MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Dicumyl Peroxide (CAS No. 80-43-3)

FROM: Michael Depa, Toxics Unit, Air Quality Division

SUBJECT: Update of the Screening Level

DATE: June 9, 2006

Since there was insufficient data with which to develop a new screening level, the initial threshold screening level (ITSL) for dicumyl peroxide will remain 0.1 µg/m³ (annual averaging time).

The following references or databases were searched to identify data to determine the screening level: Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS), the Registry of Toxic Effects of Chemical Substances (RTECS), the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLV), National Institute of Occupational Safety and Health (NIOSH) Pocket Guide to Hazardous Chemicals, Environmental Protection Bureau Library, International Agency for Research on Cancer (IARC) Monographs, Chemical Abstract Service (CAS) Online (1967- May 2006), National Library of Medicine (NLM), Health Effects Assessment Summary Tables (HEAST), and National Toxicology Program (NTP) Status Report. The EPA has not established a reference concentration (RfC) or reference dose (RfD) for dicumyl peroxide. The ACGIH and NIOSH have not established occupational exposure limits for dicumyl peroxide. The molecular structure of dicumyl peroxide is shown in Figure 1.

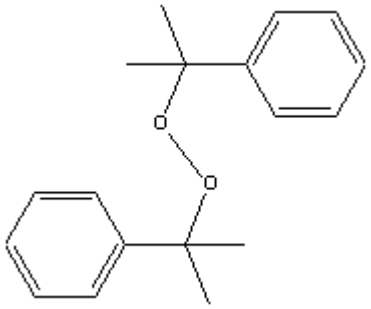

Figure 1. Molecular Structure of Dicumyl Peroxide

Physical Properties
Molecular weight: 270.37 g
Molecular formula: $C_{18}H_{22}O_2$
Boiling point: 130ºC
Vapor pressure: 0.4 mmHg
Water Solubility: <0.1 g/100 mL at 23 C
Physical State: White Powder

Human Studies
An occupational study was performed at a Swedish plant where mostly polyethylene is produced. Workers at this plant complained of nosebleeds when handling dicumyl peroxide. Eighteen workers exposed to dicumyl peroxide in a chemical plant were subjected to examination of the nose by rhinoscopy, mucocilliary function test and rhinomamometry (Petruson and Jarvholm, 1983). Two groups were used for controls: eight other workers at the plant and 20 hospital workers. At the department where the dicumyl peroxide is melted, the workers are exposed during the filling of the tanks and also from the leakage in the process. They were also exposed to dust containing polyethylene, antioxidant and peroxide when the end product (pellets of polyethylene) is packed in large boxes. RESULTS: The mucocilliary function and nasal air flow were the same in subjects exposed and those not exposed to peroxide. Nine of the workers exposed to dicumyl peroxide had visible blood vessels in the mucosa on the anterior part of the nasal septum. Four of the subjects with visible vessels were examined on two occasions, with eight months interval. The authors stated that the vessels seemed to be permanent in the exposed workers as there were no changes during eight months in the four subjects who were examined twice. Furthermore, some individuals with vessels had not been exposed to dicumyl peroxide for several years before the examination. Only 2 persons in the other groups had visible blood vessels. Both had a common cold at the time of the examination. Crusting in the nose (mostly the anterior septum) was more common in the group exposed to peroxide ($p<0.01$) than in the other two groups. Irritation and hypertrophy of the nasal mucosa occurred significantly more often ($p<0.01$) than in control groups.

Animal Studies
Groups of 2 to 6 albino rabbits (male and female) were exposed to liquid dicumyl peroxide dissolved on phosphate buffered saline at a concentration of 10 or 25 ppm for various time periods ranging from 15 minutes to four weeks (Hansson and Petruson, 1986). The test substance was dissolved in 50 µl phosphate-buffered-saline and place into the right nostril 3 times per day for 5 days per week. The authors stated that this volume was tested to be rapidly inhaled by the animal with hardly any solution left of lost. No general effects on the health or gross activity of the exposed animals could be observed by their general behavior, food consumption or weight gain as compared to controls. Rhinoscopy, electron microscopy and histopathology were performed on nasal mucosa, but not on any other tissue. Within an hour of exposure to dicumyl peroxide there was a slight inflammatory reaction, as reflected by a more intense red color on both the lateral and medial aspects of the nasal cavity. Concomitantly, there was a slight increase in the amount of fluid covering the nasal mucosa, but rarely to such and extent that the nose became wet. After at least a week of exposure to 10 ppm dicumyl peroxide an increase number of blood vessels was observed in some animals (exact number not reported). Instillation of dicumyl peroxide for one month (dose not specified) caused the appearance of visible blood vessels on both lateral and medial aspects of the nasal cavity not seen in the controls. A moderate inflammatory reaction was noticed described as the nasal mucosa appeared more reddish swollen, and moistened than in the controls. Increased amounts of debris and mucus strands were observed. A one month exposure followed by one month recovery showed increased crusting and mucus within the nasal cavity of all exposed rabbits. No general effects on the health or gross activity of the exposed animals could be observed by their general behavior, food consumption or weight gain as compared to controls. After 5 days of treatment with 10 or 25 ppm dicumyl peroxide solution there were areas of the nasal mucosa lacking cilia, with areas of goblet cells appearing. After one month of treatment with dicumylperoxide (10 or 25 ppm) the changes in the mucosa were more obvious. Scattered islands with non-ciliated cells could be observed in the carpet, normally formed by cilia. Mucus, trapping erythrocytes and leukocytes, was covering and infiltrating the cilia. Many of the ciliated cells, not only the cilia *per se*, were distorted and irregular in contour. Goblet cells were noticed in increased frequency compared to controls. Treatment with 10 or 25 ppm dicumylperoxide caused the intracellular space between adjacent epithelial cells markedly increased. There was infiltration of inflammatory cells in the connective tissue as well as in the epithelium. One week

and one month after the initiation of the treatment, many nasal mucosal cells were swollen or degeneration. Scattered cells contained an increased number of lysosomes, vacuoles, and sometimes even appeared to have lost either normal compartmentation of organelles. Metaplastic cells lacking normal cilia and microvilli were frequently observed. After one month recovery there was only partial healing of mucosa. After one month treatment and two months recovery showed that epithelial changes persisted. The 10 ppm dose group was determined to be a lowest-observed-adverse-effect-level (LOAEL) based on nasal irritation.

Toxicity Review Articles

In an article published by Hercules Incorporated (EPA, 1987), the toxicity of dicumyl peroxide was reviewed. In this publication, it is reported that the LD50 in the rat was found to be 4,800 mg/kg. Vapor inhalation at 2,920 ppm (14g/m^3) for 15-60 minutes caused respiratory irritation and central nervous system depression in rats, mice, and guinea pigs. Mice died after about four hours, but rats and guinea pigs survived the five-hour exposure. It was also reported that in a repeated inhalation study, exposure to 600 ppm (6,625 mg/m^3) produced minimum toxic effects to rabbits, rats, monkeys, and guinea pigs during 6-month inhalation studies (7 hrs/day). No effects were detected at 200 ppm (2,208 mg/m^3). The decomposition products of dicumyl peroxide were: acetophenone, dimethylbenzyl alcohol, and alpha-methyl styrene. This report did not include documentation of laboratory procedures including: strain and number of control animals, quantitative exposure analysis, histopathology, and blood chemistry.

Discussion

Nasal lesions were observed in both animals exposed to liquid dicumyl peroxide and occupationally exposed humans. In the animal study by Hansson and Petruson (1986) the dose regimen was intranasal instillation with dicumyl peroxide dissolved in saline, which is not considered an appropriate protocol for assessing inhalation risk. In the human study by Petruson and Jarvholm (1983), there was no quantitative exposure assessment of dicumyl peroxide. Both studies analyzed a very limited set of toxicity endpoints, focusing mostly on nasal toxicity. Other than body weight and food intake, no systemic toxicity parameters were assessed in the animals. Because of these shortcomings, these studies were deemed inadequate and inappropriate to use to develop an ITSL.

Since there was insufficient data with which to develop a new screening level, the initial threshold screening level (ITSL) for dicumyl peroxide will remain 0.1 µg/m^3 (annual averaging time).

REFERENCES

EPA, 1987. Technical data bulletin for Di-cup (diumyl peroxide) including toxicity data for a-methylstyrene, one of its decomposition products. EPA Office of Technical Services (OTS) Doc No. 86-870001667

Hansson H, Petruson B. 1986. Nasal mucosa changes after acute and long-term exposure to dicumylperoxide. Acta Otolaryngol. Volume 101: 102-113.

Petruson B, Jarvholm B. 1983. Formation of new blood vessels in the nose after exposure to dicumylperoxide at a chemical plant. Acta Otolaryngol. Volume 95: 333-339.