This guidance was written prior to the February 27, 1997 implementation of FDA’s Good Guidance Practices, GGP’s. It does not create or confer rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. This guidance will be updated in the next revision to include the standard elements of GGP’s.
DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

ETHYLENE OXIDE, ETHYLENE CHLOROHYDRIN, AND ETHYLENE GLYCOL

Proposed Maximum Residue Limits and Maximum Levels of Exposure
PROPOSED RULES

[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 CHLOORHYDRIN, 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, identified 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 containing high sensitive plastic components (e.g., heart pacemakers, kidney dialysis machines, and heart lung machines) as well as for other devices such as surgical sutures, surgical 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 closures and mountings of medical 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 glutaraldehyde. 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 (43 FR 3801) as a "Notice of Rebuttable Presumption Against Registration and Continued Registration of Pesticide Products Containing Ethylene Oxide," and reports on safety 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 memorandum 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-
I. TOXICITY REVIEW

The following information summarizes the toxicity data on ethylene oxide, ethylene chlorohydrid, 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 LD₅₀ of ethylene oxide (administered in aqueous solution to rats, mice, and rabbits) from oral or parenteral exposure (studies by Woodward and Woodward, 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 Woodward (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 balanced salt solution) were investigated in rabbits. The study showed that the maximum non-damaging concentration of ethylene oxide was 0.2 percent (0.1 mg/kg) for the anterior chamber injection, the maximum non-damaging 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.—Hill 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 dose 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 1 day) 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 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 26 mg/kg on day 1 due to severe pharmacologic and toxicologic 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 dogs; however, the lowest dosage administered was 5 mg/kg. All rats survived the duration of the study but experienced increased morbidity, occasional hemorrhage, and necroses 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 some times necrotic inflammatory changes, whereas dogs at a lower level dosage (18 mg/kg and 6 mg/kg) showed marked less severity 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 severe local tissue injury at the injection sites were reported. Hepatic changes such as increased liver weights at each dose, and reduced transaminases (54 (36) mg/kg) in each dog and at the mid dose (18 mg/kg) in one of four dogs, were observed. Increased ectopic hematopoeisis was observed in two of four dogs at all dosage levels. Other pharmacologic effects observed were muscular hyperactivity, 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.

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 (Ref. 85-87). Anemia of dose-related severity was reported (Ref. 4) to have developed in dogs injected subcutaneously (6 to 56 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. Allergic 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 (Hanflin, 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 Woodward, Ref. 4).

In a report (Ref. 78) of recent skin irritation studies by Shupak, sponsored by AAMI Ethylene Oxide (Z-78) Subcommittee, dermatitis and irritation in human subjects was observed in response to ethylene oxide contained in polyvinylchloride blocks and films and in petroleum. This finding supports some of the findings 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 Dro sophila melanogaster (Rapport, Ref. 17; Bird, Ref. 18; Nakao and Auerbach, Ref. 19), Neurospora crassa (Kolmark and Kilby, Ref. 20), barley (Ehrenberg, Ref. 21; Sulovks, 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 (Faber, Ref. 25), barley (Moutschen-Dahmen et al., Ref. 26), Vicia faba (Loveless, Ref. 27), Tradescantia and Lepi, Ref. 28), Dro sophila (Nakao and Auerbach, Ref. 29, Embree and Hine, Ref. 24).

Embree (Ph.D. dissertation, Ref. 30) employed 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 1 hr/day for 3 days, the frequency of chromosome aberrations increased from 0.5 (controls) to 3.4 (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-metatic and meiotic sperms. 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 somatic mutations.

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, cytogenetic analysis of the bone marrow and analysis of the male reproductive cells were carried out by the method of dominant lethal mutations. Cytogenetic analysis of the bone marrow showed an increased incidence of chromosome abnormalities in the bone marrow and of an increase in the number of abnormal spermatozoa in both normal and treated animals. Analysis of the bone marrow showed an increased incidence of chromosome abnormalities in the bone marrow and of an increase in the number of abnormal spermatozoa in both normal and treated animals.
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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 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 Rammug 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 LD50 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—mice, rats, and rabbits is summarized by Bruch (Ref. 3). The LD50'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 produce 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 (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) 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 8 hours after topical ocular instillation ranged from 4 percent for the conjunctiva than 80 mg/ml of the lens. After a single anterior chamber injection of ethylene glycol, the nondamaging concentrations ranged from 2 percent for the iris to 30 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 187 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 atonemia was noted. Total doses of 20 ml/kg and above produced deposition in the renal medulla of 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/m³), continuously for 5 to 7 months. At 5 months, liver mitochondria 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/m³ 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 established for the dog (Ref. 51). 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 0.1 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 (Rapport, Ref. 17) which suggests that ethylene glycol at high concentrations may cause mutations in Drosophila. 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 revertants.

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 ethylene glycol.

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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 practice.

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 21. 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, ethylene 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 intramuscular injection 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 articles for which ethylene oxide is used as a sterilant 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 released 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 determine the minute amounts 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 that meet the conditions of (1) batch sampling, (2) appropriate sample sizes, (3) adequate 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 proposes 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, 1973, do not 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), intravascular devices, intramuscular 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 by 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 intraocular lenses 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 component of the device. The 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 on 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., plastics, 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**

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 preclinical development 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 judgments will reconsider the risk of mutagenicity from exposure to ethylene oxide and its reaction product ethylene chlorohydrin, that he must attempt now to restrict that exposure insosfar 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 may establish 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 Woodward 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 glycol."), hematological changes were noted in both animal species and 2/4 dogs had ecotopic hematopoiesis of the spleen. Thus, the dose-response data by Woodward 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 (see paragraph C.1. under "Ethylene glycol.")) may not be applied, yielding an estimated safe dose 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.

**Ethylene glycol.**—In the Woodward and Woodard study (Ref. 4), dogs and rats received subcutaneous injections of 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.

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**B. Medical Devices for Human Use**

The Commissioner has determined that the maximum levels of exposure...
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(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 maintained by medical devices for human use at this time. The application of such exposure levels would necessitate the development of a significant number of new drugs, 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 already implanted, 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 work in concert with physicians and other health professionals to restrict the amount of patient contact from different devices to be able to work in concert with physicians and other health professionals to restrict the amount of patient contact from different devices.

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 work in concert with physicians and other health professionals to restrict the amount of patient contact from different devices.

Even though the Commissioner considers the proposed residue limits acceptable, manufacturers would be unable to meet these daily exposure levels for medical devices for human use at this time.

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 the drug is 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 level for devices would not be established.

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 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 recognizes 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 ethylene oxide, 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.

References

Copies of all references cited below are on public display in the office of the Hearing Clerk, Food and Drug Administration.

1. Report of the Subcommittee to the HEW Committee to Coordinate Toxicology and Related Programs on the "Benefits and Risks from the Use of Ethylene Oxide for Sterilization," April 1, 1977.


PROPOSED RULES

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**PROPOSED RULES**

**§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:

<table>
<thead>
<tr>
<th>Drug product</th>
<th>Ethylene oxide</th>
<th>Ethylene chlorohydrin</th>
<th>Ethylene glycol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ophthalmics (for topical use)</td>
<td>10</td>
<td>20</td>
<td>60</td>
</tr>
<tr>
<td>Injectables (including veterinary intramuscular infusions)</td>
<td>10</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Intraocular device (containing a drug)</td>
<td>5</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Surgical scrub sponges (containing a drug)</td>
<td>5</td>
<td>500</td>
<td>500</td>
</tr>
<tr>
<td>Hard gelatin capsule shells</td>
<td>500</td>
<td>25</td>
<td>35</td>
</tr>
</tbody>
</table>

(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:

- 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:

§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:

<table>
<thead>
<tr>
<th>Drug product</th>
<th>Ethylene oxide</th>
<th>Ethylene chlorohydrin</th>
<th>Ethylene glycol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical device</td>
<td>250</td>
<td>250</td>
<td>5,000</td>
</tr>
</tbody>
</table>

(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.


SHERWIN GARDNER,
Acting Commissioner
of Food and Drugs.

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