmed. Using a bacterial plate assay, Embree (Ref. 30) tested ethylene glycol on *S. typhimurium* strains TA1535, TA1537, and TA1538 without microsomal activation and found no revertents.

II. THE PROPOSED RULE

The Commissioner believes that there is need for the continued use of ethylene oxide as a sterilant for certain drug products and medical devices for human use because of a lack of acceptable alternatives. Although steam sterilization under pressure is usually considered the most economical and the most efficient sterilant, many heat-labile biochemical substances such as vitamins, amino acids, and antibiotics, as well as many plastics, cannot tolerate moist or dry heat. Further, most articles that must be sterile cannot be sterilized by ionizing radiation because of physical damage due to radiation. As previously stated, formaldehyde and glutaraldehyde were cited (Ref. 1) as possible substitutes for ethylene oxide; but no literature on tests for long-term toxicity is available for glutaraldehyde, and formaldehyde has been shown to be mutagenic. Nonetheless, when ethylene oxide is used as a sterilant during the manufacture of drug products and medical devices for human use, its residue and that of its two major reaction products may produce toxic reactions in patients. Consequently, the Commissioner is proposing herein to establish maximum residue limits and exposure levels for ethylene oxide, ethylene chlorohydrin, and ehtylene glycol.

Residue limits would be set for certain drug products for human and veterinary use, for medical devices for human use, and for certain other articles. The proposed limits are intended to take into consideration the lowest possible limits achievable under current good manufacturing practices.

Maximum daily exposure levels would also be set, but for drug products only. These proposed exposure levels are based on the toxicity data previously discussed. The Commissioner is proposing to include the residue limits and exposure levels for drug products for human and veterinary use in the current good manufacturing practice regulations in 21 CFR Part 211. The residue limits for medical devices would be included in a new 21 CFR Part 821. The Commissioner intends that these requirements will, for those patients using drugs and medical devices for human use for which ethylene oxide has been used as a sterilant, limit exposure to ethylene oxide, ehtylene chlorohydrin, and ethylene glycol to levels below those that are presently known to be harmful.

MAXIMUM RESIDUE LIMITS

A. *Drug Products and Other Articles for Human and Veterinary Use*

The notice proposes maximum residue limits for ethylene oxide, ethylene chlorohydrin, and ethylene glycol in ophthalmic preparations for topical use, injectable preparations (including veterinary intramammary infusion products), intrauterine devices containing a drug component, surgical scrub sponges containing a drug component, and hard gelatin capsule shells. The residue limits would be the maximum acceptable limits for any of these drug products or other article for which ethylene oxide is used as a sterilant during any part of the manufacturing process, including the manufacturing process for any component of the product or for the product's container. The limits would apply to the product as it appears in its market container at the time it is releasd for marketing, and throughout the period of its shelf life. The limits proposed are based on data that have been previously submitted to FDA in new drug applications, which data consist of values that are currently being net by some manufacturers.

Under the proposed regulations, each manufacturer of a drug product or other article to which the residue limits apply would be required to assure by appropriate laboratory testing that such product or other article in its market container does not exceed the residue limits when released for marketing. The Commissioner advises that a number of analytical methods (Refs. 54 through 75) are available through which residues of ethylene oxide, ethylene chlorohydrin, and ethylene glycol can be reliably determined. Gas and thin-layer chromatographic, polarographic, colorimetric, mass spectrographic, radio tracer and other methods have been published which can identify and measure minute residues of ethylene oxide and its reaction products. Nonetheless, the Commissioner recognizes that there are technical problems associated with identifying and determining the minute amounts of ethylene oxide and ethylene oxide reaction products. For example, any of the following factors may affect the amount of residue of ethylene oxide and its reaction products or how readily that residue can be detected: the applied dosage, the type and cycle of the sterilizer and conditions of aeration, the physical state, catalytic nature, and reaction kinetics of the product, the diffusion rate of ethylene oxide into and out of the product, the moisture and air content in the product, and any synergistic effects. The Commissioner advises that he will view as current good manufacturing practice any generally accepted scientific method for laboratory control of residues of ethylene oxide and its two major reaction products if it includes (1) batch sampling, (2) appropriate sample sizes, (3) sample handling techniques which assure no residue loss from the point of sample collection to that of assay completion, and (4) adequate methods to measure product residue changes from the time of sample collection during the quarantine period to the time of release of the product for shipment and sale.

The Commissioner further purposes that, for each drug product in which ethylene oxide is used as a sterilant, the manufacturer prepare a residue dissipation curve for residues of ethylene oxide, ethylene chlorohydrin, and ethylene glycol for each manufacturing procedure in which ethylene oxide is used as a sterilant. This will provide a full dissipation profile for each sterilized article and will enable a manufacturer to determine the point in time at which the product will be within the established limits for purposes of release for marketing.

As noted, the Commissioner has also proposed that the residue limits would apply during the shelf life of the product. Proposed current good manufacturing practice regulations published in the FEDERAL REGISTER of February 13, 1976 (41 FR 6878) would require expiration dating for all drug products so the application of the residue requirement throughout a product's shelf life is consistent with the purpose of the proposed current good manufacturing practice regulations that products maintain their identity, strength, quality, and purity until the time of use. In addition, under this proposal, a drug product intended to be reconstituted or diluted prior to dispensing or use would be required to conform to the established residue limits as reconstituted or diluted. This requirement is consistent with the purpose of the proposed current good manufacturing practice regulations, regarding the maintenance of a product's identity, strength, quality, and purity until its time of use.

B. *Medical Devices for Human Use*

The Commissioner also proposes to establish maximum residue limits for ethylene oxide, ethylene chlorohydrin, and ethylene glycol in certain devices intended for human use: small implants (less than 10 grams), which include sutures and contact lenses, medium implants (10 to 100 grams), large implants (greater than 100 grams), intrauterine devices, intraocular lenses, devices contacting human mucosa (mouth, nose, trachea, urinary tract), devices contacting blood but used outside the body (hemodialysis units, blood oxygenators, blood bags), devices contacting normal skin (surgical drapes, bandages), and surgical scrub sponges.

As with drug products, the residue limits proposed are the maximum acceptable limits for medical devices in their market containers at the time of release for marketing. The residue limits were derived from values developed from a Toxicity Working Group of the AAMI Ethylene Oxide (Z-79) Subcommittee, from industrial data submitted to FDA in response to the September 12, 1973 FEDERAL REGISTER notice, and from residue limits already established by current good manufacturing practice for similar products subject to approved new drug applications. For example, the proposed residue limits for intrauterine devices and surgical scrub sponges are the same as those being proposed by this notice for similar articles which are classified as drugs.

As in the case of drug products, residue limits established for certain medical devices would apply if ethylene oxide was used at a sterilant during any part of the manufacturing process of the device, including the manufacturing process for any components of the device, or the device's market container. Each device manufacturer would be required to assure, by appropriate laboratory testing, that the device as it appears in its market container does not exceed the residue limit when released for marketing. Some analytical methods that will produce reliable determinations of residues in drugs of ethylene oxide, ethylene chlorohydrin, and ethylene glycol have been discussed under paragraph A above. The Association for the Advancement of Medical Instrumentation Ethylene Oxide (Z-79) Subcom-

mittee has validated (Ref. 57) three analytical methods for the detection of residues in medical devices (Refs. 54, 55, and 56). In addition, some manufacturers and equipment producers, and certain others persons have developed methods or have sponsored the publication of methodology for determining residues on treated plastics, fabrics, and pharmaceuticals (Refs. 58 through 75).

The proposed rule would further require, as in the case of drug products, for each medical device for human use, including its component parts and market container, that the manufacturer prepare a residue dissipation curve for residues of ethylene oxide, ethylene chlorohydrin, and ethylene glycol for each manufacturing procedure in which ethylene oxide is used as a sterilant. This would provide a dissipation profile for each sterilized article and would enable a manufacturer to determine the point in time at which the medical device would be within the established residue limits so that it might be released for marketing.

The Commission is not, at this time, proposing that the residue limits established for medical devices be maintained throughout the shelf life of the device. Diffusion of ethylene oxide and its reaction products from a device is influenced by several factors, such as the type of material in the device (e.g., type of plastic), physical dimensions, exposed surface areas, and packaging. Further, residues of ethylene oxide are more likely to be converted to ethylene glycol (the less toxic of the reaction products) than to ethylene chlorohydrin. The Commissioner believes that even though a theoretical calculation could be made that the residues of either ethylene chlorohydrin or ethylene glycol could increase from the time of shipment of the device, there should also be a corresponding loss of these residues based on diffusion. The Commissioner concludes that, until more data are available regarding the diffusion of residues from device materials, he cannot reasonably expect a manufacturer to assure that devices comply with these residue limits throughout the shelf life of the device.

MAXIMUM DAILY LEVELS OF EXPOSURE

A. *Drug Products and Other Articles for Human and Veterinary Use*

The Commissioner also proposes to establish maximum daily levels of exposure to ethylene oxide and ethylene chlorohydrin, because of the potential risk of mutagenicity from exposure to drug products containing these residues. He also proposes to establish a maximum daily level of exposure to ethylene glycol because of known toxicity from exposure to drug products containing this residue.

Current calculations leading to estimates of human genetic risk are based on various assumptions and tests that are in a relatively early stage of evaluation and validation. Levels of ethylene oxide and ethylene chlorohydrin considered safe by traditional toxicological tests (for example, measurements of physiological, biochemical, or pathological changes in the body function) may not be safe when the potential for mutagenicity is considered. Nonetheless, the Commissioner's judgment is, given the potential risk of mutagenicity from exposure to ethylene oxide and its reaction product ethylene chlorohydrin, that he must attempt now to restrict that exposure insofar as products within his jurisdiction are involved. He therefore proposes to establish maximum daily levels of exposure based on available toxicity data, certain assumptions, and the application of an additional "best judgment" safety factor. The Commissioner advises that as the scientific basis for making risk judgments relative to mutagenicity improves, the agency will reconsider established maximum daily levels of exposure. This reconsideration may involve a further lowering of these exposure levels. The Commissioner proposes to establish maximum daily levels of exposure to ethylene glycol based on available toxicity data.

The Commissioner therefore proposes to establish maximum daily levels of exposure to ethylene oxide, ethylene chlorohydrin, and ethylene glycol based on the following calculations:

Ethylene oxide.—In the toxicity studies reported by Woodard and Woodard (Ref. 4), dogs and rats received subcutaneous injections of ethylene oxide for 30 days. At the lowest level of ethylene oxide administered (6 mg/kg/day) (see paragraph C.1. under "Ethylene oxide" above), some hematological changes were noted in both animal species and 2/4 dogs had ectopic hematopoiesis of the spleen. Thus, the dose-response data by Woodard and Woodard do not show a clear "no effect" level for ethylene oxide. Based on the trends shown by the dose-response data, Bruch (Ref. 3) estimated that if the lowest dose tested had been cut by 50 percent (i.e., 3 mg/kg/day), a "no effect" level had a high probability of being achieved. A 10-fold safety factor (a factor frequently used in extrapolating systemic "no effect" doses to man) was then applied by Bruch to yield an assumed safe level of 0.3 mg/kg/day for 30 days. Using that safety factor for a 70-kg man, the safe (in terms of toxicity) daily dose would be 21 mg.

However, because ethylene oxide has irreversible toxic effects, e.g., mutagenicity, for which sufficient dosage data are not available, the Commissioner, to adequately protect users of products sterilized with ethylene oxide, proposes to add an additional safety factor of 10 in proposing an acceptable exposure level. A level of 30 micrograms per kilogram per day (μg/kg/day) for 30 days is therefore proposed as an acceptable level of exposure to ethylene oxide residue.

Ethylene chlorohydrin.—In the Woodard and Woodard study (Ref. 4) dogs and rats also received subcutaneous injections of ethylene chlorohydrin for 30 days. At the lowest ethylene chlorohydrin level tested (3 mg/kg/day), and as with ethylene oxide, some of the animals showed slight hematological changes, and 1/4 dogs had ectopic hematopoiesis of the spleen (see the discussion of Animal Subchronic Toxicity, Paragraph C., under Ethylene Chlorohydrin). Again, the dose-response data by Woodard and Woodard do not show a clear "no effect" level. Based on the trends shown by the dose-response data, Bruch again estimated that if the lowest dose tested were cut by 50 percent (i.e., 1.5 mg/kg/day), a "no effect" level had a high probability of being achieved. As with ethylene oxide, Bruch then applied a 10-fold safety factor which yields an assumed safe level of 0.15 mg/kg/day for 30 days for man.

Because of mutagenic potential of ethylene chlorohydrin and because of its similarities with ethylene oxide, the Commissioner believes that the same additional safety factor is similarly appropriate for products containing ethylene chlorohydrin. Therefore, he proposes that an additional safety factor of 10 be applied, yielding an exposure level of 15 μg/kg/day of ethylene chlorohydrin residue.

Ethylene glycol.—The Woodard and Woodard study also contained data on a 30-day toxicity study in dogs and rats based on daily subcutaneous injections of ethylene glycol. At the lowest ethylene glycol level tested (50 mg/kg/day), there were some slight hematological changes in the animals. As with ethylene oxide and ethylene chlorohydrin, the dose-response data from the study do not show a clear "no effect" level. Based on trends shown by the dose-response data, Bruch estimated by cutting the lowest dose tested by 50 percent (25 mg/kg/day), a "no effect" level had a high probability of being achieved. As with ethylene oxide, Bruch applied a 10-fold safety factor, which yields an estimated safe dose of 2.5 mg/kg/day for 30 days. Because the Commissioner is not aware of evidence showing ethylene glycol to have mutagenic potential, he concludes that an additional safety factor is unnecessary.

B. *Medical Devices for Human Use*

The Commissioner has determined that the maximum levels of exposure

(30 μg/kg/day for ethylene oxide, 15 μg/kg/day for ethylene chlorohydrin and 2.5 mg/kg/day for ethylene glycol) proposed for drug products cannot reasonably be applied to medical devices for human use at this time. The application of such exposure levels would necessitate the development of a significant number of exemptions, as many medical devices as presently manufactured would be unable to meet these daily exposure levels, and with existing technology may not be readily modified to do so.

Other factors that have dissuaded the Commissioner from applying levels of exposure to medical devices for human use at this time deal with the nature, manner, and frequency of use of many medical devices. For example, devices used topically, such as sponges and pads, are used only once and would not be expected to deliver their total residue to the patient. Devices that are implanted, however, would be expected to deliver a greater percentage of their residue immediately following insertion, with a slowing of the rate of delivery thereafter. There is, at the same time, a lack of data on the rate of residue diffusion and movement from various plastic materials; and it would be impractical to expect medical device manufacturers to be able to work in concert with physicians and other health professionals to restrict the amount of patient contact from different devices use on the same day. Based on these factors, the Commissioner has concluded that he cannot effectively set proposed maximum levels of exposure for medical devices for human use. However, he invites the submission of published and unpublished data on rates of diffusion of various residues from plastic materials. The Commissioner advises, however, that the proposed residue limits for medical devices for human use have been calculated to reduce as much as possible maximum daily levels of residue exposure.

Summary of Requirements

Under these proposed requirements, a drug product would be deemed to be in compliance if the residues of ethylene oxide, ethylene chlorohydrin, and ethylene glycol do not exceed those set forth in the regulation, at the time of release of the product for marketing and throughout the shelf life, and the maximum daily level of exposure does not exceed 30 μg/kg/day for 30 days for ethylene oxide, 15 μg/kg/day for 30 days for ethylene chlorohydrin and 2.5 mg/kg/day for 30 days for ethylene glycol. Thus, if the dosage of a drug product in its recommended or approved labeling were such that the exposure levels established for the product would still be exceeded, notwithstanding compliance with the residue limits the manufacturer would still be required to reduce the amount of residue for the product so that, on the basis of the recommended dosage, the total daily exposure level would not be exceeded. In addition, for a drug product that is labeled to be reconstituted or diluted before dispensing, or use, the stated residue limits would be required to be met at the time the drug is reconstituted or diluted. A medical device for human use would be deemed to be in compliance if the residues of ethylene oxide, ethylene chlorohydrin, and ethylene glycol do not exceed those set forth in the regulation at the time of release of the device for marketing. Daily exposure levels for devices would not be established.

Even though the Commissioner considers the proposed residue limits acceptable, manufacturers should attempt to achieve even lower levels presuming current good manufacturing practices are followed and the level used will not compromise the effectiveness of the sterilant or the sterility of the product.

The Commissioner recognizes that more data are needed before the potential of ethylene oxide and its reaction products to act as mutagens can be fully assessed. He encourages the submission of any published and unpublished data concerning the use, performance, and toxicity of ethylene oxide and its two major reaction products, and any other data having a bearing on the safety and effectiveness of these compounds. The Commissioner also invites the submission of similar data for any drug products or medical devices for human use not subject to this notice so that residue limits may also be established for these products.

Final residue limits will be determined by the agency from comments and data submitted by interested persons in response to this proposal. The Commissioner notes that there are presently ongoing animal toxicity studies involving ethylene oxide and its reaction products. There are 2-year ethylene oxide studies on rats under way at Carnegie-Mellon Institute of Research. These will include teratology, mutagenicity, and a one generation reproductive study. The National Cancer Institute has also begun 2-year carcinogenicity studies on ethylene chlorohydrin and has scheduled 2-year ethylene oxide carcinogenicity tests. Results of these tests may provide the bases for revision of established values for exposure levels or residues.

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The Commissioner has carefully considered the environmental effects of the proposed regulation and, because the proposed action will not significantly affect the quality of the human environment, has concluded that an environmental impact statement is not required. A copy of the environmental impact assessment is on file with the Hearing Clerk, Food and Drug Administration.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 501, 505, 506, 507, 512, 513-521, 701, 52 Stat. 1049-1050 as amended, 1052-1053 as amended, 1055-1056 as amended, 55 Stat. 851, 59 Stat. 463 as amended; 82 Stat. 347-351, 90 Stat. 540-574 (21 U.S.C. 321, 351, 355, 356, 357, 360c-360k, 371)), the Public Health Service Act (sec. 351, 58 Stat. 702, as amended; 42 U.S.C. 262), and under authority delegated to the Commissioner (21 CFR 5.1), it is proposed that Chapter I of Title 21 of the Code of Federal Regulations be amended as follows:

PART 221—CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS

1. By adding a new § 211.70 to Subpart C to read as follows:

§ 211.70 Maximum residue limits and maximum daily levels of exposure for ethylene oxide, ethylene chlorohydrin, and ethylene glycol.

(a) Residue limits: Each drug product of a type listed in this paragraph for which ethylene oxide is used as a sterilant in the manufacture of the finished product, its components, or its market container shall not, when tested as packaged in its market container, exceed the following residue levels:

[Parts per million]

Drug product	Ethylene oxide	Ethylene chlorohydrin	Ethylene glycol
Ophthalmics (for topical use)	10	20	60
Injectables (including veterinary intramammary infusions)	10	10	20
Intrauterine device (containing a drug)	5	10	10
Surgical scrub sponges (containing a drug)	25	250	500
Hard gelatin capsule shells	35	10	35

(b) Each drug product shall conform to the limits set forth in paragraph (a) of this section during the shelf life of the product.

(c) Any drug product failing to comply with the requirements of paragraphs (a) and (b) of this section shall not be released for marketing.

(d) Each manufacturer of a drug product subject to this section shall prepare a residue dissipation curve for each manufacturing procedure in which ethylene oxide is used as a sterilant for the drug product, its components, or its market container.

(e) Each drug product intended to be reconstituted or diluted prior to dispensing, or use, shall conform to the limits set forth in paragraph (a) of this section as reconstituted or diluted.

(f) Daily exposure levels: the maximum daily level of exposure to residues of ethylene oxide and its reaction products from any drug product subject to paragraph (a) of this section, under the conditions for use in the drug product's recommended or approved labeling, shall not exceed the following limits set:

Ethylene oxide, 30 μg/kg/day/30 days
Ethylene chlorohydrin, 15 μg/kg/day/30 days
Ethylene glycol, 2.5 mg/kg/day/30 days

A product which complies with paragraph (a) of this section shall also comply with the limits set forth in this paragraph.

PART 821—CURRENT GOOD MANUFACTURING PRACTICE FOR MEDICAL DEVICES: STERILE DEVICES

2. By adding a new Part 821 consisting of one section to read as follows:

Sec.
821.100 Maximum residue limits for ethylene oxide, ethylene chlorohydrin, and ethylene glycol.

AUTHORITY: Secs. 513-521, 701, 52 Stat. 1055-1056 as amended, 90 Stat. 540-574 (21 U.S.C. 360c-360k, 371).

§ 821.100 Maximum residue limits for ethylene oxide, ethylene chlorohydrin, and ethylene glycol.

(a) Each medical device for human use of a type listed in this paragraph for which ethylene oxide is used as a sterilant in the manufacture of the finished device, its component parts, or its market container shall not, when tested as packaged in its market container, exceed the following residue levels:

[Parts per million]

Medical device	Ethylene oxide	Ethylene chlorohydrin	Ethylene glycol
Implant:			
Small (<10 grams)	250	250	5,000
Medium (10-100 grams)	100	100	2,000
Large (>100 grams)	25	25	500
Intrauterine device	5	10	10
Intraocular lenses	25	25	500
Devices contacting mucosa	250	250	5,000
Devices contacting blood (ex vivo)	25	25	250
Devices contacting skin	250	250	5,000
Surgical scrub sponges	25	250	500

(b) Any medical device for human use failing to comply with the requirements of paragraph (a) of this section shall not be released for marketing.

(c) Each manufacturer of a medical device for human use subject to this section shall prepare a residue dissipation curve for each manufacturing procedure in which ethylene oxide is used as a sterilant for the device, its component parts, or its market container.

Interested persons may, on or before August 22, 1978, submit to the Hearing Clerk (HFC-20), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, Md. 20857, written comments regarding this proposal. Four copies of all comments shall be submitted, except that individuals may submit single copies of comments, and shall be identified with the Hearing Clerk docket number found in brackets in the heading of this document. Received comments may be seen in the above office between the hours of 9 a.m. and 4 p.m., Monday through Friday.

NOTE.—The Food and Drug Administration has determined that this document does not contain a major proposal requiring preparation of an economic impact statement under Executive Order 11821 (as amended by Executive Order 11949) and OMB Circular A-107. A copy of the economic impact assessment is on file with the Hearing Clerk, Food and Drug Administration.

Dated: June 16, 1978.

SHERWIN GARDNER,
Acting Commissioner of Food and Drugs.

[FR Doc. 78-17384 Filed 6-22-78; 8:45 am]

☆ U.S. GOVERNMENT PRINTING OFFICE: 1984-421-177:10002