UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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Memorandum

Subject: Hazard Assessment for Ammonia and Monochloroamine

Active Ingredient: Ammonia
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1.0 BACKGROUND

The Agency was requested to review a new use for ammonia for use in food-contact pulp/paper. The registrant proposes to mix their product BCMW/BUSAN 1215, which contains dilute solutions of ammonia, with sodium hypochlorite (12.5%) to form monochloramine on pulp/paper. Thus, this hazard assessment will evaluate both potential occupational exposure to ammonia and potential dietary exposures to monochloramine. Therefore, the toxicity profile for ammonia focuses on the hazard associated with dermal and inhalation exposures, while the toxicity profile for monochloramine focuses on the hazard associated with oral exposures.

2.0 HAZARD ASSESSMENT

2.1 Acute Toxicity of BUSAN 1215

The acute toxicity data for the product BUSAN 1215 containing 7.59% are acceptable. All of the acute toxicity studies for BUSAN 1215 are listed in category IV, and it is a non-sensitizer. The acute toxicity data on the 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 $\geq$ 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)	

2.2. Ammonia Toxicity Profile

Ammonia is an essential mammalian metabolite for DNA, RNA and protein synthesis and is necessary for maintaining acid-base balance. It is produced and used endogenously in all mammalian species. Ammonia is excreted primarily as urea and urinary ammonium compounds through the kidneys (ATSDR 2004).

Acute. Ammonia is a corrosive substance and the main toxic effects 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. The acute toxicity of gaseous ammonia is generally considered the effect of the chemical reactivity producing an extremely sharp, irritating odor

causing eye, skin, and respiratory irritation. At concentrations exceeding 50 ppm, immediate nose and throat irritation is experienced (ATSDR 2004). Immediate lethality may occur at concentrations in excess of 5,000 ppm; however, the acute lethal exposure concentration depends on the exposure duration (ATSDR 2004).

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 topical damage caused by ammonia is probably due mainly to its reactivity and irritation properties. Its high water solubility allows it to dissolve in moisture on these surfaces, react with fatty substances, be absorbed into deeper layers, and inflict extensive damage. The severity of the damage is proportional to the concentration and duration of exposure; flushing with water immediately after contact alleviates or prevents effects (ATSDR 2004).

Ingestion of concentrated ammonium solutions may produce severe burns and hemorrhage of the upper gastrointestinal tract (ATSDR 2004).

Subchronic. Ammonia causes adverse respiratory effects in animals following inhalation exposure. Below are summaries of several inhalation toxicity studies presented in USEPA (2005a).

Broderson et al. (1976) exposed groups of 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/cu.m, respectively) for 7 days prior to inoculation with Mycoplasma pulmonis and from 28-42 days following M. pulmonis exposure. Each treatment group had a corresponding control group exposed only to background ammonia and inoculated with M. pulmonis in order to produce murine respiratory mycoplasmosis (MRM). The following parameters were used to assess toxicity: clinical observations and histopathological examination of nasal passages, middle ear, trachea, lungs, liver and kidneys. 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 was 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/cu.m was identified.

Gamble and Clough (1976) whole-body exposed female Porton rats to ammonia concentrations of 200 (+/- 50) ppm for 4, 8 or 12 days or 435 (+/- 135) ppm for 7 days. Duration of exposure was not otherwise specified. The total number of animals was 16, but the apportionment into

exposure groups was not provided. Hyperplasia of the tracheal epithelium was shown to be concentration- and time-dependent. At 4 days of exposure to 200 ppm, the epithelium had changed to transitional-stratified and by 8 days there was gross change: disappearance of cilia and stratification increasing to folds forming on the luminal surface. A mucilaginous exudate was also evident with a slight increase in submucosal cellularity. At 12 days at the 200 ppm concentration, the epithelialization had increased in thickness. Rats exposed for 7 days to 435 ppm showed acute inflammatory reactions with infiltration of neutrophils, large mononucleated cells, monocytes and immature fibroblasts in the trachea. Evidence of necrotic changes at the luminal surface included pyknotic nuclei and karyorrhectic cells.

Groups of 10 guinea pigs and 20 Swiss albino mice were exposed continuously to an ammonia-air concentration of 20 ppm (13.9 mg/cu.m) for up to 6 weeks. A separate group of six guinea pigs was similarly exposed to an ammonia concentration of 50 ppm (35 mg/cu.m) for 6 weeks, and a group of 21 Leghorn chickens was exposed to a 20 ppm concentration for up to 12 weeks. Controls (number not specified) were maintained under identical conditions, except for the ammonia. Smaller groups of chickens were exposed continually to either 200 ppm for up to 3 weeks or 1000 ppm for up to 2 weeks. The effects of ammonia were found to be both time- and concentration-dependent. While no effects were observed in guinea pigs, mice, or chickens sacrificed after 1, 2, 3 or 4 weeks of exposure at 20 ppm, darkening/reddening, edema, congestion, and hemorrhage were seen in the lungs of all three species at sacrifice after 6 weeks of exposure at that concentration. In guinea pigs exposed to 50 ppm ammonia for 6 weeks, grossly enlarged and congested spleens, congested livers and lungs, and pulmonary edema were seen. In chickens exposed to 200 ppm for 17-21 days, liver congestion and slight clouding of the cornea were observed in addition to those effects observed in the chickens exposed to 20 ppm ammonia for 6 weeks. At 1000 ppm, the same effects, in addition to congestion of the spleen, were seen in chickens after just 2 weeks of exposure, and corneal opacities developed within just 8 days of exposure. In a second series of experiments, it was found that a 72-hour exposure to 20 ppm ammonia significantly increased the infection rate of chickens subsequently exposed to an aerosol of Newcastle disease virus, while the same effect was observed in just 48 hours in chickens exposed to 50 ppm. Changes in gross and micropathology did not accompany the change in disease rate (Anderson et al., 1964).

Guinea pigs were exposed to 0 or 170 ppm (118 mg/cu.m) 6 hours/day, 5 days/week for up to 18 weeks. No adverse effects were observed in animals exposed to ammonia for 6-12 weeks (HEC=21 mg/cu.m). Mild changes in the spleen, kidney suprarenal glands and livers were observed (HEC=19 mg/cu.m) in guinea pigs exposed for 18 weeks. No effects on the lungs were observed. The upper respiratory tract was not examined (Weatherby, 1952).

Swiss-Webster mice (16-24/group) were exposed to 0 or 305 ppm ammonia (212 mg/cu.m) 6 hours/day for 5 days. Nasal lesions were observed at 212 mg/cu.m which when dose duration adjusted for the RGDR, equals a LOAEL(HEC) of 4.5 mg/cu.m (Buckley et al., 1984).

Continuous exposure of rats to ammonia at 0, 40, 127, 262, 455 or 470 mg/cu.m for a minimum of 90 days (114 days for the 40 mg/cu.m group) was conducted in male and female Sprague-Dawley and Long-Evans rats. A LOAEL of 262 mg/cu.m (HEC=28 mg/cu.m) was determined based upon nasal discharge in 25% of the rats, and nonspecific circulatory and degenerative

changes in the lungs and kidneys that were difficult to relate specifically to ammonia inhalation. A frank-effect-level of 455 mg/cu.m (HEC=48.7 mg/cu.m) was observed due to high mortality in the rats (90-98%). Nasal passages were not histologically examined (Coon et al., 1970).

Duroc pigs were exposed to ammonia concentrations of 10, 50, 100 and 150 ppm. Exposure to ammonia significantly decreased both food intake and body weight gain. Higher concentrations caused nasal, lacrimal and mouth secretions, which became less severe over time. No treatment-related gross or microscopic changes were observed in the bronchi, lungs or turbinates at necropsy (Stombaugh et al., 1969).

Various animal species were exposed to 0, 155 and 770 mg/cu.m for 8 hours/day, 5 days/week for 30 exposures (rats, guinea pigs, rabbits, dogs and monkeys). The LOAEL for lung inflammation is 770 mg/cu.m for rats (HEC=82.4 mg/cu.m) and guinea pigs. Ocular and nasal irritation was observed at 770 mg/cu.m in rabbits and dogs. The upper respiratory tract was not examined (Coon et al., 1970).

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

Neurotoxicity. 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 (ATSDR 2004).

Cerebral edema and herniation and intracranial hypertension have been noted in animal models of hyperammonemia. The mechanism of ammonia-induced encephalopathies has not been definitively elucidated. It is thought to involve the alteration of glutamate metabolism in the brain with resultant increased activation of N-methyl-D-aspartate (NMDA) receptors, which causes decreased protein kinase C-mediated phosphorylation of Na+/K+ ATPase, and depletion of ATP. This reduced ATP level may be involved in ammonia-induced coma and death. A disruption in neurotransmission has also been suggested by alteration of brain tubulin, which is an essential component of the axonal transport system (ATSDR 2004).

Chronic. 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 (ATSDR 2004).

USEPA (2005a) established an inhalation reference concentration (RfC) based on both an epidemiological study and an animal toxicity study to be protective of respiratory effects. A no-observable-adverse effect level (NOAEL) of 6.3 mg/m^3 (9.2 ppm) from an occupational study

was combined with a lowest observable adverse effect level (LOAEL) of 17.5 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 there is a lack of adequate reproductive and developmental toxicology studies for ammonia in the IRIS record (USEPA 2005a), and applied an additional 3X factor to account for these deficiencies. Based on the proposed use pattern, BCMW/BUSAN 1215 containing dilute solutions of ammonia is mixed with sodium hypochlorite (12.5%) to form monochloramine in pulp/paper. Because there is no concern for potential dietary exposure to ammonia for this proposed use pattern, it is not necessary to consider the FQPA safety factor for ammonia. However, the Agency believes the FQPA factor should be considered for the potential dietary exposures to monochloramine (see below).

Mutagenicity/Carcinogenicity. There is no evidence that ammonia causes cancer. Ammonia has not been classified for carcinogenic effects by EPA, the Department of Health and Human Services (DHHS), or the International Agency for Research on Cancer (IARC) (ATSDR 2004).

There are a few studies on the genotoxicity of ammonia. Overall, these studies suggest that ammonia and ammonia ion may have clastogenic and mutagenic properties. One study evaluated blood samples from 22 workers exposed to ammonia in a fertilizer factory and 42 control workers not exposed, and found an increased frequency of chromosomal aberrations (CAs) and sister chromatid exchanges (SCEs), increased mitotic index (MI) and increased frequency of CAs and SCEs with increasing length of exposure (Yadav and Kaushik 1997 as cited in ATSDR 2004). An increased frequency of micronuclei compared to controls was noted in mice administered ammonium intraperitoneally (Yadav and Kaushik 1997 as cited in ATSDR 2004). There were positive effects in a reverse mutation test in E. coli, but only in treatments using toxic levels of NH_4+ (98% lethality). Another study found slight mutagenic activity in *Drosophila* following exposure to ammonia gas, but at toxic levels (survival after treatment was <2%). *In vitro* tests of chick fibroblast cells showed that buffered ammonia-ammonium chloride solutions can induce clumping of chromosomes, inhibit spindle formation and result in polyploidy (Rosenfeld 1932 as cited in ATSDR 2004). Reduced cell division was noted in mouse fibroblasts cultured in media to which ammonia and ammonium chloride were added (Visek et al. 1972 as cited in ATSDR 2004).

2.3 Monochloramine Toxicity Profile

Developmental/reproductive. The developmental and reproductive toxicity of monochloramine has been examined in rats, but with suboptimal studies. However, due to the chemical relationship between monochloramine and chlorine, the Agency believes that the reproductive and developmental studies for chlorine may be used to satisfy these data gaps for monochloramine. The available studies do not indicate concerns for increased sensitivity of the fetus or offspring. Thus, the Agency believes it is appropriate to reduce the FQPA factor to 1X for monochloramine. Below are summaries of reproductive and developmental studies.

In a reproductive study by Carlton et al. (1986), chloramine was administered by gavage in deionized water at doses of 0, 2.5, 5.0 and 10 mg chloramine/kg/day to male (12/dose group) and female (24/dose group) Long Evans rats for a total of 66-76 days. Males were treated for 56 days

and females for 14 days prior to mating. Dosing continued during the 10-day mating period and afterwards females were dosed with chloramine daily during gestation and lactation. Males were necropsied at the end of the mating period. Dams and some offspring were necropsied at 21 days after birth. Other offspring were dosed with chloramine after weaning until they were 28-40 days old. No statistical differences were observed between control and exposed rats in fertility, viability, litter size, day of eye opening or average day of vaginal patency. There were no alterations in sperm count, direct progressive sperm movement, percent mobility or sperm morphology in adult males. Weights of male and female reproductive organs were not significantly different among control and test groups, and there were no significant morbid anatomic changes evident on tissue examination. There were no signs of toxicity, changes in blood counts, or effects on body weight in adult rats of either sex at any dose level. The mean weight of the pups was not affected by chloramine treatment. A NOAEL of 10 mg/kg-day for reproductive effects can be defined from this study.

Abdel-Rahman et al. (1982) administered monochloramine in the drinking water to female Sprague-Dawley rats (6/dose group) at 0, 1, 10 and 100 mg/L for 2.5 months prior to and throughout gestation. By using body weights provided by the investigators and a reference water consumption value (U.S. EPA, 1987), the intake of monochloramine was estimated to be to 0, 0.15, 1.5 and 15 mg monochloramine/kg/day. Treatment with monochloramine did not increase the number of fetal resorptions or affect fetal weight. In addition, monochloramine did not induce soft-tissue anomalies or skeletal malformations. A developmental NOAEL of 15 mg monochloramine/kg/day is provided by this study, although confidence is low due to the small number of animals exposed.

Chronic. The long-term effects of chloraminated water were examined in rats and mice (NTP 1992). In both species, there were no statistically significant findings attributable to chemical exposure at the highest dose tested of 200 ppm chloramine, or 9.5 mg chloramine/kg/day for rats and 17.2 mg chloramine/kg/day for mice. The NOAEL of 9.5 mg chloramine/kg/day in rats is chosen as the basis for the chronic oral RfD by USEPA (2005b). Although a higher NOAEL in the study of 17.2 mg/kg-day is found for mice, rats may be the more sensitive species since doses between 9.5 and 17.2 mg/kg-day were not tested in rats.

Mutagenicity/Carcinogenicity. Monochloramine is not classifiable as to human carcinogenicity (Group D) based on inadequate human data and equivocal evidence of carcinogenicity from animal bioassays. A two-year bioassay showed marginal increase in mononuclear cell leukemia in female F344/N rats. No evidence of carcinogenic activity was reported in male rats or in male or female B6C3F1 mice. Genotoxcity studies, both in vitro and in vivo, gave negative results (USEPA 2005b).

3.0 TOXICITY ENDPOINT SELECTION

Tables 2 and 3 present a summary of the recommended toxicity endpoints for ammonia and monochloramine, respectively to be used in the risk assessment.

A. Occupational Exposure to Ammonia

A.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 for dermal exposure.

A.2 Inhalation Exposure (All durations)

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

Executive Summary: Holness et al. (1989) 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/cu.m) and 0.3 ppm (0.21 mg/cu.m), 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/cu.m). Adjustment for the TWA occupational scenario results in a NOAEL(HEC) of 2.3 mg/cu.m.

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 syptomatology in the occupational study (Holness et al. 1989). 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. Since ammonia is a respiratory irritant, the Agency believes that the irritation potential would limit exposure. See USEPA (2005a) for more details on the inhalation RfC and a discussion of other supporting toxicity studies.

Margin of Exposure for Occupational Exposure: For all durations, a MOE of 30 is adequate. An uncertainty factor of 10 is used to allow for the protection of sensitive individuals (intra-species extrapolation). Because it is based on a human epidemiological study, no inter-species safety factor is required. A factor of 3 was used to account for several data base deficiencies including the lack of chronic data, and the lack of reproductive and developmental toxicology studies. This factor is not larger than 3, however, since studies in rats (Schaerdel et al., 1983) have shown no increases in blood ammonia levels at exposures 32 ppm and only minimal increases at 300-1000 ppm, suggesting that no significant distribution is likely to occur at the human equivalent concentration (HEC) level calculated.

B. Dietary Exposure to Monochloroamine

B.1 Acute Reference Dose (RfD)

An acute RfD was not identified because there were no effects attributable to a single dose.

B.2 Chronic Reference Dose (RfD)

Study Selected: Rat Chronic Oral Study (National Toxicology Program 1992)

Executive Summary. The long-term effects of chloraminated water were examined in F344/N rats and B6C3F1 mice (NTP, 1992). Groups of rats (70/sex/dose) and mice (70/sex/dose) were administered chloraminated drinking water at 0 (controls), 50, 100 or 200 ppm for 103-104 weeks. Based on body weight and water consumption data provided in the study, the intake of

chloramine was 0, 2.6, 4.8 and 8.7 mg/kg-day for male rats; 0, 3.4, 5.3 and 9.5 mg/kg-day for female rats. Consumption of chloramine in mice was 0, 5.0, 8.9 and 15.9 mg/kg-day for males; and 0, 4.9, 9.0 and 17.2 mg/kg-day for females. Interim sacrifices (10/sex/dose) were conducted at weeks 14 and 66. At these times, a complete hematologic examination and necropsy were performed in all sacrificed animals. In addition, histopathologic examination was conducted in all control and high-dose animals. At the completion of the study, a complete histopathologic evaluation was performed in all animals. A dose-related decrease in water consumption was evident in rats throughout the study; food consumption was not affected by treatment. Mean body weights of high-dose male and female rats were lower than their respective controls. However, mean body weights were within 10% of controls until week 97 for females and week 101 for males. Decreases ($p<0.05$) in liver and kidney weight in the high-dose males and increases ($p<0.05$) in the brain- and kidney-to-body weight ratios in the high- dose rats (both sexes) were related to lower body weights in these groups and were not considered toxicologically significant. Results from pathologic evaluation at weeks 14 and 66 were unremarkable. The authors found no clinical changes attributable to consumption of chloraminated water. There were no non-neoplastic lesions after the 2-year treatment with chloraminated water. A NOAEL for rats of 200 ppm chloramine, or 9.5 mg chloramine/kg/day, can be defined in this study.

In treated mice, water consumption throughout the study was also decreased in a dose-related manner. Food consumption was slightly lower in high-dose females compared with controls. Body weights of treated male and female mice were lower than in controls; the effect was dose-related. On the average, body weights of high-dose males were 10-22% lower than controls after week 37; those of high-dose females were 10-35% lower than controls after week 8. Mice exhibited no adverse clinical signs attributed to treatment with chloramine. Survival rates between treated and control mice were not significantly different. Interim evaluations revealed no biologically significant differences in organ weights or in relative organ weights. There were occasional statistically significant differences, such as decreases in liver weights and increases in brain- and kidney-to-body weight ratios in high-dose male and female mice, but these were attributed to the lower body weights and were not considered toxicologically significant. Results from hematology tests, and gross or microscopic examination of tissues and organs were unremarkable. The 2-year evaluation revealed no non-neoplastic lesions attributable to chloramine treatment. The concentration of 200 ppm chloramine, or 17.2 mg chloramine/kg/day is considered a NOAEL for mice in this study.

Dose and Endpoint for Risk Assessment: The NOAEL of 9.5 mg/kg/day (200 ppm) was selected based on no observable adverse effects in the rat chronic oral study (NTP 1992). This NOAEL is the basis of the Agency's oral reference dose (RfD) presented on the Integrated Risk Information System (IRIS) and represents Agency consensus. Although a higher NOAEL in the study of 17.2 mg/kg-day is found for mice, rats may be the more sensitive species since doses between 9.5 and 17.2 mg/kg-day were not tested in rats. Significant decreased weight gain in subchronic rat studies, such as Daniel et al. (1990), at 200 ppm was considered a consequence of decreased water consumption associated with taste aversion.

Uncertainty factors: 100 (10x interspecies extrapolation, 10x intraspecies variation, 1x FQPA safety factor). The FQPA safety factor is reduced to 1X for monochloramine because data from

existing reproductive and developmental studies across chemical class (monochloramine and chlorine) provide sufficient confidence that the reproductive and developmental issues have been addressed. Although the studies with chlorine are marginal in quality, they do give an indication that adverse effects from monochloramine are not likely to occur (see Section 2.3).

Comments about Study/Endpoint Uncertainty Factor: This study represents the best available data to assess chronic toxicity.

$$\textbf{Chronic RfD} = \frac{\text{9.5 mg/kg/day (NOAEL)}}{\text{100 (UF)}} = \textbf{0.1 mg/kg/day}$$

C. Classification of Carcinogenic Potential

Ammonia: There is no evidence that ammonia causes cancer. Ammonia has not been classified for carcinogenic effects by EPA, the Department of Health and Human Services (DHHS), or the International Agency for Research on Cancer (IARC) (ATSDR 2004).

Monochloramine: Monochloramine is not classifiable as to human carcinogenicity (Group D) based on inadequate human data and equivocal evidence of carcinogenicity from animal bioassays. A two-year bioassay showed marginal increase in mononuclear cell leukemia in female F344/N rats. No evidence of carcinogenic activity was reported in male rats or in male or female B6C3F1 mice. Genotoxcity studies, both in vitro and in vivo, gave negative results (USEPA 2005b).

4.0 FQPA CONSIDERATIONS

4.1 Special Sensitivity to Infants and Children

Ammonia: The Agency acknowledges that there is a lack of adequate reproductive and developmental toxicology studies for ammonia in the IRIS record (USEPA 2005a). However, based on the proposed use pattern, BCMW/BUSAN 1215 containing dilute solutions of ammonia is mixed with sodium hypochlorite (12.5%) to form monochloramine in pulp/paper. Because there is no concern for potential dietary exposure to ammonia for this proposed use pattern, it is not necessary to consider the FQPA safety factor for ammonia. However, the Agency believes the FQPA factor should be considered for the potential dietary exposures to monochloramine.

Monochloramine: As noted in the USEPA (2005b) IRIS record, the developmental and reproductive toxicity of monochloramine has been examined in rats, but with suboptimal studies. These studies are summarized below. However, due to the chemical relationship

between monochloramine and chlorine (U.S. EPA, 1992), reproductive and developmental studies for chlorine (Druckrey, 1968; McKinney et al., 1976; Chernoff et al., 1979; Staples et al., 1979; Meier et al., 1985) may be used to satisfy these data gaps for monochloramine. The available studies do not indicate concerns for increased sensitivity of the fetus or offspring. Thus, the Agency believes it is appropriate to reduce the FQPA factor to 1X for monochloramine.

Tale 2
Summary of Toxicological Dose and Endpoints for Ammonia [1]

Exposure Scenario	Dose Used in Risk Assessment, UF	Target Margin of Exposure (MOE) for Occupational Exposure	Study and Toxicological Effects
Dermal (all durations) (Occupational)	Labels will specify the use of gloves, full body clothing and eye protection.		
Inhalation (all durations) (Occupational)	NOAEL= 6.3 mg/m^3 (9.2 ppm) 8-hr TWA NOAEL(HEC)= 2.3 mg/m^3 (24 hour concentration)	LOC for MOE = 30 (Occupational)	Occupational Study (Holness et al. 1989) LOAEL= none See IRIS record (USEPA 2005a) for more detailed discussion.

[1] *UF = uncertainty factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, LOC=level of concern , MOE = margin of exposure, HEC = human equivalent concentration*

Tale 3 Summary of Toxicological Dose and Endpoints for Monochloroamine [1]			
Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF and Endpoints for Risk Assessment	Study and Toxicological Effects
Acute Dietary (all populations. including infants and children)	No effects attributable to a single dose.		
Chronic Dietary all populations	NOAEL=9.5 mg/kg/day UF = 100 (10X inter- and intra-species) **Chronic RfD** = 0.1 mg/kg/day	FQPA SF =1X **cPAD** = chr RfD / FQPA SF = 0.1 mg/kg/day	Chronic rat Study (NTP 1992) LOAEL = None. No observed effects at highest dose tested.

[1] *UF = uncertainty factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level*

5.0 REFERENCES

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