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Acute Toxicity of Cesium and Rubidium Compounds

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Acute Toxicity of Cesium and Rubidium Compounds. JOHNSON, G. T., LEWIS, T. R. AND WAGNER, W. D. (1975). *Toxicol. Appl. Pharmacol.* **32**, 239–245. Primary skin and eye irritation (rabbit), cutaneous sensitization (guinea pig), and po LD50 (rat) studies were conducted on the hydroxides of cesium, rubidium, and potassium and the iodides of cesium and rubidium. The hydroxides of cesium and rubidium were markedly more toxic than the iodides. The order of po toxicity of the hydroxides was potassium > rubidium > cesium; cesium iodide was more toxic than rubidium iodide. Potassium hydroxide was irritating to both intact and abraded skin, whereas cesium and rubidium hydroxide were irritating only to abraded skin. The iodides of cesium and rubidium did not affect the eye or skin. It was concluded that personal protective equipment and clothing should be worn when working with cesium, rubidium, or potassium hydroxides. These studies indicate that cesium and rubidium are only slightly toxic on an acute toxicologic basis and would pose an acute health hazard only when ingested in large quantities.

Cesium and rubidium compounds have a wide range of industrial applications because of their reactivity, crystallographic properties, and high solubilities. Various forms have been utilized in pharmaceuticals, photomultiplier tubes, photoelectric cells, spectrophotometers, scintillation counters, infrared lamps, semiconductors, vacuum tubes, and photographic emulsions. Thus, the production and handling of cesium and rubidium is growing commensurate with the increase in industrial applications.

In the course of production of cesium and rubidium compounds, the working environment may become contaminated. Sources of occupational health hazards may occur during the ore pulverization and concentration processes, the production of one compound from another, handling and packaging of the materials, and industrial utilization. However, data on the acute toxicity of cesium and rubidium compounds are sparse. It is, therefore, essential to obtain data on the toxicity of representative compounds of commercial concern in order to ascertain what health hazards are associated with their industrial uses.

Cochran *et al.* (1950), employing rats, determined the ip LD50 of five cesium compounds—cesium chloride, cesium hydroxide, cesium bromide, cesium iodide, and cesium nitrate. Each of the compounds tested, with the exception of the hydroxide, was of low toxicity.

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Khosid (1967), employing mice, determined the po LD50 of cesium chloride (2300 mg/kg), of rubidium chloride (3800 mg/kg), of cesium hydroxide (800 mg/kg), and of rubidium hydroxide (900 mg/kg).

The present study describes the acute toxicity of cesium hydroxide and iodide, rubidium hydroxide and iodide, potassium hydroxide, and a mixture of 50% cesium hydroxide and 50% potassium hydroxide (w/w) for three routes of potential industrial exposure, i.e., cutaneous, oral, and ocular.

METHODS

The following hydroxides and iodides of cesium, rubidium, and potassium were studied: (1) CsOH; (2) 50% CsOH and 50% KOH mixture; (3) KOH; (4) RbOH; (5) CsI; and (6) RbI. All test materials, with the exception of KOH, were identified by the manufacturer as "high purity" in excess of 99%. The potassium hydroxide was labeled "85% pure." These results are reported on the basis of 100% purity. All the test materials were dissolved in deionized–distilled water on a weight-to-volume basis prior to administration by the various routes.

In rat oral LD50 studies, the test materials were administered by gastric intubation as a single dose. The experimental subjects were male, Charles River, cesarean-derived, albino rats weighing 175–250 g that were fasted overnight. The 14-day survival po LD50 values and their 95% confidence limits were calculated by the probit analysis of Finney (1971).

Skin Irritation

In the primary skin irritation studies, the six test materials and the negative (distilled water) and positive (5% HCl) control compounds were tested on three groups of six albino rabbits, each group receiving two of the six compounds at 5% concentrations plus the two control compounds. For each test and control material, there were two skin test sites, one abraded and one intact. A 0.1-ml vol of the test and control compounds was applied to each of the test sites. The test sites were covered with a gauze patch measuring 20 mm^2. Each animal was provided with a leather harness to prevent the animal from disturbing the test sites (Newmann, 1963). After 24 hr of exposure, the harnesses and patches were removed and the skin reactions evaluated; a second evaluation was performed 48 hr after administration of the compounds. The technique employed for determining the degree of primary skin irritation was a modification of the Draize technique (1944).

Eye Irritation

Albino rabbits, weighing 2–3 kg, were used in the eye irritation studies. A 0.1-ml vol of the test materials at various concentrations (0.1, 0.5, 1.0, and 5.0%) was placed in one eye of each animal by pulling the lower lid of the eyeball to form a cup into which the compounds under investigation were instilled. The eyelids were held together for approximately 1 sec and the animal was then released. The animals were exposed to the test compound for either 5 min or 24 hr before washing the eye with approximately 300 ml of distilled water instilled over a 2-min period. The eyes were examined with the aid of fluorescein but without the aid of a hand slit-lamp at 1, 24, 48, and 72 hr

and at 7 days; if any injury persisted, the eyes were reexamined at 14 and 21 days. Grading of the severity of the eye irritation was performed by a modification of the method of Draize (1944) based upon the presence and degree of ulceration or opacity of the cornea and iris and erythema, chemosis and ulceration or necrosis of the conjunctival mucosa.

Skin Sensitization

Fifteen male, albino guinea pigs, weighing 300–400 g were employed for each test material in the repeated insult test for cutaneous sensitization. Five animals were assigned to the test group. The testing method was similar to that described by Landsteiner and Jacobs (1935). A 0.1-ml vol of a 0.1 % solution of the test compound was injected intracutaneously to separate skin sites of the animals three times weekly, for a total of nine treatments. Following a 2-wk period in which no further injections were made, a challenge dose of 0.1 ml of test compound was administered to both test and control animals in the same manner. Skin reactions were examined and recorded at 24, 48, and 72 hr following the challenge dose.

RESULTS

Acute Lethality

The po LD50 values and their 95 % confidence limits for the six test compounds are presented in Table 1. The hydroxides were more toxic than the iodides as indicated by the corresponding values. Potassium hydroxide was more toxic than either rubidium or cesium hydroxides; rubidium hydroxide was more toxic than cesium hydroxide. Relative potency ratios were 2.8 (CsOH/KOH), 1.8 (RbOH/KOH), and 1.8 (CsOH/RbOH). Cesium iodide was more toxic than rubidium iodide, with a potency ratio of 2.0 (RbI/CsI).

TABLE 1

ACUTE ORAL LD50 VALUES IN RATS TREATED WITH SEVERAL COMPOUNDS

Compound	No. of animals per dose	No. of dosage levels	Calculated LD50 (mg/kg)	95 % Confidence limits
CsOH	10	6	1026	929–1133
CsOH + KOH	10	6	559	510–613
KOH	9	6	365	310–429
RbOH	9	6	586	522–655
CsI	9	11	2386	2310–2467
RbI	9	9	4708	4413–5026

Lethal and certain sublethal doses of the hydroxides induced stomach and intestinal hemorrhage and adhesions of abdominal organs (stomach, pancreas, spleen, liver, and small intestines). In the higher dose range, death was related to the degree of blockage of the gastrointestinal tract from the resultant adhesions and/or the leakage of bloody fluid exudate into the peritoneal cavity. Behavioral effects noted for survivors of the LD50 study were initial hyperexcitability followed by apathy and weakness which persisted throughout the 14-day observation period. Other clinical signs were

increased respiration rate, ruffled fur, eye closing, and huddling together. A bloody nasal exudate was noted in several animals receiving the higher dosages. The most notable necropsy findings in rats that died following the administration of cesium and rubidium iodide were congested, cyanotic lungs with petechial hemorrhages and a fluid-distended stomach which appeared to result from spasm of the pyloric sphincter following the dosing. Surviving animals that received doses of iodide in which one or more animals died, i.e., doses less than the LD50 and greater than the LD50 were weak and listless for approximately 5 days postdosing. Other survivors appeared normal either initially or within 48 hr postdosing. All deaths in both the hydroxide and iodide-treated animals occurred within the first 72 hr after dosing.

Primary Skin Irritation

The results of the primary skin irritation study in rabbits are presented in Table 2. Quantitative primary irritation scores for each compound tested (each animal, intact versus abraded skin) and the 24-hr and 48-hr scores were omitted for brevity but may be found in Johnson *et al.* (1972). Of the six materials tested, the CsOH(5%) and

TABLE 2

RESULTS OF A PRIMARY SKIN IRRITATION STUDY IN RABBITS TREATED WITH SEVERAL COMPOUNDS

Compound	Intact skin	Abraded skin
CsOH (5%)	Nonirritant	Mild irritant
CsOH (5%) + KOH (5%)	Irritant	Extreme irritant
KOH (5%)	Mild irritant	Extreme irritant
RbOH (5%)	Nonirritant	Mild irritant
CsI (5%)	Nonirritant	Nonirritant
RbI (5%)	Nonirritant	Nonirritant

KOH(5%) mixture was the most irritating to the skin and contact with human intact or abraded skin should be avoided. KOH(5%) was considered a mild irritant and is safe for intact human skin provided the skin is appropriately protected. Direct contact of KOH(5%) on abraded skin, however, should be avoided. CsOH(5%) and RbOH(5%) produced comparable responses, i.e., both are nonirritating to intact skin but protection is required during possible contact with abraded human skin. CsI(5%) and RbI(5%) are considered safe for intact or abraded human skin.

Eye Irritation Study

The results of the eye irritation study in rabbits for the six test compounds are presented in Table 3. Quantitative Draize eye irritation scores for each compound tested (each animal in the two periods of contact of the material with the eye before washing and the seven observation intervals) were omitted for brevity; these data are available in Johnson *et al.* (1972). CsOH(5%), CsOH(5%) + KOH(5%), KOH(5%), and RbOH(5%) are considered extremely irritating and corrosive to the eye. Due to the severe irritating and corrosive action of these compounds to the eye of the first rabbit tested, only one rabbit was used for each test material. Based on the marked

response, an attempt was made to determine the concentrations of the six compounds that produced no ocular reaction. As shown in Table 3, CsOH(0.5%), CsOH(0.1%) + KOH(0.1%), KOH(0.1%), and RbOH(1%) produced no ocular reactions in the eye of rabbits. By contrast, there were no ocular reactions to a 5% solution of cesium or rubidium iodide instilled into the eye of rabbits.

TABLE 3

RESULTS OF EYE IRRITATION STUDY IN RABBITS TREATED WITH SEVERAL COMPOUNDS

Compound	5-min Exposure	24-hr Exposure
CsOH (5%)	Extremely irritant and corrosive (5)[a]	Extremely irritant and corrosive (3)
CsOH (0.5%)	(—)[b]	Negative (3)
CsOH (5%) + KOH (5%)	Extremely irritant and corrosive (1)	(—)
CsOH (1%) + KOH (0.5%)	Extremely irritant and corrosive (5)	Strongly irritant (3)
CsOH (0.5%) + KOH (0.5%)	(—)	Marginal (3)
CsOH (0.1%) + KOH (0.1%)	(—)	Negative (3)
KOH (5%)	Extremely irritant and corrosive (1)	(—)
KOH (1%)	Irritant	Irritant (3)
KOH (0.5%)	(—)	Marginal (3)
KOH (0.1%)	(—)	Negative (3)
RbOH (5%)	Extremely irritant and corrosive (1)	(—)
RbOH (1%)	Marginal (5)	Negative (3)
CsI (5%)	Negative (5)	Negative (5)
RbI (5%)	Negative (5)	Negative (5)

[a] Number of animals used.
[b] No test performed.

Cutaneous Sensitization

There was no evidence of erythema, swelling, or discoloration of the test sites after each of the nine sensitizing cutaneous injections or after the challenge dose for any of the six materials tested. These results indicate that none of the six compounds tested induced cutaneous sensitization in guinea pigs.

DISCUSSION

The result of these studies provide a basis for evaluating the relative acute toxicity of potassium, cesium, and rubidium hydroxide and cesium and rubidium iodide. There are no prior studies in which these compounds were assessed simultaneously for their oral toxicity, primary skin irritation, eye irritation, and cutaneous sensitization responses. The demonstration that the hydroxides of cesium and rubidium are more toxic than the iodides or chlorides is supported qualitatively by the studies of Cochran *et al.* (1959) and Khosid (1967). However, there are quantitative differences between the data reported in this paper by the oral route and that from another laboratory by a different route. Cochran *et al.* (1950), employing the ip route, reported LD50 values of 100 mg/kg for cesium hydroxide and 1400 mg/kg for cesium iodide, whereas the po values reported for this study were 1026 mg/kg for cesium hydroxide and 2386 mg/kg

for cesium iodide. The latter values are quite comparable to those reported by Khosid (1967) of 800 mg/kg for cesium hydroxide and 2300 mg/kg for cesium chloride.

The quantitative consistency of the present data with that of Khosid (1967) is probably the result of the identical route of administration, po, and the similarity of the species used, rats and mice. Although the same experimental animal was used in the present study and that performed by Cochran *et al.* (1950), the inconsistency can easily be attributed to the different routes of administration, po versus ip, respectively. Due to the corrosive nature of alkalis and the neutralization properties of alkalis by gastric acidity, the LD50 would be expected to be much lower for the ip route than the po route. Furthermore, soluble materials, e.g., cesium iodide administered ip are absorbed more rapidly and reach a higher blood concentration than the same material administered orally. The oral LD50 in rats for KOH was 365 mg/kg in the present study but was reported by Smyth *et al.* (1962) to be 1230 mg/kg. This difference between the two laboratories could be attributed to the experimental protocol; Smyth *et al.* (1962) employed nonfasted, younger rats, whereas in this study, the animals were older and fasted.

The only comparable data for the single oral LD50 for rubidium hydroxide and rubidium iodide were contained in the study of Khosid (1967). In the present study, the po LD50 for rubidium hydroxide was 586 mg/kg whereas Khosid (1967) reported 900 mg/kg. In the present study the single dose LD50 for rubidium iodide was 4708 mg/kg whereas Khosid (1967) reported 3800 mg/kg to be the value for rubidium chloride. When one considers the species differences and the different salts employed, the values for rubidium compounds between the two laboratories are in good agreement with one another.

Khosid (1967) reported that cesium and rubidium hydroxides in 0.4% solutions, when introduced into the conjunctival sac, resulted in a marked corneal inflammation, opacity, and ulceration of the lower eyelid. Similar eye effects were noted in this laboratory only when the concentrations of these alkalis were between 1 and 5%. Both laboratories failed to observe any effects following single application of cesium and rubidium salts on the skin or in the eye.

The data from this study and other laboratories suggest that personal protective equipment and clothing should be provided for persons working with potassium, cesium, and rubidium hydroxides. Cesium and rubidium iodides can be classified as slightly toxic when ingested and hence do not appear to be an acute occupational hazard.

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