Any person who will be adversely affected by the following regulation may at any time on or before February 1, 1985 submit to the Dockets Management Branch (address above) written objections thereto and may make a written request for a public hearing on the stated objections. Each objection shall be separately numbered and each numbered objection shall specify with particularity the provision of the regulation to which objection is made. Each numbered objection on which a hearing is requested shall specifically state failure to request a hearing for any particular objection shall constitute a waiver of the right to a hearing on that objection. Each numbered objection for which a hearing is requested shall include a detailed description and analysis for any particular objection shall constitute a waiver of the right to a hearing on the objection. Three copies of all documents affected by the following regulation may be seen in the office above between 9 a.m., and 4 p.m., Monday through Friday. Effective date. This regulation is effective January 2, 1985. [Secs. 201(s), 409, 72 Stat. 1784-1788 as amended (21 U.S.C. 321(g), 348)) (Secs. 201(s), 409, 72 Stat. 1784-1788 as amended (21 U.S.C. 321(g), 348))


Richard J. Ronk,
Acting Director, Center for Food Safety and Applied Nutrition.
[FR Doc. 84-34004 Filed 12-31-84; 8:45 am]
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Food and Drug Administration

21 CFR Part 520
Oral Dosage Form New Animal Drugs Not Subject to Certification; Acepromazine Maleate Tablets

Correction

In FR Doc. 84-32817 beginning on page 49090 in the issue of Tuesday, December 18, 1984, make the following correction: On page 49091, first column, second line from the bottom of the page, the EFFECTIVE DATE should have read "December 18, 1984".

BILLING CODE 1405-01-M

DEPARTMENT OF LABOR
Occupational Safety and Health Administration
29 CFR Part 1910
Occupational Exposure to Ethylene Oxide

AGENCY: Occupational Safety and Health Administration (OSHA), Labor.

ACTION: Final Rule; Supplemental statement of reasons.

SUMMARY: On June 22, 1984, the Occupational Safety and Health Administration (OSHA) published a final standard for ethylene oxide (EtO) that established a permissible exposure limit of 1 part EtO per million parts of air determined as an 8-hour time-weighted average (TWA) concentration (29 CFR 1910.1047. 49 FR 25734). The standard also includes provisions for methods of exposure control, personal protective equipment, measurement of employee exposure, training, signs, and labels, medical surveillance, regulated areas, emergencies and recordkeeping. The basis for this action was a determination by OSHA, based on human and animal data, that exposure to EtO presents a carcinogenic, mutagenic, genotoxic, reproductive, neurologic, and sensitization hazard to workers.

During the rulemaking proceedings that led to the establishment of the 1 ppm TWA, the issue of whether there was a need for a short-term exposure limit (STEL) for worker protection from EtO was raised. OSHA reserved decision on the adoption of a STEL at the conclusion of the rulemaking in order to permit peer review of the available evidence and to review more fully the arguments and pertinent data regarding the STEL issue. Upon receipt of the analyses from most of the peer reviewers, OSHA published a notice to that effect on September 19, 1984 (49 FR 36659) and invited public comment on the pertinent issues addressed in the peer reviews. Based on the entire rulemaking record, including the peer reviews and public comments received since June 22, the Assistant Secretary has determined that adoption of a STEL for EtO is not warranted by the available health evidence, and that a STEL is not reasonably necessary or appropriate for inclusion in the final EtO standard. OSHA has also asked that NIOSH fund certain additional studies related to whether a dose-rate relationship can be established for EtO, and OSHA will review the results of
I. Events Leading to This Action

On January 28, 1982, OSHA published an Advance Notice of Proposed Rulemaking [47 FR 3566] announcing its intention to conduct a reevaluation of its existing EtO standard of 50 ppm as a time-weighted average (TWA). In addition to a request for public comment on the adequacy of 50 ppm as a TWA, comment was also solicited on the question of the necessity of a STEL as follows:

- Is a short-term or ceiling limit for EtO exposures necessary and why, and what would be the technological and economic feasibility of complying with that limit? (47 FR 3566)

On April 21, 1983, OSHA published a Notice of Proposed Rulemaking for EtO that proposed to reduce the permissible 8-hour TWA for EtO from 50 ppm to 1 ppm (48 FR 17284). Although a specific STEL for EtO was not proposed, public comment on that issue was solicited by the following questions:

- Is a short-term or ceiling exposure limit for EtO exposure necessary for the PEL or action level in view of recent information regarding increased spontaneous abortions and chromosome changes in workers exposed to EtO? What monitoring methods and control technology are available to meet such a short-term limit and what would be the economic burdens, if any, of such a limit? (48 FR 17284)

and,

What are the most suitable methods for determining compliance with EtO permissible exposure limits (PEL's) of 0.5 and 1 ppm as 8-hour time-weighted averages and for ceilings ranging from 5 to 50 ppm for 30 minutes or less? What are the problems associated with such monitoring methods? Do they require special training or experience? Are there serious limitations as to the accuracy or precision of the available sampling techniques? (48 FR 17284)

Numerous comments and other data were received by OSHA in response to the STEL questions set forth in the ANPR and NPRM (Ex. 168). The final EtO rule published on June 22, 1984, (49 FR 25734) reserved decision on the question of whether the standard should contain a STEL (Ex. 167A).

In the June 22, 1984 final rule, OSHA stated that upon its review of comments submitted by the Office of Management and Budget (OMB) pursuant to Executive Order 12291 (Ex. 162), OSHA determined that certain issues relating to a STEL were important and merited further consideration. In particular, OSHA believed that questions concerning the following issues merited additional review:

- Quantification of the risk avoided by issuance of the STEL. In light of the requirement of the new standard to meet a 1 ppm PEL;
- The need for a STEL given current exposures and the 1 ppm PEL of the new standard;
- The appropriateness of relying on studies by Hemminki, Yager, and Johnson & Johnson as partial support for the issuance of a STEL;
- A decision by the American Conference of Governmental Industrial Hygienists (ACGIH) not to recommend a STEL for EtO; and
- The economic and technical feasibility of a STEL without the use of respirators.

To develop the fullest possible administrative record, all exhibits in the docket relating to the STEL (compiled as Ex. 168), were submitted to a number of scientifically qualified peer reviewers for comment, analysis, and criticism. The peer reviewers filed statements that were placed in the public docket.

Public comments on the statements filed by the peer reviewers and on the issues raised by OMB on the June 14, 1984 draft standard were solicited by a Federal Register notice published September 19, 1984 (49 FR 36595).

As noted by OSHA in its June 22 Federal Register notice, the purpose of the extended period of consideration of the STEL issues was to enable peer reviewers and the public to consider the available data on short-term EtO exposures and to submit their detailed evaluations of the evidence to the Agency. This, in turn, would allow OSHA to perform a more comprehensive examination of the need for a STEL-based upon the existing record and the analyses contained in the peer review and public comments. Both of these goals have been accomplished, and OSHA is most appreciative of those persons and organizations that participated in this phase of the rulemaking on EtO.

II. Identification of Peer Reviewers

OSHA requested peer review of the STEL data by 23 individuals and organizations. Reviewers were asked to provide comment on those aspects of the STEL issues that were within their area of expertise (toxicology, epidemiology, industrial hygiene, etc.). OSHA contacted the following peer reviewers (A number in parentheses in the list below reflects OSHA's receipt of the person's review and the exhibit number of that review in Docket H-200):

Elliot Harris, Ph.D., Deputy Director, National Institute for Occupational Safety and Health (Ex. 181)
Ralph Allen, President, American Academy of Industrial Hygiene (Ex. 175)
Vernon L. Carter, Jr., DVM College of Veterinary Medicine, Ohio State University (Ex. 178)
William Kelley, Executive Director, American Conference of Governmental Industrial Hygienists (Ex. 191)
Dr. Donald Hoops, Executive Director, American Occupational Medical Association (Ex. 186)
Dr. L.B. Russell, President, Environmental Mutagen Society (Ex. 180)
Matilda Babbitz, Executive Director, American Association of Industrial Hygienists (Ex. 171)
Richard Adamson, Ph.D., National Institute for Occupational Safety and Health (Ex. 161)
Dr. Fred Oehme, President, Society of Toxicology
Dr. John Crum, Executive Director, American Chemical Society (Ex. 170)
Richard Adanson, Ph.D., National Cancer Institute (Ex. 172)
David P. Rall, M.D., Ph. D., National Institute of Environmental Health Sciences (Ex. 171)
The following 12 members of the Department of Labor’s National Advisory Committee on Occupational Safety and Health were also requested to review and submit comments on the STEL issue:

Frank R. Barnako, Chairman of the Board, National Safety Council (Ex. 174)
Joyce C. Hearn, Representative, South Carolina Legislature
Sidney Shindell, M.D., Chairman, Department of Preventive Medicine, The Medical College of Wisconsin (Ex. 176)
Robert B. Taylor, Director, Division of Occupational Safety and Health, Tennessee Department of Labor
Tom Baker, President, Baker Electric Company
Bruce W. Karrh, M.D., Vice-President—Safety, Health and Environmental Affairs, E.I. duPont deNemours and Co., Inc. (Ex. 173)
John J. Donlon, Business Manager, Colorado Building and Construction Trades Council
R.V. Durham, Director, Safety and Health Department International Brotherhood of Teamsters, Chauffeurs, Warehousemen & Helpers of America (Ex. 179)
B. Gawain Bonner, Director, Safety and Health, Tenneco, Inc.
Ronald H. Davis, Vice President, Industrial Relations, Carolina Steel Corporation (Ex. 183)
Marcus M. Key, M.D., Professor of Occupational Medicine, The University of Texas Health Sciences Center (Ex. 177)
William E. McCormick, Former Manager, American Industrial Hygiene Association

III. Summary of Peer Reviews and Public Comments

In addition to the peer reviews, OSHA received 41 comments in response to the September 19, 1984, FR notice. Those in opposition to adoption of a STEL generally argued that the available scientific evidence did not justify issuance of a short-term limit. They contended that the STEL must be based on, among other reasons, the observation of either (1) acute effects occurring above a given level or (2) on the demonstration of a dose-rate effect associated with exposure to EtO. Those parties opposing a STEL argued that neither of these effects have been demonstrated to occur from exposure to EtO.

Proponents of adoption of the STEL generally contended that (1) the collective scientific evidence demonstrates adverse reproductive and mutagenic effects attributable to short-term EtO exposures and (2) the STEL is necessary to reduce the significant risk of cancer still present with the 1 ppm TWA. These arguments and others, and the comments presented on both sides of these issues by both public commentors and peer reviewers are discussed below.

A. Comments Opposing a STEL

Parties opposing adoption of a STEL for EtO reiterated several arguments presented prior to this supplemental rulemaking and raised new points, accompanied by new argument and calculations. They argued that:

—No evidence has been presented indicating that the potential effects of exposure to EtO are related to dose-rate (i.e., pattern of exposure);
—The collective findings of Yager, Embree, Generoso, LaBorde and Kimmel, Johnson, Garry, Pero, and Hemminki do not form a reasonable inference for a STEL;
—The STEL is “unsupported by any reasonable risk assessment or inference from the scientific evidence;”
—The studies by Hemminki, Yager, and Johnson and Johnson are flawed and inadequate to support a STEL;
—A STEL can only be justified through quantification of risk;
—Compliance and measurement feasibility for a STEL have not been demonstrated;
—The 1 ppm TWA and 0.5 ppm action level provide adequate protection from short-term exposure;
—The types of controls that will need to be employed to meet the TWA will also result in low short-term exposure;
—There is no established relationship between sister chromatid exchanges and adverse health; and
—The ACIAB has concluded that the toxicological data provides inadequate support for a STEL.

Peer Review Analyses

Those peer reviewers opposing a STEL included:

Dr. Bruce Karrh, Vice-President for Safety, Health and Environmental Affairs, E.I. duPont deNemours Co. (Ex. 173);
Ralph E. Allan, President, American Academy of Industrial Hygiene (Ex. 173);
Dr. Sidney Shindell, Professor and Chairman of the Department of Preventive Medicine, Medical College of Wisconsin (Ex. 176);
Dr. Marcus Key, Professor of Occupational Medicine at the University of Texas’ School of Public Health (Ex. 177);

Dr. Vernon Carter, Consultant in Occupational and Environmental Toxicology (Ex. 178);
Environmental Mutagen Society (committee consisting of Dr. R.J. DuFrain, Senior Scientist of the Medical and Health Science Division of Oak Ridge Associated Universities; Dr. W.M. Generoso, Senior Scientist, Oak Ridge National Laboratory; and Professor S. Abrahamson, Departments of Zoology and Genetics, University of Wisconsin) (Ex. 186); and


The Environmental Mutagen Society (Ex. 186) provided for review of the EtO STEL data by a committee of experts consisting of Dr. R.J. DuFrain, Senior Scientist of the Medical and Health Science Division of Oak Ridge Associated Universities; Dr. W.M. Generoso, Senior Scientist of the Biology Division, Oak Ridge National Laboratory; and Professor S. Abrahamson, Departments of Zoology and Genetics, University of Wisconsin.

The conclusion of the committee was that:

The prime issue as we all see it (and have each done considerable research on in our careers) is one of dose and dose-rate.

Namely, is the biological outcome (the yield of induced damage) affected by the manner and delivery of the dose (exposure)? The evidence required to support a STEL would have had to demonstrate that for some endpoint (SCE, chromosome damage, time to tumor etc.) there was a greater yield of damage (effect) from an acute treatment as compared to a chronic or fractionated treatment for the same total dose.

No such evidence was presented. (emphasis in original) (Ex. 186).

The committee contended that before a STEL can be justified there would have to be an observed dose rate effect over a certain dose range, and at the dose limitation imposed there would be an influence of [cellular] dose rate. They concluded that no such effect has been established in the Yager, Johnson and Johnson, or Hemminki studies.

Specific comments on the Yager, Johnson and Johnson, and Hemminki studies were provided by Generoso and DuFrain. With respect to the Yager study, DuFrain stated:

In this report in Science, 22 individuals were evaluated for SCE frequency in their peripheral blood lymphocytes. Extensive questionnaires were filled out and EtO measurements in the breathing zone of some of these individuals were taken while they were performing their jobs which exposed
With respect to Hemminki, Generoso concluded that although the likelihood that EtO exposure may lead to higher abortion frequency cannot be ruled out, the study "has no bearing whatsoever on the question of dose-rate effect".

In addressing the possible reason for the conclusion that a dose-rate effect has not been observed for EtO, Du Frain offered the following:...
Dr. Carter found that the observed increase in SCE in the Yager and Johnson studies is "probably valid." With respect to the health implications associated with increased frequency of SCE, however, he stated that:

As yet no relationship has been established between this response and effects of concern such as cancer and reproductive problems. It is my opinion that until such a relationship is better established, a STEL to control this response is not justified. (Ex. 178)


Dr. Dixon contended that: (1) Short-term low level exposure is not the basic issue with EO but that the significant risks are related to longer term exposure; (2) none of the health studies [Hemminki, Yager, Johnson and Johnson] adequately addresses short-term exposures or demonstrates significant adverse effects; (3) long-term studies are not relevant for addressing short-term effects; (4) that 1 ppm TWA and 0.5 ppm action level provide adequate control from short-term excursions; (5) a short-term exposure limit would result in very little reduction of overall exposure: and (6) a STEL is only appropriate for agents having severe acute toxicity potential.

Dr. Anstadt stated that there is no direct evidence to support a short-term exposure limit or to calculate a value for a STEL. In commenting on the Johnson and Johnson studies, Dr. Anstadt stated that: (i) Short-term exposure data, as used by OSHA, is not based on the scientific data; (ii) that there are some increases in some of the exposed groups at some of the sampling times when compared to worksite controls.

The EOIC provided the following discussion on the short-term control implied by the 1 ppm TWA (Ex. 189-16):

In order for the conclusion to be drawn that short-term exposures to EO are more effective at inducing SCE in human peripheral lymphocytes than the same dose received over a long-time period, such as an 8-hour working day, data for both exposure conditions have to be available and obtained by the same laboratory preferably coincidentally. (Ex. 189-16)
be imposed as a short-term exposure limit accessible to all employers.

First, and mathematically, the PEL of 1 ppm (TWA) sets an effective, maximum short-term exposure limit of 32 ppm. This is measured over a 15-minute period. Moreover, this maximum short-term level would be allowed only if there were absolutely no other exposure to EO the remainder of the working day. Any other exposure would lower the level that could be allowed to occur during the 15-minute period. Because employees exposure to EO will not likely be limited to one 15-minute period, a 1 ppm PEL effectively requires that 15-minute exposures be kept considerably lower than the theoretical 32 ppm level. * * * the existence of additional periods of exposure will necessarily result in lower maximum short-term exposures for any 15-minute period.

The EOC goes on to state that:

The position that the engineering controls necessary to achieve the PEL (and especially the action level) require good control of short-term exposure is also supported by the NIOSH peer review comments (Exhibit 181). NIOSH states that the 1 ppm PEL will actually require employers to maintain workplace concentrations near 0.5 ppm in order to ensure that random variation does not result in exposures exceeding the PEL. It further states that "it appears that some short-term exposure limit is necessary in order to satisfy the employer that the 1 ppm PEL has not been exceeded." (Emphasis supplied) This is precisely the EOC point— that the 1 ppm PEL will, as a practical matter, require employers to control short-term exposures. As NIOSH states, employers will be required to reduce short-term exposures to some, fairly low level. However, the particular level that may be appropriate will vary from facility to facility. There is simply no basis on which to justify a particular, single limit that applies uniformly to every employer * * * a basic tenet of good industrial hygiene to comply with the PEL, is that control of overall exposure levels includes control of peak or excursion levels as well. In the view of the American Conference of Governmental Industrial Hygienists suggests that, as an indication of good process control, exposures should not exceed three times the TWA for more than 30 minutes during the work day and should not exceed five times the TWA. These guidelines, although not easily applicable to very low TWA's (where the allowed range would be extremely small) or to processes where the exposure profile involves episodic fluctuation, are consistent with the trained industrial hygienists who will be involved in implementing controls to achieve the PEL will also be concerned with, and will implement controls to reduce, short-term exposures.

Finally, it should be noted that compliance with a PEL of 1 ppm (TWA) will require, as OSHA has acknowledged in the standard, the use of respirators at times when employees might be exposed to higher, short-term levels of EO. These employees will already be protected from peak exposures.

Other provisions of the standard, aside from the PEL and the action level, will also contribute to the reduction of short-term exposures. The requirements for employee education and training, and for the preparation of written compliance plans, will ensure that both employers and employees are aware of potential higher exposures. This in turn will lead to the institution of measures to assure control of such exposures.

B. Comments in Support of a STEL

In brief, the peer reviewers and public commenters who favored the need for a STEL expressed the following arguments in support of their position:

— A STEL would reduce the significant risk of cancer still present with the 1 ppm TWA;

— The collective scientific data provide sufficient qualitative support for a STEL, and a quantitative assessment of risk is unnecessary;

— Adverse reproductive and mutagenic effects are attributable to short-term EO exposure concentrations presently being experienced by workers; although these risks may not be quantifiable they are qualitatively demonstrated;

— Additional documentation suggests that sister chromatid exchange (SCE) should be viewed as an indicator of DNA damage which could potentially lead to the clinical manifestation of cancer; and

— Compliance with a STEL of 10 ppm is feasible.

The peer reviewers and public comments provided no new significant studies or other substantive health data in support of the need for a STEL, and essentially relied on the data in the record as of June 22. However, they did contain additional explicit discussion of the rationale for adoption of a STEL.

Peer Review Analyses

Peer reviewers supporting a STEL included:

— David Rall, M.D., Ph.D., Director, National Institute of Environmental Health Sciences of the Public Health Service, Department of Health and Human Services (Ex. 171);

— R.V. Durham, Director of the Safety and Health Department of the International Brotherhood of Teamsters (Ex. 170);

— Matilda Babbits, R.N., Executive Director of the American Association of Occupational Health Nurses (Ex. 180); and

— Elliot Harris, Ph.D., Director, National Institute for Occupational Safety and Health, Public Health Service, DHHS (Ex. 181).

The National Institute of Environmental Health Sciences (NIEHS) contended that a STEL is needed based on exposure pattern (short bursts), epidemiological data on EO sterilization workers, and supporting data indicating increased chromosomal aberration and sister chromatid exchange frequencies among sterilization workers (Ex. 171). NIEHS pointed to data in the record that shows that short-term exposures experienced by sterilization workers often exceed 50 ppm (Exs. 4-10, 6-15, 11-106). The Institute indicated that the epidemiological studies by Hogsted et al. (Ex. 2-8) reporting an increased incidence of leukemia, and Hemminki et al. (Ex. 6-7) reporting significantly elevated spontaneous abortion rates among sterilizer workers, are relevant to the STEL question since the exposure patterns leading to the observed health effects in the studies were short-term in nature. NIEHS acknowledged that the Hogstedt sterilization worker study has several limitations including small cohort size and potential cohort selection bias but contended that the data gain additional importance when viewed in conjunction with another Hogstedt et al. study (Ex. 6-8) that also reports an excess leukemia risk among sterilization workers.

NIEHS acknowledged that there are potential weaknesses in the Hemminki et al. study, including a potential selection bias introduced by the study questionnaire, a potential cohort selection bias, and inadequate control of confounding factors such as maternal age and prior reproductive or medical history. NIEHS concluded, however, that the Hemminki study demonstrates considerable internal consistency, and that the conclusions of the questionnaire are supported by the hospital discharge data, which should be free of reporting bias. Taken in conjunction with supporting bioassay data that demonstrate the feto-toxic potential of EO, NIEHS states that this study cannot be discounted.

Finally, NIEHS argued that available cytogenetic data on EO workers support the need for a STEL. These studies include those of sterilizer workers by Per et al. (Ex. 6-8), reporting increased chromosomal aberrations and increased unscheduled DNA synthesis in peripheral blood, and of Johnson and Johnson (Exs. 11-113, 150), reporting increased SCE frequency and a dose-effect response. NIEHS summarized the implications of the cytogenetic data as follows:

The available data demonstrate that sterilization workers may experience increased SCE frequency even given relatively low TWA EO exposures thus suggesting a possible role for short-term elevated exposures. While the predictive value of SCE data with regard to human health outcome is not yet known, this manifestation is generally regarded as an interaction with DNA material during the synthesis phase of the cell cycle. The importance of SCE data in humans gains
significance given similar findings in exposed animals and positive results of carcinogenesis bioassay studies with ethylene oxide. (Ex. 171)

Adoption of a STEL was also supported by NACOSH member R.V. Durham of the Teamsters Union (Ex. 179). Durham stated that due to the peak nature of the majority of EIO exposures, failure to adopt a STEL would be imprudent industrial hygiene practice.

With regard to the epidemiological studies by Hemminki (Ex. 6-7), Yager (Ex. 6-15), and Johnson and Johnson (Exs. 11-113, 150), Durham stated that:

While we have observed some limitations with each of these studies, we feel that as a whole these data comprise a body of overwhelming evidence in support of a STEL. The results of the Hemminki study are strikingly consistent with animal studies. The Yager study results are strikingly consistent with results from animal test systems as well. We believe that such a wealth of information cannot be overlooked. (Ex. 179)

With regard to quantification of the risk avoided by adoption of a STEL, Durham argued that:

Although OSHA was unable to quantitatively assess the risks [in their June 14, 1984 draft final standard] indicated by these studies, they were able to qualitatively infer that the human and animal data on adverse health effects warrant a STEL. We believe, therefore, that contrary to OMB's assertion that OSHA had not met the legal test of "significant risk" under the Supreme Court's Benzene decision, IUD, AFL-CIO v. American Petroleum Institute, OSHA has made an accurate "inference from the available scientific evidence" in support of a STEL (Ex. 179)

Finally, Durham cited evidence in the record provided by industry that demonstrates the feasibility of complying with a STEL (Exs. 4-34, 11-66, 11-71, 11-113) and further pointed out that Johnson and Johnson, Texaco, Medtronic, and Rohn and Haas have adopted in-house ceiling levels or peaks ranging from 5 to 15 ppm.

The American Association of Occupational Health Nurses (AAOHN) (Ex. 180) supported the need for a 5 ppm STEL with a ceiling value not to exceed 10 ppm at any time. AAOHN's concern with a STEL for EIO relates to the brief but high exposures to EIO of hospital employees using it as a sterilant.

AAOHN pointed to data indicating that EIO exposure increases mutation rates in numerous species, causes dose-related increases in leukemias and other tumors in rats, reduces sperm count and function in monkeys and elevates the frequency of SCEs. With regard to the available studies, AAOHN stated that:

While recognizing the limitations of the preliminary work by Morgan, et al. (1981) and Hogstedt, et al. (1979) we concur with OSHA in the current proposed rule: "OSHA believes exposure to EIO may increase the risk of malignancies, particularly leukemia." The work by Yager (1983) and Johnson and Johnson (1984) to reaffirm this composite view. In view of the consistent findings regarding adverse health effects from low level exposure we feel OSHA appropriately used the studies by Hemminki, Yager, Johnson and Johnson as partial support for the issuance of a STEL.

OSHA states that at the 1 ppm PEL the risk of excess cancer deaths is 1 to 2 cases per 1,000 workers exposed to EIO. We find this risk excessive and recommend an STEL at half the 10 ppm valve proposed by OSHA. Although, 10 ppm for a 15-minute STEL would be desirable over none at all we think EIO exposures greater than 10 ppm should not be permitted. This conclusion is from findings that EIO causes chromosomal damage and thus is a potential human carcinogen and that EIO causes adverse reproductive outcomes in humans.

Due to the extreme intermittency of exposure and the short duration we strongly feel that without a STEL a STEL standard alone will not adequately protect workers exposed to EIO in hospital sterilizers. (Ex. 180)

The fourth peer reviewer supporting the need for a STEL was the National Institute for Occupational Safety and Health (NIOSH) (Ex. 181). NIOSH pointed to data in the record which indicate that hospital sterilizing staff encounter intermittent peak exposures to EIO and that the best way to control exposure levels is to control the peak exposures. (Yager, Exs. 3-6, 10, 11-51, Roy, Tr. 216; AFGE, Tr. 1197). NIOSH did not agree with arguments that a 1 ppm STEL will by itself set an effective short-term limit. NIOSH contended that the example that a 1 ppm STEL sets a theoretical maximum 15 minute exposure is not a realistic argument. NIOSH stated that:

As detailed above (Ex. 4-10), EIO exposures typically occur as brief peak exposures that appear to range between 75 ppm and 125 ppm over the 3 to 4 minute period required for workers to perform their tasks of removing materials from the sterilizer and transferring them to the aerator. (Ex. 181)

NIOSH further stated that:

**"when EIO exposures are discussed in terms of 5 hour TWAs or 15 minute periods the significance of the high 3 to 8 minute exposure concentrations documented by Dr. Yager is lost. Clearly, the actual exposure concentrations documented by Dr. Yager [Ex. 4-10, Ex. 31] are not consistent with the theory [of a built in 32 ppm STEL for 15 minutes]. (Ex. 181)"

On a related point, as noted earlier, several parties opposing a STEL argued that 1 ppm TWA would actually result in employers achieving EIO levels below 1 ppm in order to allow a margin of safety and avoid exceeding the PEL due to random variation. NIOSH responded to this argument as follows:

As a practical matter, an employer would have to maintain workplace concentrations in the vicinity of 0.5 ppm in order to ensure that an "exceedance due to random variation" had not occurred. The [0.5 ppm 15 minute] scenario presented by Drs. Vorest and Hecker and Mr. Rampa of EIOIC, however, considers only a 1 ppm PEL and doesn't address the issue of an action level. A short term exposures never exceeded 16 ppm, then an employer could be reasonably assured that 8 hour TWAs exposures would not exceed 1 ppm. However, neither the EIOC nor OMB appears to have considered this point. Review of Dr. Yager's data clearly indicates that short term exposures are far in excess of 19 ppm. Therefore, as a practical matter, it appears that some short term exposure limit is necessary in order to satisfy the employer that the 1 ppm PEL has not been exceeded. (Ex. 181)

The necessity of adoption of a STEL based on the studies in the record showing observed adverse health effects was addressed at length by NIOSH. NIOSH contended that a reasonable inference from the collected data can be made that short-term exposure to EIO can lead to adverse effects in workers. NIOSH argued that:

1. Data demonstrates that EIO reacts with the genetic material of at least 13 different species with the observation of persistence of genetic damage in humans;
2. EIO exposure is capable of producing adverse mutations in mammalian germinal cells that are heritable and which can adversely affect the human genome and reproductive capacity;
3. EIO exposure causes chromosomal aberrations (Yager, Johnson and Johnson) in workers;
4. The basic findings by Hemminki (Ex. 6-7) that spontaneous abortions result from EIO exposure cannot be discounted; and
5. Data demonstrates that EIO is a potential human carcinogen.

The carcinogenic potential of EIO was described by NIOSH as being relevant to the STEL issue as follows:

There is agreement that EIO is a potential occupational carcinogen. The exact mechanism of the carcinogenic process is, however, debatable. At one extreme, it is argued that only one event is needed to initiate the carcinogenic process; at the other extreme, it is believed that many events are required. In the first example the response is linear; in the latter example, the response incorporates a threshold concentration below which a response will not occur.

Ethylene oxide appears to exert its effects by alkylation of DNA. Under most circumstances, DNA bases that have been chemically modified are removed. If, however, damage occurs at a rate that...
Finally, NIOSH argued that a STEL is particularly necessary to prevent the occurrence of SCE and the biological consequences of that damage. Furthermore, SCEs are not elicited by certain classes of genotoxic agents. However, SCEs can be used to indicate damage to DNA induced by ETO and damage to DNA is potentially harmful. Thus, it is entirely appropriate that SCEs be used as an indicator of potential harm.

Tice also characterized an article by Garry et al. (Ex. 189–14) entitled “Ethylene Oxide Induced Sister Chromatid Exchange in Human Lymphocytes Using a Microscopic Dosimetry System” as containing data indicating dose-rate effects for the induction of SCEs by ETO (Ex. 189–13).

With respect to the health implications associated with chromosomal aberrations, the American Federation of State, County and Municipal Employees stated that:

Some commenters have raised the contention that the presence of increased chromosomal aberrations in populations exposed to ETO is not pertinent, since no overt illness is directly attributable to such a finding. (Exs. 152, 153, 11–133, 175, 178, 179).

Although this conclusion is true on an individual basis, it is not true on a population basis. Studies of chromosomal aberrations in populations exposed to ionizing radiation have shown clear dose-related increases both in chromosome aberrations and in various cancers for these populations (Testimony of Geoffrey M. Karmy before the U.S. House of Representatives, October 6, 1982). (Ex. 189–14)

Other commenters contended that short-term limits are necessary to minimize exposures to substances such as ETO, that are considered to be potential carcinogens (Exs. 189–33, 189–39).

Richard Brandt, Industrial Hygienist for the State of Wisconsin comments that a STEL is warranted to prevent the occurrence of lung tissue shock and consequent blood absorption (Ex. 189–2).

In addition to supporting the need for a STEL, commenters addressed the issue of quantification of the risk reduced by issuance of a STEL. The National Union of Hospital and Health Care Employees provided the following discussion:

In terms of risk reduction, the Calleman article [20] makes a calculation of risk for the development of cancer after exposure to ethylene oxide. Their calculation indicates that a PEL of .25 ppm would be equivalent to an exposure to five REMS of low LET radiation per year. Five REMS per year is ten times that permitted for pregnant workers and to the nonworking population. There is also growing evidence that five REMS does in fact pose significant risk to the exposed individual. At this exposure level of 5 REM/year there is significant cancer risk. NIOSH (30) has determined that the risk of cancer from one x-ray is .8 excess cancers per one million. Five REMS would extrapolate to 6.5 excess cancers per million suggesting that even a TLV of .25 ppm is too high. Strengthening the case that the TLV–TWA should be .1 ppm, the ceiling .5 ppm to 1 ppm and the STEL 3 to .5 ppm. (Ex. 189–39).

The National Safety Council stated that the quantification of the risk in this instance can only be determined qualitatively because of limitations of the science of risk assessment, but that the qualitative scientific evidence on ETO clearly supports the need for a STEL. (Ex. 189–12).

IV. The ACGIH TLV Recommendation

A number of commenters opposing adoption of a STEL cited the fact that the American Conference of Governmental Industrial Hygienists (ACGIH) has not recommended a specific STEL for ETO. Commentors supporting adoption of a STEL point out, however, that the ACGIH does recommend adherence to an “exclusion limit” for ETO. The following discussion is provided to clarify the implications of the ACGIH position as it relates to the STEL determination by OSHA.

The ACGIH Chemical Substances Threshold Limit Value (TLV) Committee has a long history as a respected group involved in recommending workplace exposure standards for chemicals. This group consists of professional industrial hygienists and toxicologists, in the employ of various governmental bodies (Federal, State, Cities, Military, Universities), who serve voluntarily on the committee.

In addition, a number of industrial hygienists and toxicologists with private industry also serve, again voluntarily, as consultants to the TLV Committee, attending the regular meetings and making contributions to the development of the TLVs and their documentation. [Only the TLV Committee members vote on Documents and TLVs to be submitted to the ACGIH Board].

OSHA adopted the 1998 TLVs as Permissible Exposure Limits (PELs) under section 6(a) of the OSH Act in 1971. These 1968 TLVs are still the major
part of the OSHA PELs, those found in Table Z-1. § 1910.1000.

As toxicology has become a more sophisticated science, the TLVs have shifted from TLVs which were originally based primarily on acute exposures and effects, to a range of TLVs, ceiling limits and short term exposure limits based on available exposure information and toxicology data from human exposure, or animal tests.

Currently, the ACGIH TLV Committee uses three basic categories of TLVs:
(a) TLV-TWA (Time Weighted Average)
(b) TLV-STE (Short-Term Exposure Limit)
(c) TLV-C (Ceiling)

In addition to these, the Committee recommends Excursion Values (to be addressed in greater detail later) for substances absorbed through the skin; establishes special provisions for exposures to mixtures of substances; and provides for special treatment of "nuisance" particulates, simple asphyxiants, and special problems with physical agents which may act to increase the adverse reaction to a substance.

Much emphasis in recent years has been on carcinogenic effects of some chemicals, and the committee has devoted a great deal of effort to addressing this concern. The committee has several general classifications it uses for carcinogenic substances, determined by the level of information available about the substance’s effects in humans and experimental animals, and the mechanism of action of the substance. For some substances, no safe level has been determined from the studies.

With regard to STELs, the committee recommends them for toxic substances when the "toxicological evidence" warrants it (Ex. 184). STELs are defined by ACGIH in the TLV booklet as follows:

(b) Threshold Limit Value-Short Term Exposure Limit (TLV-STE)—the concentration to which workers can be exposed continuously for a short period of time without suffering from: (1) irritation, (2) chronic or irreversible tissue damage, or (3) narcosis of sufficient degree to increase the time-weighted average exposure which should not be exceeded at any time during a work day even if the eight-hour time-weighted average is within the TLV. Exposures at the STEL should not be longer than 15 minutes and should not be repeated more than four times per day. There should be at least 60 minutes between successive exposures at the STEL. An averaging period other than 15 minutes may be recommended when this is warranted by observed biological effects.

ACGIH also recommends the use of "Excursion limits" in those situations where there is not enough toxicological evidence to support a STEL. Excursion Limits have their basis in long experience in industrial hygiene practice and the observation that processes with workplace exposure with high variability are not "under good control" and that efforts must be made to bring these exposures under control. These high degrees of variability may be discovered by monitoring peak exposure levels to determine exposure patterns which may be caused by various aspects of the operation in question, often point source leaks, and work practices.

ACGIH addresses these situations as follows (Ex. 184):

Excursion Limits. For the vast majority of substances with a TLV, there is not enough toxicological data available to warrant a STEL. Nevertheless, excursions above the TWA-TLV should be controlled even where the eight-hour TWA is within recommended limits. Earlier editions of the TLV list included such limits whose values depend on the TLV-TLWs of the substance in question. While no rigorous rationale was provided for these particular values, the basic concept was intuitive: In a well controlled process exposure, excursions should be held within some reasonable limits. Unfortunately, neither toxicology nor collective industrial hygiene experience provide a solid basis for qualifying what those limits should be. The approach here is that the maximum recommended excursion should be related to the variability generally observed in actual industrial processes.

The ACGIH’s recommendation where "Excursion Limits" are applied is that: Short-term exposures should exceed three times the TLV-TWA for no more than a total of 30 minutes during a work day and under no circumstances should they exceed five times the TLV, provided that the TLV-TWA is not exceeded.

With regard to this recommendation, ACGIH states that:

The approach is a considerable simplification of the idea of the log normal concentration distribution but is considered more convenient to use by the practicing industrial hygienist. If exposure excursions are maintained within the recommended limits, the geometric standard deviation of the concentration measurements will be near two and the goal of the recommendation will be accomplished.

When the toxicologic data for a specific substance are available to establish a STEL, this value takes precedence over the excursion limit regardless of whether it is more or less stringent.

In comments submitted to OSHA by ACGIH (Ex. 189-19) ACGIH stated its position with regard to EtO exposure as follows:

The use of specific Short Term Exposure Limit (STEL) by the committee is generally limited to situations where the committee is advising more restrictive control on short-term exposure than that afforded by the excursion limit for the TWA-TLV. The committee has specifically addressed this issue for ethylene oxide. ACGIH policy would require a specific statement on the value of the excursion limit in the documentation for each substance for which a specific Short Term Exposure Limit (STEL) is not recommended. In its meeting on March 26-27, 1984 it specifically directed that just that type of statement be added to the documentation for ethylene oxide (1984 Supplemental Documentation package is enclosed. See page 162-2 (64) second last paragraph, "Because some studies have pointed out the importance of short-term high exposures, the ACGIH considers that control by the excursion limits given in the preface of the TLV booklet will suffice to protect from the adverse effects of ethylene oxide." (Ex. 192)

In its earlier submission (Ex 184), ACGIH had suggested this view:

Traditional industrial hygiene approaches have evaluated either short and/or long term exposure as appropriate. To intimate that short-term measurement is not a traditional industrial hygiene approach shows only a lack of familiarity with the field. I would also suggest that compliance strategy and toxicological justification are not necessarily causally linked. If a short-term limit is needed for ease of compliance monitoring, it can be justified on its own merits.

The TLV committee, however, did not have the toxicological evidence to recommend a specific STEL more restrictive than the excursion limit on the time-weighted average (TWA-TLV) recommendation. The use of the excursion limit of ACGIH is more restrictive and more protective of worker’s health than the short term limit proposed by OSHA.

Comments, both in opposition to adoption of the STEL (EIOC, Ex. 180-16; OMB, Ex. 182) and in favor of the STEL: (APSCME, Ex. 189-14; NIEHS, Ex. 171; NIOSH, Ex. 181; AAOHN, Ex. 180) who discuss the ACGIH TLV appear to recognize either the explicit or implicit need to monitor peak exposures in order to gauge the degree to which an operation is good control or poor control, and what the variation of exposure is around the actual TWA, in the process of controlling exposures to
the prescribed TWA. (The ACGIH concept of "excursion limits" and its relevance to OSHA's STEL determinations are discussed further in section V.)

In summary, the ACGIH has not recommended a STEL for ETO because the TLV Committee has determined that there are insufficient toxicological data to warrant such an action. Specifically, the committee concluded that a STEL for ETO would be recommended "only where toxic effects have been reported from higher short-term exposures in either humans or animals.

V. OSHA's Conclusions

After a thorough review of the entire rulemaking record, including the peer review and public comments received since June 22, OSHA had determined that the available health data on ETO do not necessitate establishment of a STEL to supplement the 8-hour TWA of 1 ppm. This determination is based on several factors whose significance has been highlighted by many of the comments received by the Agency in response to its Federal Register notices of June 22 and September 19. Although no new studies on the health effects of ETO have been submitted to the record during this extended comment period, there has been considerable new documentation of reasons why the existing health data do not necessitate that a STEL be established. OSHA's rationale for not promulgating a STEL is based largely upon this new information, which has provided the agency with clearer and more definitive findings than were available at the time of promulgation of the June 22 final rule.

In brief, OSHA's decision not to issue a STEL for ETO centers on three basic findings: First, the available health data do not demonstrate the risks from ETO exposure to be dose rate-dependent. In other words, the studies do not indicate that the risk from exposure to a given dose of ETO are greater when that dose is distributed at high concentrations over a short period of exposure during a workday than at a lower concentration during a longer period of time. Second, the effects of ETO are assumed to be dose dependent rather than dose-rate dependent. Reduction of the total dose is the critical factor in dealing with the significant risks of ETO exposure. Therefore, the 1 ppm TWA is sufficient to minimize significant risk, within the bounds of feasibility. Third, in terms of industrial hygiene and methods of controlling ETO, compliance with the TWA will necessitate the control of short-term exposures, particularly for employees whose exposure consists primarily of short-term bursts. Therefore, to the extent that good industrial hygiene practice calls for the reduction of short-term peak exposures, the low TWA of 1 ppm will work in the minimization of short term exposures within the workday. Further, where burst-type exposures occur more than once per day, and where there are background levels of ETO between bursts, the TWA will place internal limitations on the levels and durations of such bursts during the workday to assure compliance with the TWA. The following section discusses each of the above findings in detail, together with supporting references to the rulemaking record. In addition to these primary findings, this section will discuss other related reasons which provide further support for the Agency's determination.

1. Dose-Rate Relationship. In making its final determination on the STEL issues, OSHA has reevaluated the available health evidence in light of the peer review and public comments received since the June 22 notice was published. Although these submissions to the record included little additional health data, they did provide wide-ranging and expansive discussions of the relevance of the various studies to the setting of a limit on short-term exposures to ETO. In particular, they concentrated on the issue of whether a "dose-rate" relationship had been established between ETO exposures and the various health effects attributed to those exposures. The Agency had not previously addressed this issue in depth, and has since determined that it is particularly important in the ETO context. In brief, if the health effects of ETO are related to the total dose alone, without regard to the temporal distribution of that dose, an 8-hour TWA limit on exposures will reduce the risk of those health effects by limiting the total dose received. However, if the effects from exposure can be shown to be greater when the total dose is received in a short period of time than when it is spread over a longer period, an 8-hour TWA limit alone might not be adequate to reduce the risks. In the event of such a "dose-rate" relationship being established, a STEL might be warranted as a supplement to the TWA in order to provide protection against the additional risk attributable to concentration of the dose over short periods. After a careful evaluation of the peer review and public comments on this issue, and based on the Agency's review of the available studies on the effects of ETO exposure, OSHA has determined that none of the studies on the adverse health effects of ETO have established a dose-rate relationship between the pattern of ETO exposure and an increased risk of impairment of employee health.

Accordingly, the Agency has determined that a STEL is not warranted in the final ETO standard.

As discussed above, a finding that is critical in order for OSHA to justify the adoption of an ETO STEL is that evidence demonstrates that for some biological end-point of ETO exposure, there is a "greater yield of damage (effect) from an acute treatment as compared to a chronic or fractionated treatment for the same total dose" (Ex. 186). The findings in the record that have been most commonly cited as demonstrating that this dose-rate effect is associated with ETO exposure include those by Yager et al. (Exs. 4-10, 6-15, 22), Johnson and Johnson (Exs. 4-17-137), Garry et al. (Exs. 189-141, Hennemini et al. (Ex. 6-7); and Hogstedt et al. (Exs. 2-8, 2-22). The biological end-points observed in these studies include increased frequency of SCE and chromosome aberration in exposed workers (Yager, Johnson, and Johnson) and in vitro (Garry), increased frequency of spontaneous abortion among ETO sterilizer workers (Hennemini), and increased incidence of leukemia among ETO workers (Hogstedt); OSHA reaffirms its conclusions with respect to these studies that were reached in its final standard for ETO published June 22, 1984 (49 FR 25734). In particular, OSHA determined at that time that "... findings in humans and experimental animals exposed to ETO are indicative of damage to genetic material [DNA]. These include hemoglobin alkylation, unscheduled DNA synthesis, sister chromatid exchange and chromosomal abnormalities". OSHA further concluded that the available data demonstrate that "... ETO exposure may cause an increase in spontaneous abortions" and that "ETO is a potential occupational carcinogen." However, based upon its evaluation of the available health data and in light of the peer review analyses in the record, OSHA is unable at this time to determine that these outcomes are dose-rate effects, in addition to dose-effects.

Before a STEL can be justified based on health effects from short-term exposures "there would have to be an observe dose-rate effect over a certain dose range, and at the dose limitation imposed there would be an influence of [Cellular] dose rate" (Ex. 186). No such evidence has been presented in the rulemaking record. OSHA concurs in the conclusion by the AAHH (Ex. 175) that...
none of the pertinent "studies demonstrate that the amount of DNA damage received as a result of short-term exposures to EtO is greater than that received... by the same cumulative dose of EtO during constant exposure conditions" and that "...none of them was designed to test whether the fractionation of the EtO dose is more important to the likelihood of a clinical outcome" (AAIH emphasis).

In order to examine the potential for a dose-rate effect for EtO, it must be demonstrated that the effect accrues to a greater degree for a dose over a high dose period than for the same dose being received over longer low dose periods.

Thus, data are needed that compare the biological outcomes that result from two exposure scenarios. That is, health effects observed in a test group receiving a given total dose over a continuous period of time must be compared with the health effects observed in a separate test group receiving the same total dose over a shorter period. In order to examine whether a dose-rate relationship exists, the available data must allow for a comparison between the health effects of short-term exposures and the health effects of continuous exposures, involving the same total dose for the two patterns of exposure. Studies in which the exposed groups have each received mixed exposures, or in which all exposed groups were exposed to the same type of exposure pattern (either short-term or continuous), do not provide the kind of data to allow for that comparison. In the case of EtO, none of the studies which have been cited in support of the STEL are sufficient to enable the Agency to determine the existence of a dose-rate relationship. Accordingly, OSHA has determined that currently available studies do not justify the imposition of a STEL. The following section discusses each of these studies and its limitations in the context of OSHA's determination not to issue a STEL.

With respect to the Yager study, exposures occurred once per day with a mean concentration of 82 ppm over 3.5 minutes. EtO exposure for each worker was expressed as an estimated cumulative dose for the 6-month study period. The study results indicated that workers with cumulative doses of greater than 100 mg of EtO had significantly higher levels of SCE than workers with cumulative doses of less than 100 mg. Though this study does indicate that short-term EtO exposures can result in SCE in workers, the study does not demonstrate, and was not designated to demonstrate, that the amount of SCE observed is greater than that that would be seen in workers receiving the same cumulative dose from continuous exposure.

Dr. Yager has speculated, however, that this study may suggest the existence of a dose-rate effect for EtO. She observed that:

With the breathing zone data gathered in this study, it may be possible to determine whether the observed increase in SCE's arises exclusively from the cumulative effect of daily exposure or whether some component of the increase results from the rate at which that exposure occurs. Comparisons of day-by-day numbers of SCE's induced per cell per unit of cumulative exposure with those reported in a recent animal study (6) indicates that humans may be considerably more sensitive to SCE induction than animals.

This difference would be much less, however, if SCE induction were also a function of dose rate, since the workers were exposed to ETO for short periods at five times the mean concentration of the animals were exposed. (Ex. 6-15)

Dr. Yager concludes that:

If a dose rate effect is found for humans... then the evidence of ETO-induced SCE's may suggest that occupational exposure to ETO and other alkylating agents be controlled in terms of both cumulative dose and dose rate, (Ex. 6-15)

The animal study cited by Yager involved exposure of groups of rabbits to 0, 10, 50 or 250 ppm EtO by inhalation for 6 hours per day, 5 days per week for 12 weeks. A statistically significant increase in mean SCE was seen in the rabbits exposed to 50 and 250 ppm of EtO, but not at 10 ppm.

With respect to the interpretation suggested by Yager from comparative analysis of these studies, the Environmental Mutagen Society argued that:

The other points alluded to in this paper... are that there are dose-rate effects for SCE induction by EtO and that humans are more sensitive than rabbits with regard to elevated SCE levels following EtO exposure. Both of these contentions are unquestionably supported by hard experimental data. First, the species difference. Her protocols for blood lymphocyte culture and BrdUrd levels were different for the two species as were the exposure conditions, and thus, comparisons cannot be made only on the basis of exposure conditions to conclude either a species sensitivity difference or a dose-rate effect. The comparison of short duration exposures in humans (species with long-lived lymphocytes) with continuous exposure in rabbits (species with short-lived lymphocytes) Huff et al., Mutation Research 94:349, 1982) is not appropriate without at least the mentionation of either lung physiology or DNA repair differences or some other confounding factors as possibilities. (Ex. 186)

OSHA notes with interest that Dr. Yager has submitted a proposal to NIOSH that would evaluate a dose-rate effect of exposure to EtO on SCE. OSHA supports this further research and has submitted a letter to NIOSH urging funding of this research.

OSHA believes that these studies do raise important questions regarding existence of an EtO dose-rate effect in humans. However, neither OSHA nor Dr. Yager are able to conclude from the data that such an effect exists. (As noted above, Dr. Yager has proposed to conduct further research on dose-rate effects).

The Johnson and Johnson studies (Ex. 4-17, 137 A, B, C, D) were initiated to determine whether employees exposed to EtO showed more chromosome changes than employees thought to be unexposed. OSHA finds no indication in the record that either of the Johnson and Johnson studies were designed to test for dose-rate relationships. The observations of SCE in the first study (Ex. 4-17, 137 A, B, C) were based on exposures in three study plants that were expressed only as 8-hour TWA's. The conclusions reached in the second study (Ex. 137D) were based on historical exposure information which included data from 8-hour TWA samples and short-term exposure samples. As with the Yager data, the Johnson and Johnson data do not include comparative effect analyses from the two exposure scenarios. Thus, OSHA cannot point to either of the Johnson and Johnson studies demonstrating dose-rate effect. OSHA concurs with the conclusion expressed by the Environmental Mutagen Society that these studies only "demonstrate[s] that occupational EtO exposure causes chromosome aberrations and elevates the SCE frequency" (Ex. 186).

As noted in the June 22 FR notice, OSHA believes that the Hemminki et al. study demonstrates that EtO exposure may also result in spontaneous abortion. However, the study does not show, nor was it designed to show, that brief transient episodes of high exposure to EtO are of greater importance than the total EtO dose in leading to abortion. The results reported by Hemminki were based on estimated TWA exposures and recorded peak exposures. A dose-rate effect cannot be inferred from this report because the study group was subject to both transient and continuous EtO exposures, and a comparison of abortion rates from each exposure scenario was not made. As the committee for the Environmental Mutagen Society concluded, the Hemminki study "has no bearing whatsoever on the question of dose-rate effect" (Ex. 166).
The problem inherent with the use of any of the studies discussed above as demonstrating a dose-rate effect is that the results were seen from exposures to EtO as they actually occur in the workplace. That is, the total dose received by the workers in these studies was from either a combination of short-term and continuous EtO exposures (Hemminksi, Johnson, Hemminksi) or short-term exposure only (Yager). As such, they do not provide sufficient data to allow a meaningful comparison of the health effects of short-term excursions of EtO as opposed to the same total dose distributed over longer periods. OSHA believes that it is necessary to have data that compare the biological outcomes that result from the two exposure scenarios before a conclusion can be reached that a dose-rate effect exists. OSHA determined that such data are not presently available with respect to EtO. Assuming NIOSH funds Dr. Yager's further work and possibly other studies in this area, more definitive data may become available in the near year or two. If the data so indicate, OSHA will consider reevaluating the decision it announces today.

Finally, a dose-rate effect is not indicated with respect to the available studies demonstrating the potential carcinogenicity of EtO (Hogstedt et al., Exs. 2-8, 2-22, and Bushy Run, Ex. 2-9). The Hogstedt studies suffer the same lack of study design to test for dose-rate effect; that is, results of the study were from study populations that were exposed to both continuous and peak EtO exposures over the study period. The Bushy Run study, used by OSHA is quantifying the excess risk of leukemia from exposure to EtO, exposed groups of rats at various EtO concentrations for 6 hours per day, 5 days per week. No comparative short-term exposure study on rats was performed. In addition, OSHA has quantified the relationship between dose and carcinogenic response to EtO in terms of a cumulative dose mathematical model, based upon available data and on assumptions set forth in the risk assessment itself and in the June 22 final rule. Data do not presently exist for OSHA to explore this relationship based on EtO dose pattern. Thus, OSHA has concluded that presently available data do not demonstrate an association of EtO exposure with a dose-rate effect. Accordingly, OSHA has determined that adoption of a STEL for EtO is inappropriate.

It should be noted that an in vitro study by Garry et al. (Ex. 180-14) did reveal a dose-rate effect of EtO-induced SCE frequencies in EtO-treated human lymphocyte cultures. The ambient exposure doses were 100 ppm, 131 ppm, 218 ppm and 306 ppm for 20 minutes each. The authors conclude that the "data show an incremental change in SCE frequency with applied ambient EtO..." The authors further state, however, that "Although we indicated that in vitro sensitivity of the SCE technique in human lymphocytes, the data cannot be directly linked to the vivo response" due to factors such as respiratory rate, and EtO protein binding and inactivation.

Both of the Mutagen Society's peer reviewers, Generoso and Dufrain, suggest that further research be performed in order to resolve this issue. Similarly, the 3M Company (Ex. 169-32) states that it "recognizes that the Hemminksi, Johnson and Johnson... Yager... research raise important questions about the impact of peak exposures" but that the "significance of short-term peak concentrations is, at best, unclear at this time."

In addressing the possible reason why a dose-rate effect has not been observed for EtO, the Environmental Mutagen Society (Ex. 166) offered the following:... for high energy radiation (X or gamma rays) one is unable to determine a difference in biological damage when 1000 millirem is received in one minute or 1 millirem is received per minute over 1000 minutes or longer, because the total dose is so low, there is no dose rate effect. This may well be a possible outcome resulting from the introduction of a 1 ppm 8-hour limit exposure (for EtO).

OSHA agrees that further research may be warranted on the implications of the EtO data dealing with dose-rate effects. Therefore, OSHA has specifically requested that NIOSH fund research proposals to evaluate endpoints such as SCE or alkylation in sperm DNA in relation to the existence of a dose-rate effect from exposure to EtO. OSHA will review these studies when the results become available, and will evaluate whether the question of a short-term limit for EtO should be reexamined.

2. Dose Effects. OSHA believes that the dose effects that result from exposure to EtO will be significantly reduced by controlling exposures to the 1 ppm TWA and that available data do not demonstrate that this reduction will be jeopardized by the decision to not include a STEL. OSHA continues to believe, as concluded in the final EtO standard, that the risk of damage to genetic material, incidence of cancer, reproductive effects, neurotoxicity and sensitization "will be substantially reduced by promulgation of the 1 ppm TWA." The control of chronic exposures to EtO is felt to be of primary importance in reducing the risk from the potential effects cited above. As the Agency noted in its June 22 final rule, the Yager and Johnson studies indicated that chromosomal aberrations and SCE are induced in workers exposed to EtO levels between 1 and 10 ppm as an 8-hour TWA. Therefore, reduction of the TWA is expected to reduce that total dose and, therefore, should also reduce the incidence of cytogenic effects.

With respect to cancer induction, OSHA has demonstrated a significant reduction in risk from that under the previous TWA of 50 ppm by adoption of the 1 ppm TWA alone. For the cancer causing effects of EtO exposure, there is no indication that short-term high exposures to EtO are more hazardous than an equivalent dose spread over 8 hours.

The fetotoxic and spermatogenic effects which result from EtO exposure were described in the final standard as perhaps being "induced by changes in the DNA and which are known to be produced by many alkylating agents as EtO." There is no scientific consensus that either mutagenesis or other effects on DNA are dose-rate effects. With respect to neurotoxicity and sensitization, OSHA also concluded that the record as a whole clearly suggests that lowering the TWA [from 50 ppm to 1 ppm] will significantly reduce the risk that employees exposed to EtO will experience from these effects."

Thus, OSHA believes that the 1 ppm TWA, by itself, will provide significant worker protection from the dose-effects associated with exposure to EtO.

This view is supported by a number of commenters (Exs. 169-24, 169-32, 169-33). For example, the R.T. French Company stated that "the 1 ppm permissible exposure limit as an eight hour TWA is... sufficient to protect workers' environment given today's knowledge" (Ex. 189-24). 3M Company (Ex. 189-32) commented that they "agreed with the need for a 1 ppm PEL"... and that..." 29 CFR 1910.147 as it stands is a prudent attempt to reduce exposures to extremely low levels, on the basis of chronic animal and epidemiological information gathered to date."

Finally, the American Hospital Association characterized the adequacy of OSHA's present EtO standard as follows:... OSHA published a new standard that reduces permissible exposure to EtO by a factor of 50. Standard requirements cover methods of exposure control, personal protective equipment, measurement of...
employee exposures, training, medical surveillance, signs and labels, regulated areas, emergency procedures, and recordkeeping. When fully implemented, this standard should prove highly protective of employee safety and health. Several years in development, this standard calls for most, if not all, of the engineering and work practice controls necessary for reducing exposures to an acceptable level. (Ex. 189–35).

3. Compliance With the TWA Will Reduce the Magnitude of Short-Term Exposures. OSHA believes that the compliance program designed to maintain exposure to or below the 1 ppm TWA limit (required by paragraph (f)(1) of the standard) will also substantially reduce the magnitude of the short-term exposures. Although the 8-hour TWA limit allows excursions above the limit (provided that they are compensated by excursions below the limit during the workday), in practice, the workplace controls to reduce TWA exposure will be designed to capture ET emissions at their source, which is directly related to the magnitude of the short-term exposures. As stated by Ernest M. Dunn, M.D., in a submission by the American Occupational Medical Association: “In meeting the 1 ppm TWA standard, employers will readily deal with the short term exposures; the steps necessary to assure compliance with the 1 ppm TWA will make significant excursions very unlikely—except in accidental or special circumstances, such as where use of respirator protection must be permitted. (Ex. 187)”. This position is supported by a number of commenters (Exs. 189–16, 189–32, 189–29, 189–24, 189–34, 189–40, 165).

Paragraph (f)(1)(i) of the final standard requires that “the employer shall institute engineering controls and work practices to reduce and maintain employee exposure to or below the TWA, except to the extent that such controls are not feasible.” OSHA described the types of controls that would have to be implemented as a result of this requirement in the “Feasibility of the 1 ppm TWA” section of the preamble to the standard, at 49 FR 25768. OSHA concluded that the ET producer and ethoxylation industry sectors would use conventional technology to meet the 1 ppm TWA. Controls include use of rupture disks for minimizing low-level leakage from pressure relief devices; closed sampling devices at process sampling locations, and vapor-tight unloading connections. Magnetic level gauges, and nitrogen purge systems on tank car loading facilities. These controls reduce short-term exposure as well as the TWA exposure. For operators of large industrial sterilizers, engineering and work practices include changed evacuation systems, liquid/gas separation units to prevent excessive ET emissions during chamber evacuation, local exhaust hoods, installed over the sterilizer door, local ventilation of aeration chambers, and allowing the sterilizer contents to aerate for a short period of time after opening the sterilizer door. Hospital sterilizers are smaller than sterilizers used by medical product manufacturers, but the control of ET involves the same principles and types of control equipment and methodology used for industrial sterilizers.

OSHA found that the smaller size of hospital sterilizers makes controlling ET emissions in hospitals generally easier than in industries using large sterilizers. As in the chemical industry sectors, these controls will reduce short-term exposure along with the TWA exposure. For example, opening the sterilizer door by an employee can cause a high short-term exposure that contributes to the TWA exposure; both exposures are reduced if the sterilization chamber is evacuated before the door is opened.

Several commentors expressed concern that ET exposure could be very high for short periods of time (such as 500 ppm for 1 minute) if a STEL were not adopted (Exs. 171, 180, 181, 189–19, 189–22). Even though a 1 ppm TWA theoretically and mathematically allows a 15 minute STEL of 32 ppm (if the background concentration is zero for the remaining portion of the day), an actual high exposure duration of 3 to 5 minutes is the norm for sterilizer operations. This would permit exposure up to 160 ppm and would still meet the TWA of 1 ppm assuming no further ET exposure for the remainder of the 8-hour shift. OSHA believes, however, that in actuality, compliance with the 8-hour TWA will not allow high excursions of this degree. The reason is that there are low level ET background concentrations in the workplaces where ET is being used, and these background concentrations must be taken into account in calculating an employee’s daily dose of ET. Such background levels can often result from offgassing of sterilized products, for example. The existence of such background ET levels, together with the need to control the daily dose to a TWA of 1 ppm, makes it unlikely for an individual excursion to reach the mathematical possibility of 32 ppm for 15 minutes without resulting in an 8-hour TWA above 1 ppm. Further, the closer the background concentration gets to 1 ppm, the lower the permissible excursions will be in order for total exposure to be within the TWA. Several parties (Exs. 189–16, 189–34, 189–22) noted that an assumption of no background exposure from ET for the remainder of the shift is "an impractical assumption given the reality of...environmental exposures" (Ex. 189–34) and that these additional exposures will necessarily require the employer to further limit short-term exposures.

In addition, where more than one short-term exposure contributes to the 8 hour TWA exposure, an increase in the number of short-term exposures decreases the allowable magnitude of each excursion. Further, even the theoretical 32 ppm 15 minute limit that is "built into" a 1 ppm TWA is only possible under a unique set of circumstances, where that 15 minutes period represents an employee’s only source of ET exposure in an entire 8-hour workday. For example, for an employee who is exposed to three 15 minute sterilizer openings per day the magnitude of these exposures must be limited far below the 32 ppm figure (closer to 10 ppm) to keep the TWA below 1 ppm. When background ET levels are considered, these excursions must be limited even more. In this way, the TWA itself does act as a check on the number and extent of short-term exposures during the day. It should also be pointed out that to achieve the TWA, the reduction of short-term exposures represents the most effective method of reducing the total dose of ET for most employees, particularly those exposed to ET releases from sterilizers. This reflects the technical and practical realities of controlling exposures at their source to minimize the total dose during the workday.

OSHA has determined that short-term exposures to ET have not been demonstrated to be more harmful than the same total dose of ET received over a longer period of time during the workday. Therefore, the need to control short-term exposures is only important to the extent that it relates to the resultant reduction of total dose. Further, the exposure of short-term excursions are a necessary part of the overall compliance program for the 1 ppm TWA.

Therefore, OSHA believes that employers attempting to reduce overall exposures to the 1 ppm TWA will by necessity have to apply good industrial hygiene practice of controlling short-term levels, and that background levels and the number of short-term excursions will be factors to be considered in achieving compliance with the TWA.

OSHA also notes that the concept of "excursion limits" developed by ACGIH...
This action is taken pursuant to sections 4(b), 6(b), and 8(c) of the Occupational Safety and Health Act of 1970 (84 Stat. 1592, 1593, 1599, 29 U.S.C. 653, 655, 657). Secretary of Labor's Order No. 9–83 (48 FR 35736) and 20 CFR Part 1911.

List of Subjects in 29 CFR Part 1910

Ethylene Oxide, Occupational safety and health, Chemicals, Cancer, Health, Risk assessment.

Robert A. Rowland,
Assistant Secretary of Labor.
[FR Doc. 84–33949 Filed 12–31–84; 8:45 am]

DEPARTMENT OF DEFENSE
Office of the Secretary
32 CFR Part 1916

Defense Contracting; Reporting Procedures on Defense Related Employment

AGENCY: Office of the Secretary, DoD.

ACTION: Amendment of final rule.

SUMMARY: This rule is the fiscal year 1984 update of the section listing DoD contractors receiving negotiated contract awards of $10 million or more. The regulation is published to comply with the provisions of Section 1, Pub. L. 97–295, October 12, 1982; 10 U.S.C. 2397.


FOR FURTHER INFORMATION CONTACT: Mr. J.R. Sungenis, telephone (202) 746–0334.

SUPPLEMENTARY INFORMATION: In FR Doc. 70–15846 appearing in the Federal Register on November 25, 1970 (35 FR 10040), the Office of the Secretary of Defense published a final rule establishing criteria, prescribing procedures, and assigning responsibilities for monitoring contracting within the Department of Defense. Subsequently, paragraphs (a) and (d) of § 166.11, which constitute the list of DoD contractors receiving negotiated contract awards for $10 million or more, were updated for fiscal years 1971 (36 FR 19464); 1972 (37 FR 18727); 1973 (38 FR 25990); 1974 (39 FR 32885); 1975 (40 FR 44135); 1976 (41 FR 20466); 1977 (43 FR 1617); 1978 (44 FR 3049); 1979 (44 FR 75631); 1980 (45 FR 83486); 1981 (46 FR 60821); 1982 (47 FR 56847); and 1983 (48 FR 55729).

List of Subjects in 32 CFR Part 166

Armed forces, Government employees, Government procurement, Information requirements.

PART 166—[AMENDED]

Accordingly, for FY 1984, §166.11 of this part is revised to read as follows:

§166.11 Department of Defense contractors receiving negotiated contract awards of $10 million or more.

Fiscal Year 1984:
A & S Tribal Industries
A 1 Corp.
A A I Corp.
A A R Corp.
A B A Industries, Inc.
A L M, Inc.
A L S Electronics
A M General Corp.
A T O, Inc.
A B Corp.
Abercrombie, R.C.
Action Fmg. Co.
Actus Corp.
Advanced Technology, Inc.
Aero Corp.
Aerojet General Corp.
Aerotech Strategic Propulsion Co.
Aerotech Tech Systems Co.
Aeronca, Inc.
Aeroquip Corp.
Aerospace Corp.
Aerospace Technology Corp.
Alfab, Inc.
All Bann Enterprises, Inc.
Alliance Properties, Inc.
Allied Corp.
Alpha Industries, Inc.
Altama Delta Corp.
American Airlines, Inc.
American Cyanimid Co., Inc.
American Development Corp.
American Electronic Laboratories, Inc.
American Express Co.
American Management Systems, Inc.
American Petrofina Co. of Texas
American President Lines, Ltd.
American Systems Corp.
American Telephone & Telegraph Co.
American Telephoneservices
Ametex Enterprises, Inc.
Ametek, Inc.
Amex Systems, Inc.
Amoco Production Co., Inc. (Del.)
Anpec Corp.
Amron Corp.
Analysis & Technology, Inc.
Analytic Sciences Corp.
Analytic Services, Inc.
Analytical Services Engnr. Corp.
Analytics, Inc.
Anderson, M.C.
Andrews & Parrish Co.
Arcwell Corp.
Arete Associates
Argo Systems, Inc.