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MEMORANDUM



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DATE: January 7, 2002

SUBJECT: PROPOSED ACTION LEVEL FOR CHLORATE

Staff of the Office of Environmental Health Hazard Assessment (OEHHHA) have reviewed your Department's proposed action level of 500 $\mu\text{g/L}$ for chlorate, derived from a subchronic oral (gavage) study in rats submitted to the Department of Pesticide Regulation (DPR). From this study, a no-observed-adverse-effect level (NOAEL) of 100 mg/kg-day sodium chlorate (78 mg/kg-day chlorate) was suggested, based on hematological effects (Barrett, 1987; DPR, 1998). Several recent studies have reported adverse effects (significant organ and body weight reductions, hematological effects, changes in pituitary and thyroid glands) in rats exposed via drinking water to sodium and/or potassium chlorate at doses similar to, but slightly lower than, those used in the Barrett (1987) study. These studies provide for the identification of a clear NOAEL and lowest-observed-adverse-effect level (LOAEL). OEHHHA recommends that the McCauley et al. (1995) study be used to derive the action level, which would result in a lower value of 200 $\mu\text{g/L}$ chlorate.

Chlorates are a combination of a metal or hydrogen and the chlorate monovalent radical (refer to Table 1 – physical/chemical characteristics). Chlorates are strong oxidizers used in the manufacture of dyes, explosives, matches, printing fabrics, paper pulp processing, weed killers,

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and as a weak antiseptic (2-3 percent solutions have been used as mouthwash). Chlorates of alkali metals are approved for use in toothpaste at concentrations of 5 percent or less and for other uses at 3 percent or less by the European Union (EEC Cosmetic Directive, 1990). In addition, sodium chlorate is an active ingredient in a number of commercial herbicides. It has been formulated with other herbicides such as sodium metaborate, cacodylic acid, atrazine, bromacil, or diuron (Meister, 1999). In this use, sodium chlorate acts as a nonselective contact herbicide, and is a moderately persistent soil sterilant (three to six months) with a potential for leaching into groundwater.

Chlorate can also be a by-product of certain types of water disinfection. Potassium and sodium chlorate are formed in drinking water treated with chlorine dioxide (ClO_2) (Kurokawa et al., 1985), and metabolism studies have shown that chlorine dioxide is converted to chloride, chlorite, and chlorate in the rat (Abdel-Rahman et al., 1979a, 1979 b). Estimates are that 10 percent (pH 4.8) to 30 percent (pH 9.75) of the chlorine dioxide used in drinking water disinfection is converted to chlorate (Bolyard and Fair, 1993). Miltner (1976) concluded that the use of chlorine dioxide as a primary disinfectant at levels of 25-30 ppm would be expected to yield concentrations of 6-10 ppm residual chlorate. At this time, an action level for chlorate is needed because of concerns about its presence in Southern California in water associated with hazardous waste clean-up activities that may find its way into drinking water supplies. The origin of the chlorate in the raw water samples is unclear.

Table 1. Properties of common chlorate salts

	Sodium chlorate	Magnesium chlorate	Potassium chlorate	Calcium chlorate
CAS number	7775-09-9	10326-21-3	3811-04-9	10137-74-3
Chemical Formula	NaClO_3	$\text{Mg}(\text{ClO}_3)_2 \cdot 6\text{H}_2\text{O}$	KClO_3	$\text{Ca}(\text{ClO}_3)_2$
Molecular Weight	106.4	299.3	122.6	207.0
Water Solubility (g/100 mL)	140 (temp. not specified)	129 (18° C)	7.1 (20° C)	170 (temp. not specified)
Fatal Dose (human)		15 g – adult 2 g - children		
LD ₅₀ (rats)	1,200 mg/kg	5,250 mg/kg	1,870 mg/kg	4,500 mg/kg
LD ₅₀ (mice)	596 mg/kg			
LD ₅₀ (rabbits)	7,200 mg/kg			
LDlo (dogs)	700 mg/kg		1,200 mg/kg	
LDlo (cats)	1,350 mg/kg			
Carcinogenicity	No effects noted (IARC)	Not tested	No effects noted (Kurokawa et al., 1985)	Not tested

Metabolism/Absorption/Excretion

Chlorates are readily absorbed by the gastrointestinal tract following ingestion. The chlorate ion is not metabolized to another compound, and elimination is exclusively by the kidneys. In dogs, the chlorate ion given orally in aqueous solution is rapidly eliminated in urine (National Research Council, 1980). Seven female dogs were given 500 mg/kg doses of chlorate in 500 ml of water. From 55-70 percent was excreted in the first six hours. By 24 to 48 hours, 76-99 percent had been excreted unchanged in urine. The concentration of chlorate in blood peaked at two hours, ranging from 5-81 mg/100 ml in five dogs, and decreased to little or none by 24 hours.

In one quantitative study in rats, radioactive potassium chlorate ($^{36}\text{ClO}_3$) was rapidly absorbed via the oral exposure route, reaching a peak blood concentration after one hour (Abdel-Rahman et al., 1984a). Elimination from the blood exhibited a biphasic pattern with half-lives of 6 and 36.7 hours, respectively. After 72 hours, radioactivity was highest in plasma, followed by whole blood, stomach, testes, lung, kidney, skin, duodenum, spleen, brain, packed red blood cells, ileum, carcass, liver, and bone marrow.

General Toxicity

Chlorates are principally toxic by ingestion and inhalation. Human chlorate ingestion can produce gastritis, a late toxic nephritis, hemolysis, methemoglobinemia, hemoglobinuria, and acute renal failure. The acute toxic effects of potassium chlorate appear to be cumulative because of slow excretion of the chlorate ion; repeated 1 g ingestions have been fatal (Picaud et al., 1991). An acute or cumulative dose of 7.5-35 grams has been reported to be lethal in adults (Helliwell and Nunn, 1979); the toxic dose of potassium chlorate is often reported to be 5 g (AFOEHL, 1989). A single case of transitory amblyopia (dimness of vision) was reported following gargling with a solution of potassium chlorate (Grant, 1974).

High levels can interfere with the ability of the blood to carry oxygen, causing headache, dizziness, and methemoglobinemia. Ingestion may produce gastrointestinal distress, and may damage the kidneys. Potassium chlorate has produced renal tubular necrosis in animals (Reubi, 1978).

The primary mechanism of chlorate toxicity is rupture of the red blood cell membranes with intravascular hemolysis. The formation of methemoglobin is secondary to lysis of red blood cells, and is caused by autooxidation of the free hemoglobin. The formation of methemoglobin from free hemoglobin is irreversible, and may cause life-threatening effects. (Within the red blood cells, methemoglobin is rapidly reduced by methemoglobin reductase, but this activity is lost with cell lysis). Potassium chlorate is also a relatively powerful irreversible inhibitor of catalase.

Human Toxicity Studies

Lubbers and Bianchine (1984) studied the short-term effect of administration of chlorine dioxide and its metabolites, including chlorate, on human volunteers. Ten male subjects were administered 1,000 mL of water containing varying concentrations of sodium chlorate (range 0.01 – 2.4 ppm chlorate). The control group received deionized water. Treatments were divided into two 500 mL aliquots; administered four hours apart. The study involved a series of six treatments in 16 days, which was considered as a single time-dependent experiment. Blood and urine samples were collected from all study participants. No adverse physiological effects were identified, although there was some variation between the treatment group and the control group with regard to bilirubin and serum iron measurements. In a companion study, normal adult male subjects were administered 500 ml of a 5 ppm solution of chlorine dioxide, chlorite, or chlorate daily for 12 weeks (Lubbers et al., 1984a), corresponding to a dose of about 0.04 mg/kg. Physical examinations, collection of blood and urine samples for laboratory assays, and taste evaluations were conducted on a weekly basis during the treatment period and for eight weeks following cessation of the treatment. Any value for an individual subject that differed from the group mean by more than two standard deviations was noted. The authors reported that “no clinically important physiological effects” were observed. A small number of subjects yielded abnormal hemoglobin electrophoresis patterns, but these results were randomly distributed among the groups. In a third study, a small number of subjects with glucose-6-phosphate dehydrogenase deficiencies which might make them more susceptible to oxidative stress caused by the chlorine disinfectants was exposed to the same dose of chlorite daily for 12 weeks (Lubbers et al., 1982, 1984b). Some statistically significant trends in biochemical or physiological parameters (albumin/globulin ratio, thyroid hormone levels, mean corpuscular hemoglobin, and methemoglobin values) were observed, but were judged to be of no clinical significance. Chlorite and chlorate can be expected to have similar biochemical effects, but do not appear to be absorbed and distributed in the same fashion and are not interconvertible *in vivo*, according to the data from rat studies (Abdel-Rahman et al., 1979b, 1984a).

The effects of sodium chlorate on human erythrocytes (RBCs) were studied *in vitro* (Singelmann et al., 1984). A concentration-dependent lag phase was seen before methemoglobin was formed, presumably reflecting time required for chlorate to enter or hemolyze RBCs. Other effects on RBCs included increased permeability to cations, increased resistance to hypotonic hemolysis, and prolonged filtration time through polycarbonate membranes. This suggests an increased RBC membrane rigidity due to membrane protein polymerization, as demonstrated by sodium dodecyl sulfate polyacrylamide gel electrophoresis. Simultaneously, erythrocyte enzymes were inactivated, primarily glucose-6-phosphate dehydrogenase.

Animal Toxicology Studies

A series of small toxicity studies on chlorine dioxide and its metabolites was conducted by Abdel-Rahman and colleagues (Abdel-Rahman et al., 1979a,b, 1984a,b,c, 1985; Suh et al., 1983, 1984, and others). Male Sprague-Dawley rats (usually four animals per group) were exposed to relatively low concentrations of these chemicals in drinking water for up to 11 months. Concentrations of 10 and 100 mg/L of ClO_3^- supplied to Sprague-Dawley rats would yield doses of about 1.5 and 15 mg/kg-day, respectively, estimated from standard parameters. Several different effects were reported at both ClO_3^- doses, including decreased blood glutathione (at two and nine months), decreased osmotic fragility of erythrocytes (increasing with time), inhibition of incorporation of tritiated thymidine into nuclei in rat testes (determined at three months only), decreased RBC count and hematocrit (at nine months), and decreased body weight throughout treatments. Observed effects on the parameters that were studied tended to be similar for chlorine dioxide (exposed to 1, 10, 100, or 1,000 mg/L), chlorite (10 and 100 mg/L), and chlorate (10 and 100 mg/L). Body weights were decreased for all three treatments for all doses, with no apparent dose-response, implying effects unrelated to the treatments. It should be noted that the reported LOAEL of 1.5 mg/kg-day for chlorate for these studies is far lower than reported in any other toxicity studies. The small number of animals, variability of effects over time, lack of dose-response on several measures, effects apparently unrelated to treatment, and lack of confirmation of the observations in other studies make these data of insufficient quality for a quantitative risk assessment.

Administration of 1 percent potassium or sodium chlorate (mean consumption of NaClO_3 and KClO_3 ranged between 654 and 686 mg/kg-day) in the drinking water of male F344 rats for 25 weeks resulted in a significant decrease in mean body weights relative to the controls (Kurokawa et al., 1985). These doses of NaClO_3 and KClO_3 were the maximum tolerated doses determined from 6-week exposures of male F344 rats at concentrations of 2, 1, 0.5, and 0.25 percent in the drinking water. Adjusting for the portion of the salt that is sodium (22 percent) or potassium (32 percent), the mean consumption of chlorate in the 25-week study ranged from 445 to 535 mg/kg-day. Relative kidney weights of the group dosed with potassium chlorate were significantly increased compared with the control group, which may indicate some renal toxicity.

A subchronic oral toxicity study was carried out by Bio/Dynamics in support of registration of sodium chlorate as a pesticide. In this study, Sprague-Dawley rats (15/sex/group) were administered 0, 10, 100 or 1,000 mg/kg-day sodium chlorate by gavage, seven days per week for 90 days (Barrett, 1987a). There were no hematological, histological, or clinical chemistry treatment-related effects at any dose level. The most significant finding was a suggestion of anemia, especially in female rats, which exhibited slightly lower blood cell counts, hematocrit and hemoglobin levels. The dose of 100 mg/kg-day was identified by DPR as a no-observed effect level (NOEL) for sodium chlorate (or 78 mg/kg-day chlorate) from this study.

Bio/Dynamics also conducted a subchronic oral toxicity study of sodium chlorate in beagle dogs (Barrett, 1987b). Four dogs/sex were gavaged with sodium chlorate in distilled water at 0, 10, 60, or 360 mg/kg-day for 90 days. Some emesis was reported (one female dog only during the first three weeks of dosing), along with a notation from a range-finding study that doses of 360 mg/kg-day were emetic. DPR reported a NOEL of 60 mg/kg-day for this study.

Male and female Sprague-Dawley rats (10/sex/group) were exposed to 3.0, 12.0, or 48.0 mM sodium chlorate in drinking water for 90 days (McCauley et al., 1995). The mean water consumption varied between exposure groups from 100 to 200 ml/kg-day. Females consistently drank more water (23-42 percent more than males), resulting in mean doses of 30, 100 and 512 mg/kg-day chlorate in males, and 42, 158, and 800 mg/kg-day chlorate in females. Both males and females in the high dose group demonstrated significantly lower final body weights. Females in the high dose group showed significant decreases in relative organ weights for adrenals, thymus, and spleen, while relative brain weight was significantly increased. In males, small decreases in heart, kidney, and liver weights were observed in the high dose group, while brain and testes relative weights had small increases in this same group. Red blood cell counts and percent hemoglobin were decreased in both sexes in the high dose group. Pituitary gland vacuolization and thyroid gland colloid depletion were prominent in both sexes in the mid and/or high dose animals. NOAELs for the body and organ weight changes were 100 and 150 mg/kg-day in males and females, respectively. NOAELs for the pituitary and thyroid effects were 30 and 42 mg/kg-day, respectively.

Carcinogenicity/Mutagenicity

Little data exist on the carcinogenic potential of any of the chlorates in either humans or experimental animals. No lifetime cancer bioassays have been identified for chlorates. Administration of 1 percent sodium or potassium chlorate in the drinking water of rats either pretreated or not with N-ethyl-N-hydroxyethylnitrosamine (EHEN) for 25 weeks did not promote rat renal carcinogenesis (Kurokawa et al, 1985). (The treatment dose of 1 percent NaClO₃ and KClO₃ in this experiment was assumed to be the maximum tolerated dose as determined in a 6-week toxicity test.) Non-neoplastic regenerative changes of the renal tubules were observed in all groups. Final body weights of rats given the chlorates were significantly decreased from those given distilled water. Various hematologic parameters were affected in the treated group. Decreases in erythrocyte count, hematocrit, and hemoglobin were observed. Alterations in morphology and decreases in osmotic fragility and in glutathione content of the erythrocytes were also noted.

Sodium chlorate was reported to be mutagenic in the Ames Salmonella microsome assay and caused mutations in fruit flies (Eckhardt et al., 1982). Also, sodium chlorate caused DNA damage in repair-deficient E. coli strains at concentrations between 1,000 and 10,000 µg/ml

(May, 1989a). However, no effects were observed in Ames assays on strains TA98, TA100, TA1535, TA1537, and TA1538, with and without rat liver activation, in tests up to 5,000 µg/plate in another study (May, 1989b). Sodium chlorate had no adverse effects in Chinese hamster ovary cells in concentrations up to 5,000 µg/ml (Hodson-Walker, 1989). It also did not induce chromosome aberrations, micronuclei, or sperm abnormalities in mice (Meier et al, 1985; Eckhardt et al., 1982), and was negative for clastogenicity (micronuclei) in the mouse bone marrow erythrocyte test (MacKay, 1989). In an unscheduled DNA synthesis test with HeLa S3 cells, sodium chlorate decreased the incorporation of thymidine in a dose-dependent fashion between 100 and 10,000 µg/ml, indicating toxicity, but there was no indication of unscheduled DNA synthesis (Seeburg, 1989). Overall, the results of these tests can be considered as mostly negative, with little indication of carcinogenic potential.

Developmental/Reproductive Data

No reproductive studies were found for chlorate in humans. Intramuscular administration of potassium chlorate to pregnant rats resulted in a prolonged gestation period in most cases, and reduced neonatal weight relative to the controls. According to the author, newborn rats also showed a “marked” increase of hematopoietic residue and lipid deposit over controls, and occasionally, exposure resulted in the appearance of hyaline droplets and casts in newborn kidneys (Miyoshi, 1959). The number of animals per treatment group/number affected, duration of exposure, and information on dose levels was not available (article in Japanese).

Suh et al. (1983, 1984) exposed female rats to 1 or 10 mg chlorate/L in their drinking water for ten weeks. Fetuses were taken on the 20th day of gestation and examined for external, visceral and skeletal malformations. No significant adverse findings were reported.

Schroeder (1987) conducted a teratogenicity study in rats for registration of sodium chlorate as a pesticide. Sprague-Dawley rats (24/dose) were gavaged with 0, 10, 100, or 1,000 mg/kg-day of sodium chlorate in water at 5 ml/kg on days 6 through 15 of gestation. No treatment-related effects were reported on body weight, food consumption, clinical signs, or any developmental parameters. DPR, in evaluating this study, considered the maternal and developmental NOEL to be 1,000 mg/kg-day (DPR, 1998).

High chlorate levels were found in the testes of rats after oral administration of potassium chlorate, but it is not known if chlorate can affect male fertility (Abdel-Rahman et al., 1984). The chlorates in general induce extracellular methemoglobinemia following initial lysis of erythrocytes. As such, Hazardous Substances Data Bank (HSDB, 2001) lists sodium chlorate as a Class A (unconfirmed human reproductive hazard) for reproductive hazard because it is unclear whether extracellular methemoglobin induction following erythrocyte lysis carries the same theoretical fetal risk as does intracellular methemoglobin induction. Potassium chlorate, on

the other hand, is listed in Class E (known not to affect animal reproduction but no human data) for reproductive hazard.

Sensitive subpopulations

Infants (and presumably the fetus) are much more sensitive than adults to intracellular methemoglobin inducers. This is due to a relative deficiency in methemoglobin reductase in red blood cells of newborns, because the fetal form of hemoglobin is more sensitive to reducing agents, and because the fetus has a greater oxygen demand. However, it is not clear whether the newborn or the fetus may be more sensitive to the hemolytic effect of chlorates than adults. The extracellular autooxidative formation of methemoglobin from lysed cells is irreversible and complete in both adults and fetuses, so there would be no difference in sensitivity in this step.

Persons with pre-existing blood conditions, especially anemia, or those with kidney diseases, might be more sensitive. Persons with genetic diseases such as hereditary methemoglobinemia and glucose-6-phosphate dehydrogenase deficiency (which increases the hemolytic susceptibility of humans to oxidizing agents), and other persons who may be unusually susceptible to oxidants may also be at greater risk than the general population.

Action Level Derivation

The Department of Health Services' proposed action level of 0.5 mg/L (500 µg/L) for chlorate is derived from a subchronic study in which Sprague-Dawley rats were administered 0, 10, 100 or 1,000 mg/kg-day sodium chlorate by gavage for 90 days (15/sex/group) (Barrett, 1987). One mid-dose male died on day 69, and one high-dose female on day 30. There were no histological or clinical chemistry treatment-related effects at any dose level. The most significant finding was anemia, especially in female rats, which exhibited lower blood cell counts, hematocrit and hemoglobin levels than controls. In most cases, these parameters were statistically significantly lower than mean control values. Mean group body weights for low and high dose females were statistically significantly lower than for control animals throughout most of the study. Due to the lack of a dose-related decrease in mean group body weights for mid-dose females and treated males, the authors felt that the body weight variations were not related to sodium chlorate administration. A slight decrease ($p < 0.05$) in adrenal weight was found for high-dose animals when compared to controls. Although not statistically significantly different from control values, there was also a trend toward a decrease in the adrenal to body weight ratio for high-dose animals, with males more affected than females. A NOAEL of 100 mg/kg-day sodium chlorate (or 78 mg/kg-day chlorate) was derived from this study. The proposed action level calculation included an uncertainty factor of 1,000.

Related adverse effects on body weight, adrenal weight, and hematological effects have been reported by other authors at or below the levels used in the Barrett (1987) study. Kurokawa

et al. (1985) reported a significant reduction in body weights, and significant increases in kidney weights in male rats exposed to mean doses of 654-686 mg/kg-day sodium or potassium chlorate in drinking water for 25 weeks (range 445-535 mg/kg-day chlorate). McCauley et al. (1995) observed significant biological changes (reduction in organ and body weights, and hematological effects) in male and female rats exposed to mean doses of 100 and 158 mg/kg-day chlorate in drinking water, respectively, for 90 days.

OEHHA recommends these other studies with lower adverse effect levels be utilized for the derivation of an action level for chlorate. OEHHA proposes that the drinking water study of McCauley et al. (1995) serve as the basis for the derivation of the estimated safe levels of chlorate in drinking water. The study by McCauley et al. (1995) is subchronic (90 day), and includes both male and female animals (gender differences were observed). An added advantage of this study compared to that of Barrett (1987) is that the route of exposure is via drinking water.

Since biologically significant changes were noted in the mid and high dose groups of both sexes in the McCauley et al. (1995) study, a NOAEL of 30 mg chlorate/kg-day in males and 42 mg chlorate/kg-day in females can be established (mean water consumption differed considerably between males and females). Uncertainty factors of 10 each for intraspecies and interspecies differences, and 10 for subchronic to chronic duration were applied. There could be concern about the lack of a cancer bioassay and the potential for extra sensitivity of neonates and newborns to chlorates, but the available data do not reveal a carcinogenic potential nor indicate a specific developmental risk (Schroeder, 1987). No extra uncertainty factor for sensitive human subpopulations appears warranted at this time, although there is a paucity of data concerning postnatal reproductive/developmental effects in animals and humans, and no multi-generation reproductive study exists for these compounds.

A public health protective concentration (C) for chlorate was derived using the following equation:

$$C = \frac{\text{NOAEL} \times \text{BW} \times \text{RSC}}{\text{UF} \times \text{DWC}}$$
$$C = \frac{30 \text{ mg/kg-day} \times 70 \text{ kg} \times 0.2}{1,000 \times 2 \text{ L/day}} = 210 \text{ } \mu\text{g/L}$$

where:

NOAEL = no-observed-adverse-effect level (pituitary gland vacuolization and thyroid gland colloid depletion),

BW = body weight (adult),
RSC = relative source contribution,
UF = uncertainty factor,
DWC = drinking water consumption (adult).

The relative source contribution of 0.2 is intended to acknowledge potential co-exposures to the related drinking water disinfection byproducts chlorite and chlorine dioxide, which have toxic effects similar to chlorate. Due to differences in water consumption, male rats were consistently exposed to a lower dose than were females in this study. The health-protective levels for chlorate would be 210 and 290 µg/L (ppb) for males and females, respectively.

OEHHA recommends an action level of 200 µg/L (ppb) chlorate based on the male rat data (rounded). We believe this level would be adequate to protect against any potential toxic effects in humans. This conclusion is supported by the human studies of Lubbers and coworkers, who found no effects in adult male humans with subchronic chlorate doses of 2.5 mg/day. This dose would correspond to a drinking water concentration of 1.25 ppm with a drinking water consumption of 2 L/day. The recommended action level is about one/sixth this no-observed-effect level.

Should you have any questions about this review, please contact me at (510) 622-3168 or Ms. Moira Sullivan at (510) 622-3213.

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