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June 21, 2006

NIOSH Docket Office
M/S C-34
Robert A. Taft Laboratories
4676 Columbia Parkway
Cincinnati, Ohio 45226

06-05-06A06:42 RCVD

Re: Centers for Disease Control and Prevention Request for Information on Waste Halogenated Anesthetic Agents: Isoflurane, Desflurane, and Sevoflurane, NIOSH Docket - 064
(71 FR 8859, February 21, 2006)

Dear Sir/Madam:

ORC Worldwide welcomes this opportunity to provide comments on the NISOH Request for Information concerning "Waste Halogenated Anesthetic Agents: Isoflurane, Desflurane, and Sevoflurane" published in the *Federal Register* on February 21, 2006.

ORC is an international management and human resources consulting firm whose Washington, D.C. office has for more than 3 years specialized in providing a wide array of occupational safety and health consulting services to American businesses. Currently, more than 150 large (mostly Fortune 500) employers in diverse industries are members of ORC's Occupational Safety and Health Groups. The focus of these groups is to promote effective occupational safety and health programs and practices in business and to facilitate constructive communications between business and government agencies responsible for establishing national occupational safety and health policy. The activities of ORC's Occupational Safety and Health Groups are based on the premise that providing safe and healthful working conditions is the mutual concern of employers, employees and government agencies.

It should be noted that companies that are members of ORC's Occupational Safety and Health Groups have provided information, opinion and advice to ORC in the development of its comments. However, these comments are solely those of ORC and may differ from the views and comments of individual member companies.

**General Comments**

Agents such as isoflurane, desflurane, and sevoflurane are inhalation anesthetics for use in hospitals and veterinary clinics. These "newer" agents have improved safety and typically provide better induction and emergence transitions for patients during anesthesia than older halogenated gases, such as chloroform and trichloroethylene, that are included in the 1977 NIOSH REL.

Regarding occupational exposure guidelines, regulatory and advisory agencies worldwide have recommended exposure limits for each of these materials. While a few jurisdictions have adopted the recommendation contained in the 1977 NIOSH REL (2 ppm) for waste halogenated anesthetic gases, in general, many of the occupational exposure guidelines for these newer anesthetic agents are higher and appear to reflect the recognition of the improved clinical safety profiles. A few of these guidelines are shown below.

| Agency/ Jurisdiction | Enflurane (TWA-ppm) | Sevoflurane (TWA-ppm) | Isoflurane (TWA - ppm) | Desflurane (TWA - ppm) |
|---|---|---|---|---|
| | | | | |
| ACGIH TLV | 75 | | | |
| Alberta – Canada | 75 | | | |
| Quebec - Canada | 75 | | | |
| Belgium | 75 | | | |
| Ireland | 50 | | 50 | |
| Netherlands | 20 | | 20 | |
| Spain | 75 | | 50 | |
| United Kingdom | 50 | | 50 | |
| Sweden | 10 | 10 | 10 | 10 |
| Finland | | 10 | 10 | 10 |
| Norway | | 20 | | 20 |
| U.S. Manufacturer/ Distributor | 75 | 60 | 60 | |

Similarly, pharmaceutical manufacturers typically conduct studies in animals and human volunteers/patients in support of their new products during development; this testing is done in conformance with requirements (e.g. U.S. Food and Drug Administration (FDA) New Drug Application (NDA) process) for new product registration. Subsequently, many pharmaceutical manufacturers use these data to establish occupational exposure guidelines for their products.

For example, based on a review of pre-clinical and clinical data, one manufacturer has established an occupational exposure limit (OEL) of 60 ppm for Sevoflurane as an 8-hour time-weighted average (TWA). This OEL recommendation for Sevoflurane is consistent with occupational exposure limits established for similar inhalation agents such as Enflurane (ACGIH, UK/HSE) and Isoflurane (UK/HSE, Ireland), anesthetic agents that have similar pharmacological and toxicological properties as Sevoflurane. The toxicology information for Sevoflurane is summarized and communicated on the Material Safety Data Sheet. Similarly, this manufacturer has established OELs of 75 ppm for Enflurane and 60 ppm for Isoflurane.

**Short-term Effects**

The clinical safety of the anesthetic agent sevoflurane is well-documented in the scientific literature. Similarly, the safety of low-level inhalation exposures to Sevoflurane is supported by the results of a study in which the effects of sub-anesthetic concentrations of sevoflurane and nitrous oxide were investigated in healthy volunteers. Subjects were exposed to sevoflurane at concentrations of 0, 0.2% and 0.4% (as end-tidal concentrations) using inspired gas concentrations up to 1% (10,000 ppm). The exposure duration was 68 minutes. Analgesia, mood and psychomotor performance were monitored as endpoints of the study. Sevoflurane concentrations up to 0.4% (end-tidal concentration) resulted in an increase in the self-reported rating of "sleepiness" in the healthy subjects, and an increase in the self-reported rating of "lightheaded" on the mood scale. These effects are consistent with the known pharmacology of this anesthetic agent. However, during the exposure period, the subjects were able to complete the mood forms and perform the psychomotor tests. Overall, the observable effects from breathing up to 10,000 ppm sevoflurane for 68 minutes were not very profound. (Janiszewski DJ et al. (1999). Anesth Analg 88:1149-1154.)

**Long-term Effects – Reproduction**

Over the last 25 years or so, several epidemiological studies have reported on the potential adverse effects of occupational exposures to waste anesthetic gases on the incidence of spontaneous abortions and/or congenital abnormalities in women. Most of these early studies were based on self-reported exposures and outcomes, and consequently were subject to recall biases. Often, the response rates to the surveys were low, and the studies were not controlled for other important risk factors. These early studies were also subject to many other methodological flaws. Consequently, many investigators have since concluded that the scientific evidence suggesting the association between occupational exposure to waste anesthetic gases and reproductive toxicity in women is weak or non-existent.

- Burm AGL. Occupational hazards of inhalational anaesthetics. (2003). Best Practice & Res Clin Anaesth 17(1):147-161.

- Shuhaiber S and Koren G. Occupational exposure to inhaled anesthetic. Is it a concern for pregnant women. (2000). Can Fam Physician 46(12):2391-2392.

- Ahlborg G and Hemminki K. Reproductive effects of chemical exposures in health professions. (1995). JOEM 37(8):957-961.

- Eger EI Fetal injury and abortion associated with occupational exposure to inhaled anesthetics. (1991). AANA J 59(4):309-312.

- Schenker MB et al. Adverse reproductive outcomes among female veterinarians. (1990). Am J Epid 132(1):96-106.

- Johnson JA et al. Effect of waste anesthetic gas and vapor exposure on reproductive outcome in veterinary personnel. (1987). Am Ind Hyg Assoc 48(1):62-66.

- Buring JE et al. Health experiences of operating room personnel. (1985). Anesthesiology 62:325-330.

- Hemminki K et al. Spontaneous abortions and malformations in the offspring of nurses exposed to anaesthetic gases, cytostatic drugs, and other potential hazards in hospitals, based on registered information of outcome. (1985). J Epid Commun Health 39:141-147.

- Tannenbaum TN and Goldberg RJ. Exposure to anesthetic gases and reproductive outcome: a review of the epidemiologic literature. (1985). J Occup Med 27(9):659-668.

- Lauwerys R et al. Anaesthetic health hazards among Belgian Nurses and Physicians. (1981). Int Arch Occup Environ Health 48:195-203.

- Rosenberg PH and Vanttinen H. Occupational hazards to reproduction and health in anaesthetists and paediatricians. (1978). Acta anaesth scand 22:202-207.

- Ferstandig LL. Trace concentrations of anesthetic gases: a critical review of their disease potential. (1978). Tox Anaesth Analg 57:328-345.

- Rosenberg P and Kirves A. Miscarriages among operating theatre staff. (1973). Acta anaesth scand 53:37-42.

Similarly, studies in animals that evaluated the adverse effects of sevoflurane on fertility or fetal development also indicated little potential for adverse effects at sub-anesthetic concentrations. For sevoflurane, reproduction studies have been performed in rats and rabbits at doses up to 1 MAC (minimum alveolar concentration) without CO2 absorbent and have revealed no evidence of impaired fertility or harm to the fetus due to sevoflurane at 0.3 MAC (about 6,600 ppm), the highest nontoxic dose.

**Long-term Effects - Other**

For these newer anesthetic agents, no epidemiological studies were found suggesting a tumorigenic/carcinogenic potential from either clinical use, or long-term low-level inhalation exposures of these agents.

Carcinogenesis studies in animals have not been conducted for sevoflurane. However, no mutagenic effects of sevoflurane were noted in the Ames test, a mouse micronucleus test, a mouse lymphoma mutagenicity assay, a human lymphocyte culture assay, a mammalian cell transformation assay, or in a [32P] DNA adduct assay. Also, no chromosomal aberrations were induced in cultured mammalian cells.

**Summary**

Based on a review of the pre-clinical and clinical information for sevoflurane, isoflurane and desflurane, and in consideration of data from studies in the literature, when comparing safety profiles, these newer inhalation anesthetics do not appear to belong in the same "class" as older anesthetic agents such as diethyl ether, trichloroethylene, or even halothane. Thus, the proposed REL recommendation for these materials should reflect this distinction.

In regards to the specific topics for which NIOSH requested information, ORC offers the following comments:

*1. Identification of industries or occupations in which exposures to isoflurane, desflurane, or sevoflurane may occur*

Sevoflurane, Isoflurane and Desflurane are commonly used in veterinary clinics and animal research facilities for the anesthetizing of a variety of animals. Hospitals use the gases during surgeries.

*2. Trends in production and use of isoflurane, desflurane, or sevoflurane over the past 10 years*

One company reports to ORC that they have increased production of these types of gases and expects to continue to increase production and sales in the foreseeable future.

*3. Descriptions of procedures with a potential for exposure to isoflurane, desflurane, or sevoflurane*

Waste Disposal: Gas is vented using a local exhaust ventilation system or directly to the outside atmosphere.

Anesthetizing of animals: Although the majority of animals in veterinary medicine receive IV induction followed by inhalational gas for maintenance, there is a small percentage of cases where the animal is mask induced. In those few cases, a mask is placed over the muzzle of the animal. There is potential for gas to escape the scavenging system. Once the animal is unconscious an endotracheal tube (ETT) is placed and the animal is reconnected to the hose. There is potential for gas to escape when the mask is removed while the ETT is being placed. Off-gassing while the animal is undergoing the procedure could occur but only if the cuff was not fully
inflated or there was a leak in the bag, hose or some other part of the anesthesia machine.

*4. Current occupational exposure concentrations of isoflurane, desflurane, or sevoflurane in various types of occupational scenarios and, if available, data to document these concentrations*

One company reports to ORC that they have performed exposure monitoring during research operations with results of 0.5 – 1 ppm for a 3-4 hours exposure period. Manufacturing exposure monitoring was not available at the time of this letter but the process is entirely contained within a closed system. Exposures would only occur during emergency situations.

*5. Case reports or other health data that demonstrate adverse health effects in workers exposed to isoflurane, desflurane, or sevoflurane, or animal data (published or peer-reviewed data are preferred*

One company reports to ORC that the data that the company has collected is considered proprietary.

*6. Descriptions of work practices and engineering controls used to reduce or prevent workplace exposure*

One company reports that all research operations are conducted within local ventilation systems. In hospital and veterinary operations, scavenger systems are used during anesthetization. There are open and closed scavenger systems. Improper use of the open scavenger systems can lead to employee exposure. User should follow these guidelines to help minimize potential occupational exposure during anesthetizations:

- Ensure good mask fit
- Avoid spilling the liquid gas
- Check machines for leaks frequently
- Ensure that the anesthetic gases are cleared from lines before disassembling the units

*7. Educational materials for worker safety or training on the safe handling of these halogenated agents*

One company reports to ORC that they will submit training materials separately.

*8. Data pertaining to the technical feasibility of establishing a more protective REL for isoflurane, desflurane, and sevoflurane*

One company reports no data for this topic. One company reports that based on information submitted in this response, that they do not feel a more protective REL for isoflurane, desflurane, and sevoflurane is necessary.

ORC appreciates the opportunity to present comments on the request for information and attendant issues and would be happy to discuss any of these comments further with NISOH staff.

Sincerely,

Frank A. White
Senior Vice President