UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

February 13, 2008

MEMORANDUM

SUBJECT: **Ammonia (BCMW/Busan 1215)**: Toxicology Review of Proposed New Use in Industrial Water Systems

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I. ACTION REQUESTED

Review human health toxicity of ammonia for proposed new uses in industrial water systems.

II. BACKGROUND

The registrant, Buckman Laboratories International, Inc., has submitted an amendment for the product Busan 1215 (aka BCMW) to add a new use in industrial water systems. Busan 1215 is an aqueous dilution of ammonia sulfate, which is applied in conjunction with sodium hypochlorite (at a minimum of 1:1 molar ratio) to form monochloramine according to the amended label. The registrant proposes to use Busan 1215 in controlling algae, bacteria and fungi in "industrial cooling towers, recirculation cooling water systems, evaporative condensers, influent water systems, brewery and food pasteurizers, industrial fresh water systems, airwashers, seawater desalination and reverse osmosis systems, paint spray booth sumps, non-fish containing decorative fountains and ponds used for cooling purposes, sewage and wastewater systems." Busan 1215 is also intended to be used in both seawater and freshwater influent systems to control algae, bacteria, fungi and mollusks.

Busan 1215 can be used in intermittent or continuous treatment, by mixing 0.5 fluid ounces of Busan 1215 with 1.0 fluid ounces of sodium hypochlorite (up to 15% wt/ml) to achieve a total chlorine residual of at lease 1 ppm in excess of the system oxidant demand. A total chlorine residual of 1 to 2 ppm for intermittent treatment and 0.5 to 1 ppm for continuous treatment is needed; the maximum total chlorine residual is 5 ppm in water for both intermittent and continuous treatment. The frequency and duration of the treatment vary depending upon the severity of the situation. Generally the water is treated for 5 to 60 minutes every 1 to 6 hours. An initial cleanup before treatment should be carried out for badly fouled systems.

III. RESULTS AND DISCUSSION

1. Acute Toxicity of Busan 1215

The acute toxicity data for the product Busan 1215 containing 7.59% of ammonia are acceptable. All of the acute toxicity studies for Busan 1215 are classified as category IV, and Busan 1215 is a non-sensitizer. The acute toxicity data on Busan 1215 is summarized below in Table 1.

Table 1. Acute Toxicity Data on Busan 1215

Guideline No./ Study Type	MRID No.	Results	Toxicity Category
870.1100 Acute oral toxicity	46435108	LD_{50} > 5000 mg/kg	IV
870.1200 Acute dermal toxicity	46435109	LD_{50} > 5000 mg/kg	IV
870.1300 Acute inhalation toxicity	46435110	LC50 ≥ 2.08 mg/L (4-hr)	IV
870.2400 Acute eye irritation	46435111	Minimally irritating (rabbit) Irritation cleared within 48 hours	IV
870.2500 Acute dermal irritation	46435112	Slightly irritating	IV
870.2600 Skin sensitization	46435113	Not a skin sensitizer (guinea pig)	N/A

N/A – not applicable

2. Ammonia Toxicity Profile

The Agency conducted a hazard assessment of ammonia for use in food-contact pulp/paper products in December 2005 (D3113637); detailed discussion of ammonia toxicity can be found in this document. A summary of its toxicity is provided below.

Ammonia is a corrosive substance, and the main toxic effects of acute toxicity are restricted to the sites of direct contact with ammonia (i.e., skin, eyes, respiratory tract, mouth, and digestive tract). It is an upper respiratory irritant in humans. Immediate nose and throat irritation is experienced at concentrations exceeding 50 ppm, and immediate lethality may occur at concentrations in excess of 5,000 ppm; however, the acute lethal concentration depends on the exposure duration.

The skin is extremely sensitive to airborne ammonia or ammonia dissolved in water. Dermal exposures to liquid ammonia or concentrated solutions and/or ammonia gas are frequently occupationally related and produce cutaneous burns, blisters, and lesions of varying degrees of severity. The severity of the damage is proportional to the concentration and duration of exposure; flushing with water immediately after contact alleviates or prevents effects.

Ingestion of concentrated ammonium solutions may produce severe burns and hemorrhage of the upper gastrointestinal tract.

Ammonia caused adverse respiratory effects in animals following inhalation exposure. In F344 rats (6/sex/dose) continuously to 25, 50, 150 or 250 ppm ammonia (HEC = 1.9, 3.7, 11.2 or 18.6 mg/m^3, respectively) for 7 days prior to inoculation with Mycoplasma pulmonis and from 28-42 days following M. pulmonis exposure (in order to produce murine respiratory mycoplasmosis [MRM]), all levels of ammonia, whether produced naturally or derived from a purified source, significantly increased the severity of rhinitis, otitis media, tracheitis and pneumonia characteristic of M. pulmonis. Furthermore, there was a significant concentration response between observed respiratory lesions and increasing environmental ammonia concentration for gross and microscopic lesions. All lesions observed were characteristic of MRM. Gross bronchiectasis and/or pulmonary abscesses and the extent of gross atelectasis and consolidation were consistently more prevalent in exposed animals at all concentrations than in their corresponding controls. The severity of the microscopic lesions in the nasal passages, middle ears, tracheas and lungs was significantly greater in all exposed groups compared with controls. Increasing ammonia concentration was not associated with an increasing frequency of M. pulmonis isolations. Additionally, rats not exposed to M. pulmonis and exposed to ammonia at 250 ppm developed nasal lesions (epithelial thickening and epithelial hyperplasia) unlike those observed in inoculated rats. Based upon these data in M. pulmonis exposed rats, a LOAEL (HEC) of 1.9 mg/m^3 was identified.

Other adverse respiratory effects, which were concentration- and time-dependent, were seen in respiratory tract in rats, guinea pigs, mice and chickens. These adverse effects included, but not limited to, a mucilaginous exudate, acute inflammatory reactions with infiltration of neutrophils, large mononucleated cells, monocytes and immature fibroblasts in the trachea, hyperplasia of the tracheal epithelium, necrotic changes at the luminal surface (pyknotic nuclei and karyorrhectic cells) of the trachea, darkening/reddening, edema, congestion, and hemorrhage in the lungs. Ophthalmological changes, such as clouding of the cornea and corneal opacities, were also observed in chickens.

No developmental or reproductive studies have been conducted by the registrant for ammonia.

No neurotoxicity studies have been conducted by the registrant. Studies in the scientific literature indicate that neurological effects have been observed in humans following inhalation and dermal exposure. These effects have been limited to blurred vision, most likely due to direct contact, but more severe exposures, which result in significant elevation of blood ammonia levels (hyperammonemia) can result in diffuse nonspecific encepthalopathy, muscle weakness, decreased deep tendon reflexes and loss of consciousness.

A few studies on the genotoxicity of ammonia suggest that ammonia and ammonia ion may have clastogenic and mutagenic properties. Ammonia has not been classified for carcinogenic effects by the Agency, the Department of Health and Human Services (DHHS), or the International Agency for Research on Cancer (IARC).

Chronic occupational exposure to low levels of airborne ammonia (< 25 ppm) had little effect on pulmonary function or odor sensitivity in workers at some factories, but studies of farmers exposed to ammonia and other pollutants in livestock buildings indicated an association between exposure to pollutants, including ammonia, and an increase in respiratory symptoms and/or decrease in lung function parameters. The contribution of ammonia to these respiratory symptoms is unclear.

USEPA (2005) established an inhalation reference concentration (RfC) based on both an occupational study and an animal toxicity study to be protective of respiratory effects. A no-observable-adverse effect level (NOAEL) of 6.4 mg/m^3 (9.2 ppm) from an occupational study was combined with a lowest observable adverse effect level (LOAEL) of 17.4 mg/m^3 (25 ppm), which has a human equivalent concentration (HEC) of 1.9 mg/m^3, for respiratory effects in a rat subchronic inhalation study. The Agency acknowledges that certain database deficiencies exist including a lack of adequate reproductive and developmental toxicology studies for ammonia in the IRIS record; an additional 3X factor is applied to account for these deficiencies.

3. Toxicity Endpoint Selection

3.1. Occupational Exposure to Ammonia

3.1.1 Dermal Exposure (all durations)

No endpoint was selected because the labels will specify the use of gloves, full body clothing and eye protection. Thus, there is no potential concern for dermal exposure.

3.1.2 Inhalation Exposure (all durations)

Study Selected: Holness et al. (1989), occupational study of workers

Executive Summary: Holness et al. investigated production workers exposed to ammonia in a soda ash facility. All of the available 64 production workers were invited to participate and 82% agreed to be evaluated. The control group consisted of 31 other plant workers from stores and office areas of the plant without previous exposure to ammonia. The mean age of the workers was 38.9 years and duration of exposure was 12.2 years. Weight was the only statistically significant difference in demographics

found after comparing height, weight, years worked, % smokers and pack-years smoked. The mean TWA ammonia exposures based on personal sampling over one work shift (average sample collection 8.4 hours) of the exposed and control groups were 9.2 ppm (6.4 mg/m^3) and 0.3 ppm (0.21 mg/m^3), respectively.

A questionnaire was administered to obtain information on exposure and work histories and to determine eye, skin and respiratory symptomatology (based on the American Thoracic Society [ATS] questionnaire [Ferris, 1978]). Spirometry (FVC, FEV-1, FEF50 and FEF75) was performed according to ATS criteria at the beginning and end of each work shift on the first workday of the week (day 1) and the last workday of the week (day 2). Differences in reported symptoms and lung function between groups were evaluated using the actual values and with age, height and pack-years smoked as covariates in linear regression analysis. Baseline lung function results were expressed as percent of predicted values calculated from Crapo et al. (1981) for FVC and FEV-1 and from Lapp and Hyatt (1967) for FEF50 and FEF75.

No statistical difference in the prevalence of the reporting symptoms was evident between the exposed and control groups, although workers reported that exposure at the plant had aggravated specific symptoms including coughing, wheezing, nasal complaints, eye irritation, throat discomfort and skin problems. The percentage of exposed workers reporting hay fever or familial history of hay fever was significantly less than controls, suggesting possible self-selection of atopic individuals out of this work force. The atopic status of the worker and control groups was not determined by skin prick tests to common aeroallergens. Furthermore, the workers complained that their symptomatology was exacerbated even though there was no statistical difference between groups. Since the study was cross-sectional in design with a small population, it is possible that selection bias may have occurred.

Baseline lung functions (based on the best spirometry values obtained during the four testing sessions) were similar in the exposed and control groups. No changes in lung function were demonstrated over either work shift (days 1 or 2) or over the workweek in the exposed group compared with controls. No relationship was demonstrated between chronic ammonia exposure and baseline lung function changes either in terms of the level or duration of exposure, probably due to lack of adequate exposure data for categorizing exposures and thus precluding development of a meaningful index accounting for both level and length of exposure.

Based on the lack of subjective symptomatology and changes in spirometry, this study establishes a free-standing TWA NOAEL of 9.2 ppm (6.4 mg/m^3). Adjustment for the TWA occupational scenario results in a NOAEL (HEC) of 2.3 mg/m^3.

Dose and Endpoint for Risk Assessment: The 8-hour TWA NOAEL of 9.2 ppm (6.4 mg/m^3) was selected based on lack of evidence of decreased pulmonary function or changes in subjective symptomatology in the occupational study. The 24-hour adjusted NOAEL is 2.3 mg/m^3. This 24-hour NOAEL is the basis of the Agency's inhalation reference concentration (RfC) presented on the Integrated Risk Information System (IRIS) and represents Agency consensus (USEPA 2005).

Margin of Exposure for Occupational Exposure: For all durations, a MOE of 30 is adequate.

Comments about Study/Endpoint/Margins of Exposure: An uncertainty factor of 30 (UF = 30) is determined, where 10x is used to allow for the protection of sensitive individuals (intra-species extrapolation). Because it is based on a human occupational study, no inter-species safety factor is required. A factor of 3x was used to account for several data base deficiencies including the lack of chronic data and the lack of reproductive and developmental toxicology studies.

A summary of toxicological doses and endpoints selected for ammonia is shown in Table 2.

[redacted]			
Dermal (all durations) (Occupational)	Not selected. Labels will specify the use of gloves, full body clothing and eye protection.		
Inhalation (all durations) (Occupational)	8-hr TWA NOAEL = 6.4 mg/m^3 (9.2 ppm) 24-hr adjusted NOAEL (HEC) = 2.3 mg/m^3 UF = 30 (10x for intraspecies extrapolation and 3x for database deficiencies)	LOC for MOE = 30	Occupational Study (Holness et al., 1989) LOAEL = none Lack of evidence of decreased pulmonary function or changes in subjective symptomatology See IRIS record (USEPA 2005) for more detailed discussion.

TWA = time-weighted-average, UF = uncertainty factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, MOE = margin of exposure, HEC= human equivalent concentration

The proposed use of Busan 1215 in industrial water systems is considered an indoor non-food use. There may be potential inhalation concern for occupational exposure to ammonia for the proposed new use, assuming that proper worker's protection will be applied. Based on the Registrant statement, Busan 1215 is to be mixed with sodium hypochlorite through a chemical feed system, and a diagram and direction included suggesting a closed-system operation (pages 20 and 24 of the Supplemental Report: Mammalian Toxicology and Environmental Fate and effects Data). It is indicated that Busan 1215 is transported through semi-bulk transfer tote bins, which are specifically designed to be connected directly to a "base" tote feed container. Busan 1215 is introduced to a treatment water system via a chemical feed skid to allow the introduction of Busan 1215 to a pipe where continuous flow through dilution water is available. In addition, the Registrant indicates that proper personal protective equipment (PPE) is required during the operation. It should be noted that in order to be qualified as a closed-system application for hazard and human exposure assessment, the Registrant needs to clearly specify the uses in such manner in the amended label. In addition, the Registrant needs to revise the label to include the requirement of using proper worker's protection (gloves, full-body clothing and eye protection, etc.).

IV. CONCLUSIONS

RASSB agrees that the concerns for hazard and human exposure from the proposed use of Busan 1215 in industrial water systems may be minimal, if it is used in a closed-system operation. RASSB recommends that the label be revised to specify the uses are in a closed loading and delivery system and to include the requirement of using proper worker's protection when applying Busan 1215 to minimize human exposures from the use.

V. REFERENCES

Busan 1215. Amended Product Label. Buckman Laboratories, Inc., Memphis, Tennessee.

Smegal, D to Copeland, D. 2005. Memorandum: Hazard Assessment for Ammonia and Monochloroamine. December 9, 2005. D313637.

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