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# Bromate-induced ototoxicity

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**Abstract**

For decades, it has been known that ingested potassium bromate and sodium bromate can induce hearing loss. Hearing loss onset, following high-dose ingestion, is generally rapid occurring within 4–16 h and of a severe to profound degree. Unlike the sensorineural hearing loss which is generally irreversible, bromate-induced tinnitus, which is less well-studied, may reportedly be permanent or temporary. It is not clear whether actual bromate-induced vestibulotoxicity occurs in clinical populations. The primary sites of lesion for bromate-induced ototoxicity appear to be in the cochlea. However, possible effects on the VIIIth nerve and central auditory system have not been fully investigated. Based on animal studies, in the cochlea, bromate damages the stria vascularis, Reissner's membrane, inner and outer hair cells, Claudius cells and inner sulcus cells. Physiologically, bromate reduces the endocochlear potential, cochlear microphonics, and electrophysiologic auditory thresholds. Possible mechanisms are discussed.

The effects of long-term low-dose bromate exposure on hearing have not been studied. These effects, if they occur, may not be readily detected in many clinical populations, because idiopathic hearing loss occurs commonly in the population as a whole. Further it is unknown whether or not chronic bromate ingestion may exacerbate noise-induced hearing loss. Further study to determine the maximum safe exposure level for long-term administration and to develop possible antidotes is warranted.


*Keywords:* Ototoxicity; Bromate; Bromide; Hearing; Auditory

## 1. Introduction

Bromate-induced ototoxicity has been reported in the literature primarily as a consequence of patients ingesting permanent wave neutralizer containing potassium bromate ($KBrO_3$) (Higo, 1957; Matsumoto et al., 1980; Gradus et al., 1984; De Vriese et al., 1997) or sodium bromate ($NaBrO_3$) (Kotum et al., 1990; Sashiyama et al., 2002). Potassium bromate, which has no color, taste, or odor, has also been used historically as a flour additive (American Industrial Hygiene Association, 1981). However, $KBrO_3$ is largely converted to potassium bromide in the baking process (Kurokawa et al., 1990) thus reducing its toxicity. Although most reports of bromate-induced ototoxicity are the result of either $KBrO_3$ or $NaBrO_3$ ingestion, Deshimaru et al. (1976) reported a case of ototoxicity secondary to ingestion of a combination of $KBrO_3$ and sodium bromate ($NaBrO_3$). $KBrO_3$ has been reported to be more toxic than $NaBrO_3$ (Quick et al., 1975; Matsumoto et al., 1980).

Reports describe a range of ages including children who accidentally ingest permanent wave neutralizer (Gradus et al., 1984) or potassium bromate pellets (Quick et al., 1975) to adults attempting suicide with permanent wave solution or other form of bromate (Deshimaru et al., 1976). Acute effects of bromate toxicity include nausea (Gradus et al., 1984), vomiting (Gradus et al., 1984), diarrhea (Gradus et al., 1984; Matsumoto et al., 1980;

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De Vriese et al., 1997), abdominal pain (Matsumoto et al., 1980; De Vriese et al., 1997), peripheral neuropathy (Deshimaru et al., 1976), anemia and hemolysis (De Vriese et al., 1997; Sashiyama et al., 2002) hypotension (Gradus et al., 1984; Matsumoto et al., 1980) renal insufficiency or failure (Deshimaru et al., 1976; Matsumoto et al., 1980; Gradus et al., 1984; De Vriese et al., 1997) and central nervous system dysfunction including seizures, lethargy, drowsiness and irritability (Matsumoto et al., 1980; De Vriese et al., 1997). Evaluation of hearing is sometimes delayed in light of the other more obvious and sometimes life threatening symptoms (Gradus et al., 1984), which generally have an onset within 1 h of ingestion (Mack, 1988). Deaths secondary to bromate toxicity have been reported with oral lethal doses of $KBrO_3$ of 200–500 mg/kg (Mack, 1988).

## 2. Characteristics of clinical bromate-induced hearing loss

The actual onset of clinical high-dose bromate-induced ototoxic hearing loss is rapid, and occurs within 4–16 h after ingestion (Matsumoto et al., 1980). The hearing losses reported were invariably sensorineural with no reports of outer or middle ear involvement (Matsumoto et al., 1980; Gradus et al., 1984; Kotum et al., 1990; De Vriese et al., 1997; Sashiyama et al., 2002) as is typical for many ototoxins (Morata et al., 1994; Mattsson, 2000; Campbell, 2004; Rybak et al., 2006). When ototoxic hearing loss is reported, it is generally of a severe to profound degree (Quick et al., 1975; Matsumoto et al., 1980, Kamata et al., 1983; Gradus et al., 1984; De Vriese et al., 1997). The issue of whether or not delayed or progressive hearing loss occurs has not been well-explored in the literature. Most reports have not described audiometric configuration although Kamata et al. (1983) reported sloping severe to profound sensorineural hearing loss most pronounced in the mid to high frequency regions. Additionally no studies have fully investigated the effects of low-dose long-term exposure in human or animal studies.

The incidence of bromate-induced ototoxic hearing loss is not known. As reviewed by Gradus et al. (1984), hearing loss was either not assessed or not reported in many pediatric case reports. When hearing was assessed, Matsumoto et al. (1980) reported deafness to occur within 4–6 h of ingestion in 21 of 24 adult cases. De Vriese et al. (1997) reviewed published reports from 1947 to 1997, including the Matsumoto et al. (1980) study. They reported confirmed "deafness" in 2 of 9 pediatric and 23 of 27 adult cases in which hearing status was reported with no apparently no hearing loss assessment in 12 pediatric cases. Lichtenberg et al. (1989) reported an additional case in which a 23 month old child had normal hearing following a near lethal bromate poisoning. Thus, which patients will have permanent bromate-induced ototoxicity cannot be easily predicted on the basis of other symptoms and findings. Warshaw and Carter (1985) reported three pediatric cases: one had formal audiologic testing with normal findings; one was lost to follow-up and another apparently had no formal testing but his mother reported apparently normal speech and hearing 11 months later. In some pediatric cases the standard for normal hearing and the methods to assess hearing were not described, but "no apparent hearing loss" was reported (Lue et al., 1988; Warshaw and Carter, 1985). Hearing assessment in ill and/or very young children, particularly before the advent of reliable electrophysiologic measures and otoacoustic emissions, was frequently problematic. Hearing loss in children is frequently not clinically obvious.

Bromate-induced hearing loss appears to be irreversible although some treatment regimens have been shown to be effective in reducing bromate's other toxic effects. The onset of ototoxicity can be very rapid, possibly complete within 24 h (Matsumoto et al., 1980; Warshaw and Carter, 1985). Consequently effective, timely, treatment may be difficult. In many reports, the time when hearing tests were first performed relative to the exposure and the time course of the hearing loss was frequently not reported so the efficacy of any intervention, if any, may be difficult to ascertain. In the initial stages of bromate-induced ototoxicity, the patient may be so ill that auditory testing is not the primary concern while lifesaving measures are performed. Additionally the patient state (e.g. vomiting, unresponsiveness) may preclude behavioral auditory testing or even auditory electrophysiologic testing at some time points. Currently, there are no well-documented reports in the clinical literature of the exact time course of bromate-induced ototoxicity.

A number of therapeutic regimens for bromate's other toxicities have been reported including: dialysis, demulcent drinks (e.g. milk or flour water) (Gradus et al., 1984), administration of emetics and gastric lavage (Gradus et al., 1984; Warshaw and Carter, 1985), hemodialysis or peritoneal lavage or dialysis (Quick et al., 1975; Gradus et al., 1984; Warshaw and Carter, 1985; De Vriese et al., 1997; Sashiyama et al., 2002), active charcoal (Warshaw and Carter, 1985; De Vriese et al., 1997), and sodium thiosulfate (Gradus et al., 1984; Warshaw and Carter, 1985; Lue et al., 1988; Lichtenberg et al., 1989). Oral sodium thiosulfate is no longer recommended because it may exacerbate the condition (De Vriese et al., 1997).