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Covington & Burling Draft
May 20, 1992

SUMMARY OF DATA ON AMMONIUM BICARBONATE

Abstract. Ammonium bicarbonate is commonly used as a leavening agent in baking powder formulations, a fertilizer, and a flavorant in tobacco products, and has numerous commercial applications. It has been recognized as GRAS by the FDA for multiple uses in food.

When used as a tobacco additive, ammonium bicarbonate increased the phenol content and decreased the amount of cresols and B(a)P in cigarette smoke.

One study reported an association between the intake of cough medicine containing ammonium bicarbonate by pregnant women and congenital anomalies in their children. However, no such association was reported in a subsequent study.

Acute doses of ammonium bicarbonate have been associated with weak ammonium poisoning in children and some deaths in infants. Acute doses of ammonium bicarbonate have also decreased glutamine levels in the liver of and increased glutamine levels in the tissue of rats.

There was no evidence of tumor formation in a chronic feeding study in female rabbits, and the compound tested negatively in genotoxic and mutagenic studies. There are no published subchronic studies on ammonium bicarbonate.

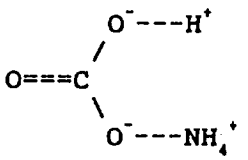
I. Background. Ammonium bicarbonate (CH_5NO_3), also known as ammonium hydrogen carbonate, is the monoammonium salt of carbonic acid. The compound is used commonly as a leavening agent in baking powder formulations because of its complete decomposition into CO_2, H_2O, and NH_3 at temperatures above 60°C. Ammonium bicarbonate is used in cooling baths (1 kg dissolved in five liters of water at 17°C lowers the temperature to 7°C), fire extinguishers, and the manufacture

of porous plastics and ceramics, dyes, and pigments. Ammonium bicarbonate and ammonium salts also are used as fertilizers (Windholz, 1976). In fact, ammonium bicarbonate was the major fertilizer used in China in 1985 (Anonymous, 1985). Ammonium bicarbonate has additional applications in accelerating the decomposition in compost heaps and as an additive in defatting textiles, cold wave solutions for hair styling, chrome leather tanning, and removing gypsum from heat exchanges and other processing equipment (Windholz, 1976). A highly purified preparation of this compound is used in pharmaceuticals (Snell and Hilton, 1966).

Ammonium bicarbonate is one of various NH_3-CO_2 compounds which belong to the system NH_3-CO_2-H_2O. The compounds include: ammonium bicarbonate (NH_4HCO_3), ammonium carbonate ($(NH_4)_2CO_3 \times H_2O$), ammonium sesquicarbonate ($(NH_4)_2CO_3 \times 2NH_4HCO_3 \times H_2O$), and ammonium carbamate ($NH_4CO_2NH_2$) (Ullmann, 1974). Ammonium bicarbonate is the most stable of these compounds. During storage under ambient conditions, ammonium carbonate and ammonium carbamate decompose to ammonium bicarbonate, ammonium, water, and carbon dioxide (Ullmann, 1974; Windholz, 1976; List and Hörhammer, 1972; Hofmann and Hofmann, 1945). In contrast to ammonium bicarbonate, ammonium carbonate, also known as 'hartshorn' (Windholz, 1976), is not defined well and cannot be produced commercially in a pure form. The preparation process of ammonium carbonate creates two mixed salts composed of ammonium bicarbonate and ammonium

carbamate ($NH_4CO_2NH_2 \times 2NH_4HCO_3$ and $NH_4CO_2NH_2 \times NH_4HCO_3$). The usual commercial form of ammonium carbonate contains about 50 mole percent carbamate (Snell and Hilton, 1966; Wilson et al., 1968; Sclar and Carrison, 1963; DAB9, 1986).

Ammonium bicarbonate has the following chemical and physical properties:



molecular weight:	79.06
mp:	107.5°C
volatile with decomp.:	60°
soluble:	water
insoluble:	alcohol, acetone

Ammonium bicarbonate is prepared as a shiny, hard, colorless or white, prismatic or crystalline, mass (Windholz, 1976). It is synthesized by the counter current absorption of carbon dioxide in an aqueous ammonia solution. The crystalline salt precipitates as the saturation of the solution occurs, and the crystals are filtered off. The resultant salt slurry is centrifuged, dried, cooled, and crystallized (Snell and Hilton, 1966; Ullmann, 1974).

Ammonium bicarbonate is used by the tobacco industry as a flavorant. During the nicotine extraction process, an aqueous solution of ammonium bicarbonate is sprayed on the tobacco. This pretreatment process makes the resulting tobacco less harsh than non-pretreated tobacco. In this

process, ammonium bicarbonate can be applied at 1-3 percent of the dry weight of tobacco (mass/mass) (Grubbs et al., 1987). An aqueous solution of about 5 percent ammonium bicarbonate is used in the production of smoking material made of expanded carboxymethyl starch and powdered tobacco (Battard, 1985), and there is a patent for its use in the tobacco swelling process (Armstrong et al., 1972).

Ammonium bicarbonate was recognized by the FDA as GRAS in the 1950's. FDA has since affirmed the ingredient's GRAS status for multiple uses as a food ingredient, dough strengthener, leavening agent, pH control agent, and texturizer to be used at levels not to exceed good manufacturing practice (21 C.F.R. § 184.1135 (1991); 48 Fed. Reg. 52438, 52439 (1983); Kilgore and Li, 1980). Ammonium bicarbonate also is permitted for use in cocoa products (21 CFR Part 163). The cocoa fraction maximum use level for the manufacture of cocoa and chocolate products is 50 g/kg, when used alone or with hydroxides, other hydrogen carbonates, or carbonates (Codex Alimentarius).

Ammonium carbamate, which decomposes below pH 10 to ammonium carbonate and ammonium bicarbonate (Wilson et al., 1968), is permitted for use as an additive for snuff and for white snuff powder under the German Tobacco Ordinance (Tabakverodnung, 1990). Ammonium carbonate, which in usual commercial form consists of about 50 mole percent carbamate and 50 mole percent bicarbonate, is approved for use as a

tobacco additive at a 4 percent maximum inclusion level in the United Kingdom (Fourth Report of the Independent Scientific Committee on Smoking & Health, 1988). In addition, carbonates are permitted for use in tobacco in Spain (Codigo Alimentario, 1985). Ammonium salts are approved for use in foods by many countries. In Belgium and France, ammonium salts of carbonic acid are permitted substances for tobacco and all tobacco products (Arrête Royal of December 28, 1979 and Decree of November 23, 1978, respectively).

II. Use in Tobacco.

A. Function. Ammonium bicarbonate is used by the tobacco industry as a flavorant during the nicotine extraction process, making the resulting tobacco less harsh than non-treated tobacco.

B. Use Level. Information on the levels of ammonium bicarbonate in commercially available tobacco products was not found in the available literature. The Industry maximum use level for ammonium bicarbonate is less than 1 ppm.

III. Chemistry & Pyrolysis. Ammonium bicarbonate was tested at a 5 percent level in 1R1 tobacco for its ability to alter the chemical composition of cigarette smoke. The concentrations of selected smoke components were compared with smoke components from untreated 1R1 cigarettes. The results for TPM and tar were reported on a per gram of tobacco burned

basis. Results for other smoke components were presented as the change in percent composition of the treated tobacco smoke components as compared to the untreated tobacco smoke components. For TPM, tar, and nicotine, no significant changes were observed. The phenol content of smoke was 16 percent higher, while the content of o-cresol, m- and p-cresol, and B(a)P were reduced to 57 percent, 89 percent, and 62 percent, respectively, compared to the smoke composition of untreated 1R1 cigarettes (Burton and Benner, 1972).

IV. Toxicology

A. Metabolism. Ammonia and ammonium ion are integral components of normal metabolic processes and play an essential role in the physiology of man and other species (Windholz, 1976; Coulson and Hernandez, 1955).

B. Acute Human Toxicity. In a study by Moeschlin (1980), a 1-2 percent aqueous solution of ammonium carbonate led to weak ammonium poisoning in children (30 g for a two-year old child) and to some fatalities in infants. Single cases also were reported in which unknown oral doses of ammonium carbonate led to severe poisoning or fatality, even in adults (Wirth et al., 1967; Lewin, 1962).

C. Chronic Animal Studies. No published studies on the chronic toxicity of ammonium bicarbonate were found. Pursuant to the FDA's review of food ingredients classified as GRAS, however, the Select Committee on GRAS Substances

reviewed those studies relevant to the oral toxicity of ammonium compounds. According to a summary of the information from the Select Committee report, no evidence of tumor formation was found after feeding female rabbits ammonium carbonate, chloride, hydroxide, and sulfate in doses up to 700 mg/kg body weight for 5 to 16 months. 43 Fed. Reg. 14064, 14066 (1978).

D. Acute & Subchronic Animal Studies. In mice, the LD_{50} of intravenously injected ammonium bicarbonate was 3.10 ± 0.2 mmol/kg (approx. 245 mg/kg) (Wilson et al., 1968). In rats, intraperitoneal injection of 10.6 mmol (approx. 838 mg/kg) ammonium bicarbonate led to a more than 130 percent increase of glutaminase I and a more than 50 percent decrease of glutamine in the liver (Petit et al., 1974). In freeze-clamped kidneys of fasted rats, a single intraperitoneal injection of 2.5 mmol of NH_4HCO_3/kg (approx. 198 mg/kg) body weight resulted in a 29 percent decrease in the tissue concentration of 2-oxoglutarate and a slight increase in the tissue concentration of glutamine. A constant infusion of NH_4HCO_3 over 60 minutes at a rate of 15 mmol/min (approx. 1.2 mg/min) produced a similar result, with a significant increase in tissue glutamine content and renal vein glutamine concentration (Vinay et al., 1978).

In cats, an intravenous injection of 0.8 mmol/kg (approx. 63 mg) ammonium bicarbonate produced electro-encephalographic changes, which were reversible within 30

minutes (Watanabe, 1978). In anesthetized dogs with a mean weight of 17.5 kg, a 15 minute infusion of 13 mmol (approx. 1.03 g) ammonium bicarbonate slightly increased the oxygen consumption by the brain, which persisted during the following 30 minutes, and largely increased glucose utilization by the brain, which returned to control values after the infusion was turned off (James et al., 1974).

In the previously cited Wilson study, the LD_{50} of intravenously administered ammonium carbonate ($(NH_4)_2CO_3$) for mice was 0.99 ± 0.14 mmol/kg (approx. 95 mg/kg). The LD_{50} of ammonium carbamate ($NH_2CO_2NH_4$), administered by the same route, was determined to be 1.02-0.11 mmol/kg (approx. 80 mg/kg) for mice, dogs, and sheep. One mole of ammonium carbamate contained two moles of ammonia, whereas one mole of ammonium bicarbonate contained only one mole of ammonium. It was concluded that the ammonium carbonate would be at least twice as toxic as ammonium bicarbonate (Wilson et al., 1968).

No published studies on the subchronic toxicity of ammonium bicarbonate were found. However, up to 3 g/100 g basal diet of ammonium carbonate was given to male chicks in a 14-day feeding study without any effect. The same study found that ammonium was more toxic as the sulphate than as the carbonate salt (Sibbald and Cave, 1976). It is not known whether there is any difference in subchronic toxicity between ammonium as the carbonate salt or bicarbonate salt; moreover,

the amount of carbonate converted or previously converted to bicarbonate before feeding is not known.

E. Genotoxicity & Mutagenicity. Ammonium bicarbonate was evaluated in Salmonella typhimurium strains TA92, TA1535, TA100, TA1537, TA94, and TA98 with and without metabolic activation; no mutagenic activity was observed. In vitro chromosomal aberration tests using a Chinese hamster fibroblast cell line, without any metabolic activation system were also negative for mutagenic activity (Ishidate et al., 1984).

In another study, ammonium bicarbonate toxicity was assessed in Saccharomyces cerevisiae (strain-D4) and in S. typhimurium (strains TA1535, TA1537, TA1538, TA98, and TA100), with and without microsomes from the liver and lungs of the mouse, rat, and monkey. Ammonium bicarbonate was not active in any assay (Litton Bionetics, 1977).

F. Reproductive Toxicity & Teratology. Ammonium bicarbonate is one of the most common ingredients in cough mixtures. In Australia, cough medicine was suspected to be associated with a higher rate of congenital anomalies when used by women during their entire pregnancy (Nelson and Forfar, 1971). However, another study reexamined the use of cough mixtures containing ammonium bicarbonate by pregnant women and did not find any statistically significant association between the maternal use and adverse neonatal outcomes (Colley et al., 1982).

No published animal studies on the reproductive/ teratologic toxicity of ammonium bicarbonate were found.

References

Anonymous (1985), China: the way forward, Nitrogen, February: 20-24

Armstrong, R.G., Deszyck, E.J., Madures, J.W., Young, R.H. (inventors), Philip Morris Inc. (assignee) (1972): Tabakprodukt und seine Herstellung, German Offenlegungsschrift 2, 143, 388, März, 9, p 22, Int. CL.: A 24 b, 15/04.

Arrêté royal (28 décembre 1979) relatif à la fabrication et à la mise dans le commerce de tabac, de produits à base de tabac et de produits similaires, amendé le 3 mars 1981, le 8 mai 1982 et le 20 décembre 1982. (tiré de "Législation alimentaire" janvier 1983).

Battard, J.C. (inventor), Societé Nationale d'Exploitation Industrielle des Tabacs et Allumettes (assignee) (1985): Procédé de fabrication d'un matérieau à fumer et matériau à fumer, European Patent, Application 0 208 566, p 13, Int. Cl4: A 24 B 3/14, 15/4.

Burton, H.R., Benner, J.F. (1972), Investigations on the effect of chemical modifiers on tobacco and tobacco smoke, Tob. Health Workshop Conf., 3: 341-364.

21 Code of Federal Regulations (1991).

Codex Alimentarius Commission, Codex Alimentarius, Vol. 14., Food Additives, p 378.

Codigo Alimentario (1985), Tercera Parte, Capitulo XXV, Seccion 8: Tabaco, Boletin Oficial del Estado, 4th Edition, Madrid.

Colley, D.P., Kay, J., Gibson, G.T. (1982), Three common Australian cough mixtures: a study of their use in pregnancy, Aust. J. Pharm., 63: 213-217.

Coulson, R.A., Hernandez, T. (1955), Renal excretion of carbon dioxide and ammonia by the alligator, Proc. Soc. Exp. Biol. Med., 88: 682-687.

DAB9 (1986), Deutsches Arzneibuch 9, Ausgabe, Amtliche Ausgabe, Stuttgart: Deutscher Apotheker Verlag, Frankfurt: Govi-Verlag GmbH, p 195.

Décret no. 78-1108 (23 novembre 1978) Pris pour l'application de la loi du 1er août 1965 sur les fraudes et falsification en matiére de produits on de services en ce qui concerne le tabac, les produits du tabac et leurs succédanés,

Ammonium bicarbonate, ammonium chloride, ammonium carbonate, ammonium hydroxide, and mono- and dibasic ammonium phosphate. Proposed affirmation of GRAS status as human food ingredients; 43 Fed. Reg. 14064 (1978).

Affirmation of GRAS status of human food ingredients; 48 Fed. Reg. 52438 (1983).

Fourth Report of the Independent Scientific Committee on Smoking & Health: Her Majesty's Stationery Office (1988), ISBN 0 11 321131 7.

Grubbs, H.J., Prasad, R., Howell, T.M. (inventors), Philip Morris Products Inc. (assignee) (1987): Process for the removal of basic materials from plant products. European Patent Application 0 280 817, p 24, Inc. Cl.4 A24B 15/24.

Hofmann, K.A., Hofmann, U.R.(eds.) (1945), Anorganische Chemie, Braunschweig: Friedr. Vieweg & Sohn.

Ishidate, M., Sofuni, T., Yoshikawa, K., Hayashi, M., Nohmi, T., Sawada, M., and Matsuoka, A. (1984), Primary mutagenicity screening of food additives currently used in Japan, Fd. Chem. Toxic., 8(22): 623-636.

James, I.M., Macdonnell, L., Xanalatos, C. (1974), Effect of ammonium salts on brain metabolism, J. Neurol. Neurosurg. Psychiat., 37: 948-953.

Kilgore, W.W., Li, M.Y. (1980), Food additives and contaminants, Casarett and Doull's Toxicology: The Basic Science of Poisons, Doull, J., Klaassen, C.D., Amdur, M.O. (eds.), Macmillan Publishing Co., Inc., New York, pp 593-607.

Lewin, L. (ed.) (1962), Gifte und Vergiftungen, Ulm: Karl F. Haug Verlag.

List, P.H., Hörhammer, L. (eds.) (1972), Hagers Handbuch der pharmazeutischen Praxis für Apotheker, Arzneimittelhersteller, Arzte und Medizinalbeamte, Berlin, Heidelberg, New York: Springer Verlag.

Litton Bionetics (1977), Mutagenicity evaluation of FDA 75-85 Ammonium bicarbonate, NTIS Order Number: PB-278 462/7, Litton Bionetics, Inc., Springfield, Va.

Moeschlin, S. (ed.) (1980), Klinik und Therapie der Vergiftungen, Stuttgart, New York: Georg Thieme Verlag.

Nelson, M.M., Forfar, J.D. (1971), Associations between drugs administered during pregnancy and congenital abnormalities of the fetus, Br. Med. J., 1: 525.

Petit, M.A., Nordmann, J., Nordmann, R. (1974), Modifications des enzymes du métabolisme hépatique de la glutamine et du glatamate après administration de sels d'ammonium, Biochimie, 56: 1155-1156.

Sclar, C.B., Carrison, L.C. (1963), Phase composition of commercial "Ammonium Carbonate", Science, 140: 1205-1207.

Sibbald, I.R., Cave, N.A. (1976), The responses of chicks to ammonium, calcium, magnesium, potassium and sodium sulphates and to ammonium and potassium carbonates, Poult. Sci., 55(6): 2209-2213.

Snell, Hilton (1966), Ammonium bicarbonate, Encyclopedia of Industrial Chemical Analysis, New York, Interscience Vol. 5: 327-331.

Beck, C.H. (1990), Verordnung über Tabakerzeugnisse (Tabakverordnung) vom 20. Dez. 1977, Lebensmittelrecht, Bundesgesetze und-verordnungen über Lebensmittel und Bedrafsgegenstände, Band II, München.

Ullmann (1974), Ullmanns Encyklopädie der technischen Chemie, Weinheim: Verlag Chemie.

Vinay, P., Lemieux, G., and Gougoux, A. (1978), Ammonia detoxification by the rat kidney in vivo, Can. J. Biochem., 56: 305-314.

Watanabe, K. (1978), Electroencephalographic study on enhancing effect of blood gas abnormalities on ammonia toxicity, Acta Schol. Med. Univ. Gifu, 26: 334-360.

Wilson, R.P., Davis, L.E., Muhrer, M.E., and Bloomfield, R.A. (1968), Toxicologic effects of ammonium carbamate and related compounds, Am. J. Vet. Res., 29: 897-906.

Windholz, M. (1976), The Merck Index, 9th edition, Rahway: Merck & Co.

Wirth, W., Hecht, G., and Gloxhuber, C. (eds.) (1967), Toxikologie-Fibel für Ärzte, Naturwissenschaftler, Juristen und Studierende, Stuttgart: Georg Thieme Verlag.