ever, were subjected to methodological criticisms because it was not always clear, for example, that the diagnoses of Reye's syndrome were firmly established nor that there were no biases in the recollection of what medications were used.

Based on these admittedly limited studies, the CDC recommended in November of 1980 that parents exercise caution in administering aspirin to children with influenza or chicken pox. Four months later, a consensus development conference at the National Institutes of Health issued the same advice. Shortly afterward, a fourth study, this time from the state of Michigan, also found an association between aspirin use and Reye's syndrome risk. But none of these studies was convincing enough to stem the debate.

The Food and Drug Administration, under conflicting pressure from aspirin manufacturers and the Committee on the Care of Children and from the Health Research Group at first proposed warning labels for aspirin and then called for more data before reaching a decision.

In the meantime, by all accounts, sales of children's aspirin fell and, coincidentally, the incidence of Reye's syndrome dropped in children aged 10 and younger "rather dramatically, by about 50 percent" according to Walter Dowdle of the CDC. The proportion of older children and teenagers with Reye's syndrome increased. Teenagers presumably choose their own medication and do not see pediatricians when they get influenza and so, says Dowdle, they are less likely to cease using aspirin because of a Reye's syndrome warning.

This was the background for the CDC study, which was undertaken at the request of the Public Health Service. "There was no question that we needed a more definitive study," Denny says. But it was not expected to be easy. Like the state studies, the CDC's was to be a case-control one, but it was to have a larger number of cases and to have a more stringent experimental design. "This is one of the most complicated epidemiological studies," Denny remarks. "There are so many variables and the disease is so fantastically rare. And the study is done in a milieu where most pediatricians are telling parents not to use aspirin. It becomes very touchy."

The CDC wanted to go right ahead and do a full-scale study, but the Institute of Medicine committee requested that it begin with a pilot study to see if its methodology was even feasible. "We anticipated that that's precisely what it would do," says Denny. "We would see the results, adjust the protocol, and get on with the larger study. We certainly didn't expect to see what we saw."

So why do the larger study? The Institute of Medicine committee notes that a full-scale study would not expose anyone to excess risk of Reye's syndrome because it is to be a case-control study. Therefore, no ethical dilemmas arise. And there still is much to be learned about Reye's syndrome. A larger study may point to additional risk factors for the disease and may help determine whether there are particular doses of aspirin that are safe and others that are high enough to cause excess risk. In addition, everyone would feel a bit more comfortable if the pilot study's results were confirmed.

But, says Dowdle, none of this is meant to detract from the merits of the pilot. The results are sufficiently strong that they cannot be ignored and the study was done rigorously and carefully. "We stand behind the pilot study," Dowdle says. "We think it is a superb study and we think its results are better than those of any other study of Reye's syndrome that went before it."

—GINA KOLATA

Agency Scraps Plan to Limit Ethylene Oxide

A new scientific argument prompts OSHA to reverse itself and drop a controversial proposal

In a major policy reversal, the federal agency in charge of establishing regulations governing hazards in the workplace has decided not to limit short-term exposure to ethylene oxide, a colorless gas widely used to sterilize medical supplies and equipment. Although such a restriction had been supported by the agency's own staff, two other federal health agencies and labor groups, it had been opposed by manufacturers and others and attacked by the Office of Management and Budget. The decision, announced on 2 January by the Occupational Safety and Health Administration (OSHA), illustrates the difficulties faced by regulators when confronted by an obvious and acknowledged health problem but have somewhat incomplete research data.

OSHA's decision not to limit short-term exposure to ethylene oxide left intact a standard issued in June that restricts long-term exposure to the chemical. The long-term limit was supported by industry, which had already instituted controls in anticipation of the regulation. Data collected during the past several years have shown that ethylene oxide is a mutagen and a carcinogen in animals. As for humans, there is evidence, although limited, that at low levels of exposure, it is associated with leukemia, spontaneous abortions, and chromosomal changes. About 75,000 persons are potentially exposed to the gas in bursts of high concentration. Ethylene oxide frequently is released when the chamber door of a sterilizing machine is opened and from the protective wrappings of freshly sterilized material.

OSHA has asserted in the past that a long-term standard should be supplemented by a short-term limit to keep exposure to a minimum. The long-term standard restricts exposure to 1 part per million (ppm) averaged over 8 hours. That means a worker could be exposed to brief, but high, concentrations of ethylene oxide during the day without exceeding the long-term limit. For instance, a person could be exposed to 480 ppm for 1 minute but not exceed the long-term limit if no additional exposure occurred. According to information gathered by OSHA staff, two or more peak exposures per day "are common" and employees could be exposed "to several hundred ppm over very short periods of time." With this in mind, OSHA reasoned that a short-term standard was prudent to further reduce the cancer risk.

Industry, however, resisted the idea, and on 14 June, the day before the agency was to announce the final rule on the short-term limit, the Office of Manage-

ment and Budget picked up industry's criticisms and repeated them in a letter to the agency. As a result, OSHA reconsidered the proposal (*Science*, 10 August, p. 603).

The budget office, along with Union Carbide, the main manufacturer of ethylene oxide, the Health Industry Manufacturers Association, and others, argued that the long-term limit automatically sets a 32 ppm restriction for a 15 minute exposure, and that tougher controls were not supported by the agency's risk assessment or current studies. In a letter to OSHA, the budget office argued that the agency's risk assessment was "wholly contrived" and that the principal studies all had "major flaws."

Attention has focused on the findings of three studies of workers, which initially led OSHA to propose a short-term limit:

- In one study, 14 hospital workers were exposed to an average of 19 ppm for 15 minutes from 6 to 120 times during a 6-month period. Results showed that an increased number of genetic aberrations called sister chromatid exchanges were related to exposure. It is not clear if these chromosomal changes lead to adverse health effects, but many scientists agree that they are cause for concern. The investigation was led by Janice Yager of the University of California at Berkeley.
- A much larger study by Johnson & Johnson of its own employees revealed similar data, and as a result, the company set a 10 ppm short-term limit and supported OSHA's efforts to establish the same standard.
- The third study suggested that an increased number of spontaneous abortions occurred when women were exposed to ethylene oxide on the job. The principal investigator, Kari Hemminki of the Finnish government's Institute of Occupational Safety and Health, based the conclusion on interviews with more than 1000 women in a survey of all hospitals in Finland.

After OSHA decided to reconsider its short-term limit proposal, it sent these data out for peer review. The reviewers included the agency's advisory board, three other federal health agencies, and 11 other organizations. Many of the comments rehashed old arguments, but three reviewers, in particular, raised a new criticism and recommended against a short-term limit. Their critique played an important role in the agency's decision to withdraw the proposal.

The three scientists, who examined the data as members of the Environmental Mutagen Society, said that a short-term limit should be established only if the studies had shown that short-term exposure was more harmful than long-term exposure. "No such evidence was presented," stated Seymour Abramson of the University of Wisconsin at Madison, Russell Du Frain of Oak Ridge Associated Universities, and Walderico Generoso of Oak Ridge National Laboratories.

Du Frain noted that the two chromosomal studies were not flawed, as the White House budget office charged, but simply were not designed to generate data needed to support a short-term limit. The studies "used standard . . . methods for cytogenetic evaluations, and what appear to be appropriate, or at least acceptable statistical methodologies."

On the other hand, two other federal agencies contend that the preponderance of data does support a short-term limit.

He and the other reviewers from the mutagen society, who are all specialists in dose-related effects on cells, said it is difficult to predict whether the same dosage causes more harm when delivered in a short burst than over a long period. The two chromosomal studies do not explicitly address this point and, instead, look at the response of workers to a cumulative dose of ethylene oxide. In a letter to OSHA, they pointed out that in high-energy radiation, for example, "one is unable to determine a difference in biological damage when 1000 millirems are 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 ethylene oxide]."

On the other hand, two federal health research agencies contended that the preponderance of data indicates that short-term exposure poses health problems and should be limited. The National Institute of Occupational Safety and Health and the National Institute of Environmental Health Sciences acknowledge that none of the studies reveals unequivocal evidence that there is a dose-rate effect with ethylene oxide. But all three studies, including the Finnish study, provide consistent findings, agency representatives argue. Both agencies say that even though the studies measure cumulative dose, workers are usually exposed to ethylene oxide in short-term bursts when loading and unloading the sterilizers, and changing the tanks of gas. "You have to look at the patterns of exposure," said John Dement, the scientist who reviewed the issue for the environmental health agency. "Without controlling the peaks, you're not controlling the process."

At OSHA, staff members who worked on the issue were unanimous that a limit on short-term exposure be set. They said in a memo to the agency's director of health standards Leonard Vance that the need for dose-rate data was a "very narrow perspective."

Opponents of the agency proposal and OSHA itself have made much of the fact that a national organization of industrial hygienists has not adopted a short-term limit. But the organization does, in fact, suggest that lower exposure is prudent. The American Conference of Governmental Industrial Hygienists requires strong toxicological evidence before it will recommend a short-term limit for a particular chemical. Citing this lack of evidence for ethylene oxide, the group recommends, as a matter of policy, that workers restrict exposure to five times the long-term limit. For ethylene oxide, it says exposure should not exceed 5 ppm for any time period. This rule of thumb, the group says, is to ensure that the long-term limit is not exceeded.

OSHA now is urging the National Institute of Occupational Safety and Health to fund more studies that will specifically examine the effects of short-term exposure. The reviewers from the mutagen society say that the experiments are fairly straightforward and could be done quickly. Generoso of Oak Ridge is currently conducting a dose-rate experiment with mice and testing the mutagenic effects of ethylene oxide on the animals' germ cells. Janice Yager hopes to conduct a rabbit study to examine short-term exposure of ethylene oxide and its effect on sister chromatid exchange, but she has only secured partial funding so far. Once the experiment is begun, she says, it will take a year to collect and analyze the data. OSHA says that once more data are available, it may reexamine its position. In the meantime, the province of Ontario, Canada, has proposed to impose a short- and long-term limit on ethylene oxide identical to the standards OSHA had originally planned.—**MARJORIE SUN**