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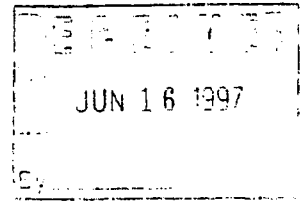
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Date: ~~April 8, 1997~~ June 13, 1997

To: Mr. Hugh Hanes

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From: George Cruzan, Ph.D., D.A.B.T.

Subject: Recent Articles of Relevance to Beryllium

Enclosed are abstracts of two review article from Critical Reviews in Toxicology which indicate that sulfuric acid mist does not cause cancer in animals and there is insufficient evidence to conclude it causes lung tumors in humans. This raises questions regarding the role of sulfuric acid mist in lung cancer incidence at Lorain plant.

An article on *in vitro* reaction of beryllium with blood cells. The significance is hard to determine since we have no data relating airborne exposure to blood levels.

NGK-IL-B 06760

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*Critical Reviews in Toxicology*, 27(3):233-251 (1997)

## Epidemiologic Evidence on the Relationship between Mists Containing Sulfuric Acid and Respiratory Tract Cancer

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**KEY WORDS:** sulfuric acid, larynx cancer, lung cancer, nasal and other respiratory cancer.

**ABSTRACT:** This review identified and evaluated 25 epidemiologic studies pertaining to the carcinogenicity of mists containing sulfuric acid (MSA). Few studies were designed with acid mists as the principal exposure under investigation, and in all studies exposure assessment was limited. The results of the follow-up studies from industries with high or moderate exposure potential and the case-control studies indicate, in aggregate, a moderate association between MSA and larynx cancer. The data suggest a dose-response relationship. However, many of the results from individual studies are imprecise, and confounding by smoking, alcohol, and other occupational agents is not adequately adjusted for. The biologic plausibility and the possible carcinogenic mechanism remain uncertain. There is little evidence in support of a causal relationship between exposure to MSA and lung cancer. Information is inadequate for drawing any meaningful inference about the association between exposure to MSA and nasal cancer.

### I. INTRODUCTION

Strong inorganic acids, such as sulfuric, hydrochloric, nitric and phosphoric acids, are used in a variety of industries. Sulfuric acid is the most widely used of the strong inorganic acids.<sup>1</sup> Because of their low volatility and their affinity for water, strong inorganic acids tend to exist in the work place primarily as mists. The term "mist" refers to a liquid aerosol formed by the atomization of a liquid or by condensation of a vapor.<sup>2</sup> Mists containing strong inorganic acids tend to be widespread within the work environments where they are used or manufactured.

Several epidemiologic studies have been conducted among workers with potential exposure to strong inorganic acids. Some of these studies have reported excesses of certain respiratory tract cancers (nasal cavity, nasal sinuses, larynx, and lung). In addition, the studies have reported mists con-

taining sulfuric acid (MSA) as the common exposure. The International Agency for Research on Cancer (IARC) evaluated industrial processes using or manufacturing strong inorganic acids and judged that "Occupational exposure to strong inorganic acid mists containing sulfuric acid is carcinogenic to humans" (Group 1).<sup>3</sup> Apart from the IARC review, no comprehensive, in-depth assessment of the epidemiologic literature pertaining to the potential carcinogenicity of MSA has been published. The purpose of this review is to evaluate critically all epidemiologic studies pertaining to the possible relation between exposure to MSA and the occurrence of cancer, in particular cancer of the respiratory tract.

The specific type of strong inorganic acid mist exposure differs by industry. Exposure to MSA alone occurs in sulfuric acid, isopropanol, soap, detergent, ethanol, and lead battery production and in copper and zinc refining. Exposure to mists con-

## A Review of the Chronic Toxicity, Carcinogenicity, and Possible Mechanisms of Action of Inorganic Acid Mists in Animals

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**ABSTRACT:** Occupational exposure to inorganic acid mists containing sulfuric acid has been associated with increased laryngeal cancer. The primary objective of this review was to compile the literature regarding chronic toxicity and carcinogenicity of inorganic acid mists in laboratory animals. Several chronic toxicity studies had exposures of 1 year or longer. Whereas numbers of animals were limited, no evidence of neoplastic or preneoplastic lesions was reported. Two studies evaluated the carcinogenicity of inorganic acid mists in rats; however, one was limited by a short duration of exposure and the other did not achieve a maximum tolerated dose. A large lifetime study in hamsters evaluated the carcinogenicity of 100 mg/M<sup>3</sup> sulfuric acid mist, as well as its ability to act as a promoter or co-carcinogen for benzo(a)pyrene. No evidence of carcinogenic potential was shown. Although an increase in papillomas was noted in the benzo(a)pyrene + H<sub>2</sub>SO<sub>4</sub> group, the co-carcinogenic or promoting potential was considered equivocal. Thus, no evidence from experimental animals strongly supports or refutes the induction of cancer by inorganic acid mists. A possible mechanism that could be associated with inorganic acid mist carcinogenicity relates to the genetic consequences of lowering the pH. Reduced pH can induce chromosomal aberrations, enhance depurination, and deamination of cytosine in DNA. This mechanism has not been evaluated in tissues of the respiratory tract.

**KEY WORDS:** sulfuric acid, neoplasms, hamsters, rats, promotion, co-carcinogenesis

### I. INTRODUCTION

The carcinogenic potential of occupational exposure to inorganic acid mists containing sulfuric acid has been reviewed recently by the International Agency for Research on Cancer<sup>1</sup> and by Sathakumar et al.<sup>2</sup> An association has been seen in several cohort and case control studies between cancer of the larynx and use of inorganic acids in the work place. This has led to the suggestion of a possible causal link between inorganic acid mists and cancer of the larynx, although confounding due to cigarette smoking and alcohol consumption could not be ruled out, and exposure to acid mists was not measured in some critical studies. Much less evidence is available that supports a causal role of inorganic acid mists in the induction of lung or nasal cancer.

Ordinarily, information on the carcinogenicity of chemicals in experimental animals plays an important role in identifying potential human carcinogens and in addressing dose-response relationships. Genotoxic chemicals that are multisite, multispecies, and multisex carcinogens provide the greatest probability of being human carcinogens. In contrast, those agents that are nongenotoxic and only induce tumors at a single site in one sex of one species have the least probability of being a human carcinogen. The IARC Monograph on inorganic acid mists was unusual in that no animal data were considered by the Working Group to assist in their evaluation of the carcinogenic potential of inorganic acid mists.<sup>1</sup> The objective of this review was to determine if any reports on chronic toxicity and carcinogenicity are available, whether such reports provide sup-

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## Toxicological Effects of Beryllium on Platelets and Vascular Endothelium

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**Toxicological Effects of Beryllium on Platelets and Vascular Endothelium.** Togna, G., Togna, A. R., Russo, P., and Caprino, L. (1997). *Toxicol. Appl. Pharmacol.* 144, 262-267.

Although ample research has described the toxic effects of the metal beryllium on the respiratory apparatus, less is known about its effects on the vascular apparatus, including pulmonary blood vessels. We investigated the *in vitro* effects of beryllium on endothelial vascular adenosine diphosphatase activity and prostacyclin production in bovine aortic endothelium, and on nitric oxide release in isolated rabbit arteries. Rabbit and human platelet responsiveness was also evaluated. Beryllium inhibited vascular endothelial adenosine diphosphatase activity, prostacyclin production, and nitric oxide release, thus inducing functional alterations in vascular endothelial cells. It also induced platelet hyperreactivity to arachidonic acid, as shown by a lowering of the threshold of aggregating concentration and by concurrently increasing thromboxane production. In contrast, beryllium left the response to aggregating and nonaggregating concentrations of ADP and collagen unchanged. These findings show that beryllium may impair some vascular endothelial functions and alter the interaction between platelet and endothelial mediators. © 1997 Academic Press

On account of its chemical and metallurgical qualities, the metal beryllium (Be) is widely used in industrial processes (Pruess, 1986). Be and many of its compounds have long been recognized as among the most toxic substances (Tepper *et al.*, 1961; Krejer and Scheel, 1966).

Toxicological data in animals (Sanders *et al.*, 1975; Sendelbach *et al.*, 1986; Haley *et al.*, 1990) and epidemiological studies in humans (Stoeckle *et al.*, 1969; Freiman and Hardy, 1970; Wagoner *et al.*, 1980; Steenland and Ward, 1991; Pappas and Newman, 1993) clearly show that Be induces pulmonary toxic effects, including acute chemical pneumonitis, chronic interstitial granulomatosis, and pulmonary fibrosis. As yet, scarce information is available on the possible effects of Be on pulmonary blood vessels or even on vascular apparatus, whether in animals or humans. In regard to this aspect, only pathological changes such as edema, intra-alveolar hemorrhage, and capillary damage are described in Be-exposed rats (Sendelbach *et al.*, 1986; Haley *et al.*, 1990).

These changes, however, are sufficient to justify the hypothesis of an involvement of vascular vessel walls and platelets.

We undertook this study to investigate whether Be impairs vascular endothelial functions, such as adenosine diphosphatase (ADPase) activity and the release of endothelium-derived vasoactive factors (prostacyclin, PGI<sub>2</sub>, and nitric oxide, NO), and whether it affects platelet reactivity to various agonists.

### MATERIALS AND METHODS

#### Materials

The following substances were used: beryllium chloride, phenylephrine hydrochloride, sodium nitroprusside, arachidonic acid (Fluka Chemie), acetylcholine chloride, calcium chloride, calcium ionophore A23187, ADP trisodium citrate dihydrate (Sigma Chemicals Co., St. Louis, MO); collagen (Menarini, cod. D1110, Florence, Italy); [<sup>3</sup>H]TXB<sub>2</sub> (140 Ci/mmol) and [<sup>3</sup>H]6-keto PGF<sub>1α</sub> (168 Ci/mmol) (New England Nuclear, Boston, MA). Concentrations of beryllium chloride (BeCl<sub>2</sub>) are expressed in terms of Be.

#### Experimental Protocols: 1. Vascular Wall Functions

Bovine thoracic aorta segments (about 25 cm) of descending part were used to assess vascular ADPase activity and vascular PGI<sub>2</sub> production. Thoracic rabbit aorta segments were used to assess vascular reactivity to endothelium-dependent and -independent relaxing agents.

**Endothelial ADPase activity.** ADPase activity was evaluated by measuring the degradation rate of exogenous ADP incubated with aortic bovine endothelium, according to the method previously described (Caprino *et al.*, 1996). In brief, bovine aorta segments, obtained from adult male animals, butchered in a local slaughterhouse, were sectioned longitudinally and then placed with the luminal surface facing upward in a Plexiglas device containing eight wells. The endothelial surface exposed in each well (450 mm<sup>2</sup>) was incubated for 1 hr at room temperature with 3 ml of 50 mM Tris-HCl solution, pH 7.6, or Tris-HCl solution containing Be, at concentrations ranging from 1.25 to 10 μg/ml. At the end of the incubation period 25 μM of ADP was added to each well, and the Plexiglas device was shaken lightly. After 5, 20, and 40 min, 0.9 ml of incubation medium was withdrawn and residual ADP measured by the method reported by Jaworski *et al.* (1974), with slight modifications (Caprino *et al.*, 1996). In each device, five wells were filled with the same Be concentration; the remaining three wells (Be-free) were used as controls. Five bovine aorta segments were used for each Be concentration.

Blank trials, without aorta patch, were run under the same experimental conditions (device, incubation times, amount of exogenous ADP), and ADP was measured in medium-filled wells in the presence or absence of Be.

