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Acute and subacute oral toxicity of periodate salts in rats

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ABSTRACT

Periodate salts are being developed as potential replacements for perchlorate due to potential health hazards associated with exposure to perchlorate. The aim of this study was to investigate acute and subacute effects of periodate salts in rats. Acute oral toxicity of potassium and sodium periodate was determined using the Sequential Stage-Wise Probit method. The LD_{50} for potassium periodate was 732 (95% CI = 539–838, slope = 13.4) and 685 mg/kg (95% CI = 580–809, slope = 10.6) for females and males, respectively. The LD_{50} for sodium periodate was 318 (95% CI = 292–347, slope = 24.3) and 741 mg/kg (95% CI = 704–779, slope = 31.2) for females and males, respectively. In the subacute study, rats were administered sodium periodate at five doses (1/16 LD_{50} up to LD_{50}) or distilled water for 14-days via oral gavage. Female rats in the 318 mg/kg-day group and male rats in the 185, 370, and 741 mg/kg-day groups exhibited moribundity, kidney toxicity, uremia, and a stress response. $BMDL_{10}$s of 17.2 and 33.7 mg/kg-day were derived for females and males, respectively. Comparison with the NOAEL for perchlorate-induced thyroid toxicity in rats (0.009 mg/kg-day) suggests sodium periodate is less toxic than perchlorate on a subacute basis.

1. Introduction

Periodates, polyatomic anions with the chemical formula IO_4^-, are being developed as alternatives to perchlorates for use as an oxidizer in military pyrotechnic devices (Ball, 2012; Fields, 2012; Moretti et al., 2012). Alternatives to perchlorates are being pursued due to the environmental and health hazards associated with these compounds. The use of perchlorate has been widely scrutinized due to the potential for the compound to cause thyroid dysfunction and developmental abnormalities in pregnant and nursing mothers, fetuses, and newborns (Brechner et al., 2000; Buffler et al., 2006; Crump et al., 2000; Kelsh et al., 2003; USEPA, 2013; York et al., 2005). Sodium and potassium periodate have been identified as potential replacement incendiary oxidizers that fulfill the pyrotechnic requirements and are presumed, based on structure, to be less toxic than those currently in use. Periodate ions are slightly larger than perchlorate ions, leading munitions developers to speculate that the ions are too big to interact with thyroid receptors in the same manner as perchlorate (Ball, 2012; Fields, 2012; Moretti et al., 2012). However, if transported into the cell by the sodium-iodide symporter (NIS), periodate ions will bring iodide into the follicular lumen of the thyroid that could then be incorporated into thyroid hormones. Furthermore, alteration of blood iodine levels can have profound effects on thyroid status. High blood iodide levels disrupt thyroxinogenesis by blocking the release of T_3 and T_4 from the follicle (Capen and Martin, 1989). Therefore, the increase in available iodine with periodate dosing in the present study may result in iodine-induced thyrotoxicosis.

Existing toxicity data on periodates are limited to an intraperitoneal LD_{50} in mice of 58 mg/kg for sodium periodate (Lewis, 1996) and an oral LD_{50} of 7.07 g/kg for pentacalcium orthoperiodate (PCOP) in fasted male rats (Kuhajek and Andelfinger, 1970). Metabolism studies in the rat have demonstrated prompt reduction of intravenously injected metaperiodate to iodate and subsequently to iodide (Anghileri, 1965; Taurog et al., 1966). Thus, in the present study, observed effects may be the result of rapid reduction of periodate to iodate and ultimately to iodide.

The toxicity of iodates and iodides varies greatly with the route of administration and the feeding state of the animal. Potassium periodate is four to six times more toxic when administered intraperitoneally than orally to fasted mice (LD_{50} 136 and 531–815 mg/kg, respectively). Sodium and potassium iodate are nineteen and eleven times more acutely toxic, respectively, than sodium and potassium iodide when given intraperitoneally to fasted mice (Webster et al., 1957). The cation does not appear to

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modify iodide and iodate acute toxicity. Oral LD_{50} values of 1650 and 1862 mg/kg have been reported for sodium and potassium iodide, respectively, in fasted mice; while sodium and potassium iodate are approximately 3 times more toxic with LD_{50} values of 505 and 531 mg/kg, respectively (Webster et al., 1957). When administered to fed mice, potassium iodate is 1.8 times less toxic than when administered to fasted mice. No difference in iodide toxicity was observed between fasted and fed mice (Webster et al., 1957).

Webster et al. (1957) reported effects of sodium iodate and potassium iodate oral exposure included alternate hyperactivity and lassitude, weakness, prostration, dyspnea, and diarrhea. Transient increases in gastrointestinal pH and degeneration of parietal cells, hemolytic effects including hemoglobinuria and hemosiderin deposits in the kidneys were observed. Mortality was attributed to renal damage. Symptoms of iodide exposure were similar, except with slower onset and the absence of changes in gastrointestinal pH, degeneration of parietal cells, and hemoglobinuria (Webster et al., 1957).

To determine whether sodium periodate and/or potassium periodate provide reduced health hazard alternatives to currently fielded oxidizers, acute and subacute oral toxicity tests were conducted in rats.

2. Materials and methods

2.1. Test substance

Neat potassium periodate (CAS # 7790-21-8; lot 10174755; purity: 100.5%) and sodium periodate (CAS # 7790-28-5; lot B27Z025; purity: 99.07%) were purchased from Alfa Aesar, Ward Hill, MA, USA.

2.2. Experimental design

This study was conducted using male and female Sprague Dawley (Crl: CD (SD) CD®) rats obtained from Charles River Laboratories, Wilmington, Massachusetts. Animal use procedures were approved by the Army Public Health Center (APHC) Institutional Animal Care and Use Committee. Animal care and use was conducted in accordance with *The Guide for the Care and Use of Laboratory Animals* and all applicable Federal and DOD regulations. The USAPHC Animal Care and Use Program is fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International. All animals were housed in temperature-, relative humidity-, and light-controlled rooms. The target conditions of the rooms were 68–72 °F and 30–70 percent humidity. An automatically controlled 12:12-h light/dark cycle was maintained, with the dark period beginning at 1800 h. A certified pesticide-free rodent chow (Harlan Teklad®, 2016C Certified Rodent Diet) was available *ad libitum*. Filtered tap water was provided *ad libitum* via an automated watering system.

Dosing solutions/suspensions were prepared by weighing the required amount of potassium or sodium periodate and adding a measured volume of deionized water. For the acute study, fresh dosing solutions/suspensions were prepared for each day/round of dosing. For the 14-day study, six dosing solutions, 3.1, 6.2, 12.5, 25, 50, and 100 milligrams per milliliter (mg/ml) of sodium periodate, were prepared at the start of the study in sufficient volume for use throughout the study. Dosing solution concentrations were verified via high performance liquid chromatography with ultra violet detection and were within 96–109% of nominal concentrations. As such, all results are reported using the nominal concentrations. Additionally, a stability test conducted on a representative solution indicated that the compound was stable under the test and storage conditions.

The acute toxicity of sodium periodate and potassium periodate was assessed using the Sequential Stage-Wise Probit (SSWP) method (ASTM, 2010; Feder et al., 1991a, 1991b). In the absence of historical data or literature values, doses for the first stage of dosing were set at the default starting value of 175 mg/kg with half-log dose intervals (3.2 dose progression factor) (USEPA, 2002a).

The Approximate Lethal Dose (ALD) method was also used to determine the acute toxicity of sodium periodate in fed female rats (Deichman and LeBlanc, 1943). This test was conducted to determine if differences exist between the lethal dose in fasted (overnight) (*i.e.*, SSWP LD_{50}) and fed rats and to assist in determining dose levels for the 14-day study. The ALD consisted of six doses and a control, with one female rat receiving each dose. Dose selection for the sodium periodate ALD was based on the results of the SSWP but included an adjustment factor based on the 2-fold increase in LD_{50} between fasted and fed animals that has been demonstrated for iodate (Webster et al., 1959). Dose intervals were set at approximately 1.5× the previous dose to a maximum of 2000 mg/kg.

Fifty-eight female and forty-seven male Sprague Dawley (Crl: CD (SD) CD®) rats were used for the acute portion (SSWP and ALD) of this study. Females were approximately 10 weeks old and weighed 221.1 ± 15.3 grams (g), while males were approximately 9 weeks old and weighed 307.5 ± 19.0 g. All sodium periodate and potassium periodate doses were administered according to body weight measured on the day of dosing using a stainless steel 16-gauge gavage needle. Constant concentration dosing was used within each round of dosing. However, due to difficulties encountered in delivering the very concentrated suspensions without injuring the animals, concentrations were reduced after the first round of dosing; dosing volume limitations (i.e., 10 ml/kg) were not exceeded. All animals were observed for a period of 14 days.

A 14-day oral toxicity study was performed with the most acutely toxic of the two periodate salts (sodium periodate) to determine the effects of repeated daily dosing. Sixty female (215.4 ± 11.1 g) and sixty male (269.8 ± 11.7 g) Sprague Dawley (Crl:CD(SD) CD®) rats approximately 10 weeks old were assigned to dose groups using a stratified random procedure, with animals stratified within sex according to body weight and dose groups assigned randomly. Body weight did not differ among dose groups prior to initiation of dosing. Dose selection for the 14-day study was based on the results of the acute study (*e.g.*, 0.25×, 0.13×, 0.063×, 0.031×, 0.016× the LD_{50}) with an adjustment factor for differences between fed and fasted rats calculated based on the results of the ALD. The solutions/suspensions were administered in volumes of 6.36 and 7.41 milliliter per kilogram (ml/kg) based on daily body weight for females and males, respectively, using a stainless steel 16-gauge gavage needle. The vehicle control group received a volume of deionized water equivalent to the highest exposure group. Females and males were each divided into three time-separated groups to facilitate necropsy. Animals from each dose group were approximately evenly distributed across necropsy groups.

2.3. Observations, body weight, food consumption

During the dosing period, observations for mortality and signs of toxic effects were made at least twice daily. Acute study animals were weighed daily while 14-day animals were weighed on study days 0, 1, 3, 7, and 13. Terminal (fasted) body weight was obtained the morning of necropsy following overnight fasting. Food consumption was determined on study days 0, 1, 3, 7, and 13 for each pair of animals. Because rats were pair housed and individual food consumption could not be determined, food consumption was then calculated per gram of rat by dividing the food consumed by the