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Provisional Peer-Reviewed Toxicity Values for

Rubidium Compounds

(CASRN 7440-17-7, Rubidium)
(CASRN 7791-11-9, Rubidium Chloride)
(CASRN 1310-82-3, Rubidium Hydroxide)
(CASRN 7790-29-6, Rubidium Iodide)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

AUTHORS, CONTRIBUTORS, AND REVIEWERS

CHEMICAL MANAGERS

Puttappa R. Dodmane, BVSc&AH, MVSc, PhD
National Center for Environmental Assessment, Cincinnati, OH

Scott C. Wesselkamper, PhD
National Center for Environmental Assessment, Cincinnati, OH

DRAFT DOCUMENT PREPARED BY

SRC, Inc.
7502 Round Pond Road
North Syracuse, NY 13212

PRIMARY INTERNAL REVIEWER

Paul G. Reinhart, PhD, DABT
National Center for Environmental Assessment, Research Triangle Park, NC

This document was externally peer reviewed under contract to:

Eastern Research Group, Inc.
110 Hartwell Avenue
Lexington, MA 02421-3136

Questions regarding the contents of this PPRTV assessment should be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300).

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COMMONLY USED ABBREVIATIONS AND ACRONYMS

α2u-g	alpha 2u-globulin
ACGIH	American Conference of Governmental Industrial Hygienists
AIC	Akaike's information criterion
ALD	approximate lethal dosage
ALT	alanine aminotransferase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
BW	body weight
CA	chromosomal aberration
CAS	Chemical Abstracts Service
CASRN	Chemical Abstracts Service Registry Number
CBI	covalent binding index
CHO	Chinese hamster ovary (cell line cells)
CL	confidence limit
CNS	central nervous system
CPN	chronic progressive nephropathy
CYP450	cytochrome P450
DAF	dosimetric adjustment factor
DEN	diethylnitrosamine
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
FEV_1	forced expiratory volume of 1 second
GD	gestation day
GDH	glutamate dehydrogenase
GGT	γ-glutamyl transferase
GSH	glutathione
GST	glutathione-S-transferase
Hb/g-A	animal blood-gas partition coefficient
Hb/g-H	human blood-gas partition coefficient
HEC	human equivalent concentration
HED	human equivalent dose
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
IVF	in vitro fertilization
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
MN	micronuclei
MNPCE	micronucleated polychromatic erythrocyte
MOA	mode of action
MTD	maximum tolerated dose
NAG	N-acetyl-β-D-glucosaminidase
NCEA	National Center for Environmental Assessment
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
NZW	New Zealand White (rabbit breed)
OCT	ornithine carbamoyl transferase
ORD	Office of Research and Development
PBPK	physiologically based pharmacokinetic
PCNA	proliferating cell nuclear antigen
PND	postnatal day
POD	point of departure
POD_{ADJ}	duration-adjusted POD
QSAR	quantitative structure-activity relationship
RBC	red blood cell
RDS	replicative DNA synthesis
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	regional gas dose ratio
RNA	ribonucleic acid
SAR	structure activity relationship
SCE	sister chromatid exchange
SD	standard deviation
SDH	sorbitol dehydrogenase
SE	standard error
SGOT	glutamic oxaloacetic transaminase, also known as AST
SGPT	glutamic pyruvic transaminase, also known as ALT
SSD	systemic scleroderma
TCA	trichloroacetic acid
TCE	trichloroethylene
TWA	time-weighted average
UF	uncertainty factor
UF_A	interspecies uncertainty factor
UF_H	intraspecies uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
UF_D	database uncertainty factor
U.S.	United States of America
WBC	white blood cell

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR RUBIDIUM CHLORIDE (CASRN 7791-11-9)

BACKGROUND

A Provisional Peer-Reviewed Toxicity Value (PPRTV) is defined as a toxicity value derived for use in the Superfund Program. PPRTVs are derived after a review of the relevant scientific literature using established Agency guidance on human health toxicity value derivations. All PPRTV assessments receive internal review by a standing panel of National Center for Environment Assessment (NCEA) scientists and an independent external peer review by three scientific experts.

The purpose of this document is to provide support for the hazard and dose-response assessment pertaining to chronic and subchronic exposures to substances of concern, to present the major conclusions reached in the hazard identification and derivation of the PPRTVs, and to characterize the overall confidence in these conclusions and toxicity values. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of this substance.

The PPRTV review process provides needed toxicity values in a quick turnaround timeframe while maintaining scientific quality. PPRTV assessments are updated approximately on a 5-year cycle for new data or methodologies that might impact the toxicity values or characterization of potential for adverse human health effects and are revised as appropriate. It is important to utilize the PPRTV database (http://hhpprtv.ornl.gov) to obtain the current information available. When a final Integrated Risk Information System (IRIS) assessment is made publicly available on the Internet (http://www.epa.gov/iris), the respective PPRTVs are removed from the database.

DISCLAIMERS

The PPRTV document provides toxicity values and information about the adverse effects of the chemical and the evidence on which the value is based, including the strengths and limitations of the data. All users are advised to review the information provided in this document to ensure that the PPRTV used is appropriate for the types of exposures and circumstances at the site in question and the risk management decision that would be supported by the risk assessment.

Other U.S. Environmental Protection Agency (EPA) programs or external parties who may choose to use PPRTVs are advised that Superfund resources will not generally be used to respond to challenges, if any, of PPRTVs used in a context outside of the Superfund program.

This document has been reviewed in accordance with U.S. EPA policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

QUESTIONS REGARDING PPRTVs

Questions regarding the content of this PPRTV assessment should be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300).

INTRODUCTION

Rubidium (Rb; atomic symbol) is a metallic element that has two naturally occurring isotopes: ^{85}Rb (72.15%) and the radioactive ^{87}Rb (27.85%). There are no minerals in which rubidium is the primary element; however, it is found naturally within the Earth's crust in trace amounts in the rock-forming silicate minerals, such as potassium feldspars and micas. These minerals must be chemically reduced to produce pure rubidium metal (Wagner, 2011). Rubidium metal is used in atomic clocks and global positioning systems (GPS) as an atomic resonance frequency standard (Wagner, 2011). The radioactive decay of ^{87}Rb to ^{87}Sr (half-life of 4.9×10^{10} years), resulting in the emission of a negative beta particle, is used in radiometric dating of some rocks and minerals (Wagner, 2011). Rubidium metal is also used as a reagent in making zeolite catalysts and in photoelectric cells. Additionally, it can be used as an intermediate for preparing rubidium salts (O'Neil, 2006).

Rubidium is a soft, ductile, silvery-white metal, which, due to its low melting point of 39°C, may also be a liquid at higher ambient temperatures (Wagner, 2011). Rubidium metal reacts violently with water in an exothermic reaction that produces hydrogen gas. If this reaction occurs in the presence of oxygen or air, a spontaneous explosion will result (Wagner, 2011). In addition, rubidium ignites in oxygen, burning with a characteristic red-violet flame (O'Neil, 2006). The U.S. Department of Transportation (DOT) classification code for shipping rubidium is Label 4.3 Dangerous When Wet (Wagner, 2011).

Rubidium chloride, rubidium hydroxide, and rubidium iodide are water soluble. These compounds have several established therapeutic applications. For example, rubidium chloride has been used as an antidepressant (O'Neil, 2006) and rubidium iodide has been used as an iodine source for the treatment of goiter (Wagner, 2011). Rubidium compounds are also used in scientific research. For instance, rubidium hydroxide and rubidium chloride are catalysts used in chemical syntheses (O'Neil, 2006).

Rubidium chloride, rubidium hydroxide, and rubidium iodide are all solids at room temperature. Because these compounds are hygroscopic (i.e., absorb water from air), they are generally stored and shipped in tightly sealed containers (Wagner, 2011). Rubidium iodide will discolor when exposed to light or air (O'Neil, 2006) and emit toxic vapors when heated (Wagner, 2011). As salts (rubidium chloride and rubidium iodide) or alkali (rubidium hydroxide) will exist as ions in the environment and, therefore, are not expected to volatilize from either water or soil. However, due to their high water solubility, they are expected to leach readily from soil to groundwater. The empirical formulas for rubidium chloride, rubidium hydroxide, and rubidium iodide are RbCl, Rb(OH), and RbI, respectively (see Figure 1). A table of physicochemical properties for rubidium and selected rubidium compounds for which any toxicity data could be located is provided below (see Table 1).

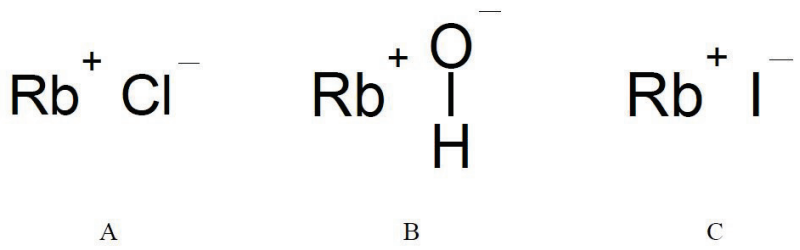

Figure 1. Structures of Rubidium Salts and Alkali:
(A) rubidium chloride, (B) rubidium hydroxide, and (C) rubidium iodide

Table 1. Physicochemical Properties of Rubidium, Rubidium Chloride, Rubidium Hydroxide, and Rubidium Iodide

Property (unit)	Rubidium 7440-17-7	Rubidium Chloride 7791-11-9	Rubidium Hydroxide 1310-82-3	Rubidium Iodide 7790-29-6
Physical state	Soft, ductile, silvery-white solid, but can be a liquid at higher ambient temperatures[a]	White crystalline powder[b]	Grayish-white deliquescent mass[b]	White crystals or crystalline powder that discolors on exposure to air or light[b]
Boiling point (°C)	689[a]	1,390[a]	ND	1,300[a]
Melting point (°C)	39[a]	715[a]	301[a]	642[a]
Density (g/cm^3)	1.522 (solid, 18°C), 1.472 (liquid, 39°C)[a]	2.76[b]	3.203[b]	3.55[b]
Vapor pressure (mm Hg at 25°C)	ND	ND	ND	ND
Solubility in water	Reacts violently[a]	139 g/100 mL at 100°C; 77 g/100 mL at 0°C[a]	180 g/100 mL at 15°C[a]	163 g/100 mL at 25°C; 152 g/100 mL at 15°C[a]
Relative vapor density (air = 1)	ND	ND	ND	ND
Atomic/ molecular weight (g/mol)	85.4678[b]	120.92[b]	102.48[b]	212.37[b]

[a]Wagner (2011).
[b]O'Neil (2006).

ND = no data.

A summary of available toxicity values for rubidium and selected rubidium compounds from U.S. EPA and other agencies/organizations is provided in Table 2.

Table 2. Summary of Available Toxicity Values for Rubidium, Rubidium Chloride, Rubidium Hydroxide, and Rubidium Iodide

Source[a]	Value (applicability)	Notes	Reference
Noncancer			
IRIS	NV	NA	U.S. EPA (2016)
HEAST	NV	NA	U.S. EPA (2011)
DWSHA	NV	NA	U.S. EPA (2012)
ATSDR	NV	NA	ATSDR (2016)
IPCS	NV	NA	IPCS (2016);WHO (2016)
Cal/EPA	NV	NA	Cal/EPA (2014); Cal/EPA (2016a); Cal/EPA (2016b)
OSHA	NV	NA	OSHA (2006); OSHA (2011)
NIOSH	NV	NA	NIOSH (2016)
ACGIH	NV	NA	ACGIH (2015)
Cancer			
IRIS	NV	NA	U.S. EPA (2016)
HEAST	NV	NA	U.S. EPA (2011)
DWSHA	NV	NA	U.S. EPA (2012)
NTP	NV	NA	NTP (2014)
IARC	NV	NA	IARC (2015)
Cal/EPA	NV	NA	Cal/EPA (2011); Cal/EPA (2016a); Cal/EPA (2016b)
ACGIH	NV	NA	ACGIH (2015)

[a]Sources: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; Cal/EPA = California Environmental Protection Agency; DWSHA = Drinking Water Standards and Health Advisories; HEAST = Health Effects Assessment Summary Tables; IARC = International Agency for Research on Cancer; IPCS = International Programme on Chemical Safety; IRIS = Integrated Risk Information; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration.

NA = not applicable; NV = not available.

Literature searches were conducted in July 2013 and June 2016 for studies relevant to the derivation of provisional toxicity values for rubidium (CASRN 7440-17-7). The searches included the following rubidium compounds: rubidium chloride (CASRN 7791-11-9), rubidium hydroxide (CASRN 1310-82-3), rubidium nitrate (CASRN 13126-12-0), dirubidium dichromate (CASRN 13446-73-6), rubidium fluoride (CASRN 13446-74-7), rubidium dichloride (CASRN 39356-55-3), rubidium carbonate (CASRN 584-09-8), rubidium sulfate (CASRN 7488-54-2), rubidium hydrogen sulfate (CASRN 15587-72-1), and rubidium iodide (CASRN 7790-29-6). Searches were conducted using U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature. The following databases were searched: PubMed, ToxLine (including TSCATS1), and Web of Science. The following databases were searched outside of HERO for health-related values: ACGIH, ATSDR, Cal/EPA, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA Office of Water (OW), U.S. EPA TSCATS2/TSCATS8e, NIOSH, NTP, and OSHA.

REVIEW OF POTENTIALLY RELEVANT DATA (NONCANCER AND CANCER)

Of the rubidium compounds evaluated, only rubidium chloride provided useful toxicity information for the potential derivation of provisional toxicity values. Tables 3A and 3B provide an overview of the relevant databases for rubidium chloride and include all potentially relevant repeated dose short-term-, subchronic-, and chronic-duration studies. Principal studies are identified in bold. Reference can be made to details provided in Tables 3A and 3B. The phrase "statistical significance," used throughout the document, indicates a p-value of < 0.05 unless otherwise specified.

Table 3A. Summary of Potentially Relevant Noncancer Data for Rubidium Chloride								
Category[a]	**Number of Male/Female, Strain, Species, Study Type, Study Duration**	**Dosimetry[b]**	**Critical Effects**	**NOAEL[b]**	**BMDL/ BMCL[b]**	**LOAEL[b]**	**Reference**	**Notes[c]; Comments**
Human								
1. Oral (mg/kg-d)								
Short-term	**0 M/31 F, capsule, up to 3 wk**	**2.6−10.3 (Average doses: Wk 1 = 5.3, Wk 2 = 5.8, Wk 3 = 5.6)**	**Weight gain (8/31), diarrhea (7/31), nausea/vomiting (2/31), confusion (4/31), excitement/ agitation (4/31), polyuria (2/31), adverse reaction (2/31)**	**NDr**	**NDr**	**5.3**	Placidi et al. (1988)	**PR; PS No control group; only 16 people completed 3 wk of treatment; hematology and serum chemistry results were not made available.**
Short-term	0 M/10 F, capsule, 15 d	5.1	None	5.1	NDr	NDr	Tuoni et al. (1987)	PR; Serum chemistry related to kidney function and kidney function test data available; serum chemistry related to liver or other organ function was not available.
Short-term	2 M/18 F, 60 d	5.1, 10.3	Skin rashes and diarrhea, described as "slight adverse effects"	NDr	NDr	5.1	Torta et al. (1993)	PR; Written in Italian; marked antidepressant effect
Short-term	15 subjects (sex not reported), 3 wk	7.7	None	7.7	NDr	NDr	Brundusino and Cairoli (1996)	PR; Written in Italian; "lack of side effects"

Table 3A. Summary of Potentially Relevant Noncancer Data for Rubidium Chloride								
Category[a]	**Number of Male/Female, Strain, Species, Study Type, Study Duration**	**Dosimetry[b]**	**Critical Effects**	**NOAEL[b]**	**BMDL/ BMCL[b]**	**LOAEL[b]**	**Reference**	**Notes[c]; Comments**
Short-term	0 M/2 F subjects, solution, administered intermittently over 35- or 44-d period	Unspecified amounts of a 50 g/L solution administered	None	NDr	NDr	NDr	Paschalis et al. (1978)	PR; Hematology, serum chemistry or histopathological analysis of any organ were not performed; "no severe effects"
Short-term	4 subjects (sex not reported), solution, (1 patient intermittently for 86 d)	14.3 or 21.4 (single dose) 1 patient administered a total of 32.4 g over 86 d intermittently (5.4 mg/kg-d)	Minimal or moderate increase in proportion of lower frequency signals in EEG, transient decrease in pulse rate	NDr	NDr	NDr	Fieve et al. (1971)	PR; Only blood and urine electrolyte analysis performed; no adverse effects reported
Short-term	5 subjects (sex not reported), 15−86 d	Unspecified amount	None	NDr	NDr	NDr	Fieve and Meltzer (1974); Fieve et al. (1973)	PR; No serum chemistry or hematology is available; "no immediate or long-term effects"
Short-term	15 subjects (sex unspecified), up to 80 d	Unspecified amount	None	NDr	NDr	NDr	Meltzer and Fieve (1975)	PR; No serum chemistry or hematology is available; "no immediate or long-term effects"
2. Inhalation (mg/m^3)								
ND								

Table 3A. Summary of Potentially Relevant Noncancer Data for Rubidium Chloride								
Category[a]	**Number of Male/Female, Strain, Species, Study Type, Study Duration**	**Dosimetry[b]**	**Critical Effects**	**NOAEL[b]**	**BMDL/ BMCL[b]**	**LOAEL[b]**	**Reference**	**Notes[c]; Comments**
Animal								
1. Oral (mg/kg-d)								
Short-term	3−4 M/3−4 F, Beagle dog, capsules, 30 d	0 (*n* = 3), 48 (*n* = 3), 145 (*n* = 4)	Gastrointestinal irritation, emesis, colonic congestion	NDr	NDr	48	Stolk (1974)	PR; Hematology, serum chemistry present; histology data not made available; apparent portal-of-entry effects
Short-term	10−20 M/0 F, Swiss-Webster mouse, drinking water, 3 wk	0, 299, 597, 896	Convulsive seizures in response to sound stimuli, and death	299	NDr	597 (FEL)	Alexander and Meltzer (1975)	PR; No hematology, serum chemistry, or histopathology of any tissue were performed; only clinical signs and audiogenic convulsions were recorded.
Short-term	10 M/0 F, Swiss-Webster mouse, drinking water, 3 wk	0, 896	Convulsive seizures	NDr	NDr	896 (FEL)	Alexander et al. (1980)	PR; No hematology, serum chemistry, or histopathology of any tissue were performed; only clinical signs and audiogenic convulsions were recorded.

Table 3A. Summary of Potentially Relevant Noncancer Data for Rubidium Chloride								
Category[a]	**Number of Male/Female, Strain, Species, Study Type, Study Duration**	**Dosimetry[b]**	**Critical Effects**	**NOAEL[b]**	**BMDL/ BMCL[b]**	**LOAEL[b]**	**Reference**	**Notes[c]; Comments**
Short-term	10 M/0 F, S-D rat, drinking water, 10 d	0, 167	Decreased saliva flow rate from submandibular gland, increased saliva concentrations of protein, Ca^{2+} and increased activity in NAG	NDr	NDr	167	Abdollahi et al. (1998)	PR; No hematology, serum chemistry, or histopathology of any tissue were performed; biological significance of effects is unclear.
Short-term	10 M/0 F, Swiss mouse, drinking water, 10 d	0, 747, 1,494	Decrease in duration of phenobarbital-induced sleep	NDr	NDr	747	Allain et al. (1974)	NPR; No hematology, serum chemistry, or histopathology of any tissue were performed; biological significance of effect is unclear.
Short-term	5−8 M/0 F, S-D rat, drinking water, 4 wk	0, 834	Increased general motor activity and brain stem levels of cAMP	NDr	NDr	834	Chow and Cornish (1979)	NPR; Hematology, serum chemistry, or histopathology of any tissue was not performed; biological significance of effects is unclear.

Table 3A. Summary of Potentially Relevant Noncancer Data for Rubidium Chloride

Category[a]	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b]	Reference	Notes[c]; Comments
Subchronic	10 M/10 F, Wistar rat, gavage, 30 d	0, 500, 1,000, 2,000	Death (dose- and time-dependent), decreased RBC count (qualitatively), and decreased hemoglobin in females; slightly congested liver, bronchitis or bronchopneumonia with thickened alveolar walls and cellular infiltration in males; mild kidney congestion in both sexes	NDr	NDr	500 (FEL)	Tomizawa et al. (1974) as summarized in Stolk (1974)	PR; Comprehensive study with hematology, clinical chemistry, and histopathology. However, actual data were not presented.
Subchronic	10 or 60 M/0 F, S-D rat, drinking water, varying durations (up to 8 wk)	0, 167, 333, 500	Convulsive seizures in response to sound stimuli, and death	167	NDr	333 (FEL)	Alexander and Meltzer (1975)	PR; No hematology, serum chemistry, or histopathology of any tissue were performed; only clinical signs and audiogenic convulsions were recorded.
Subchronic	Up to 60 M/0 F (numbers per group unspecified), Wistar rat, drinking water, 8 wk	0, 176, 353, 529	None (no convulsions or death in this strain of rats)	529	NDr	NDr	Alexander and Meltzer (1975)	PR; No hematology, serum chemistry, or histopathology of any tissue were performed; only clinical signs and audiogenic convulsions were recorded.

Table 3A. Summary of Potentially Relevant Noncancer Data for Rubidium Chloride

Category[a]	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b]	Reference	Notes[c]; Comments
Subchronic	2 M/2 F, rat (strain unspecified), diet, up to 300 d	0, 14.1, 141, 282, 423, 564	Death, convulsions, decreased body-weight gain	141	NDr	282 (FEL)	Glendening et al. (1956)	PR; No histopathology, hematology, or serum chemistry were performed; Na^+ and K^+ were restricted in the diet which confounded the interpretation of the results.
2. Inhalation (mg/m^3)								
ND								

[a]Category (treatment/exposure duration, unless otherwise noted): Short-term = repeated exposure for >24 hours ≤30 days (U.S. EPA, 2002); long-term (subchronic) = repeated exposure for >30 days ≤10% lifespan for humans (more than 30 days up to approximately 90 days in typically used laboratory animal species) (U.S. EPA, 2002); chronic = repeated exposure for >10% lifespan for humans (more than approximately 90 days to 2 years in typically used laboratory animal species) (U.S. EPA, 2002).
[b]Dosimetry: Oral doses are expressed as ADD (mg/kg-day).
[c]Notes: PR = peer reviewed; NPR = not peer reviewed; PS = principal study.

ADD = adjusted daily dose; cAMP = cyclic adenosine monophosphate; EEG = electroencephalogram; F = female(s); FEL = frank effect level; M = male(s); NAG = *N*-acetyl-β-D-glucosaminidase; ND = no data; NDr = not determined; RBC = red blood cell; S-D = Sprague-Dawley.

Table 3B. Summary of Potentially Relevant Cancer Data for Rubidium Chloride								
Category	**Number of Male/Female, Strain, Species, Study Type, Study Duration**	**Dosimetry**	**Critical Effects**	**NOAEL**	**BMDL/BMCL**	**LOAEL**	**Reference**	**Notes**
Human								
1. Oral (mg/kg-d)								
ND								
2. Inhalation (mg/m^3)								
ND								
Animal								
1. Oral (mg/kg-d)								
ND								
2. Inhalation (mg/m^3)								
ND								

ND = no data.

HUMAN STUDIES

Oral Exposures

Short-Term-Duration Studies

Limited clinical trials have been conducted of orally administered rubidium chloride as an antidepressant (see Table 3A). No severe side effects were observed in any of these studies. The trials, conducted in the United States (Meltzer and Fieve, 1975; Fieve and Meltzer, 1974; Fieve et al., 1973; Fieve et al., 1971), Italy (Brundusino and Cairoli, 1996; Torta et al., 1993; Placidi et al., 1988; Tuoni et al., 1987), and the United Kingdom (Paschalis et al., 1978), administered oral doses ranging from about 180−1,000 mg/day for 15−86 days to small numbers of patients with various types of depression in hospital settings. Brief reviews of the trials conducted before 1988 were prepared by Williams et al. (1987) and Placidi et al. (1988). All of the reports noted that oral treatment with rubidium chloride was without severe side effects. However, the most comprehensive trial (Placidi et al., 1988), which included the largest number of patients (n = 31) at doses ranging from 2.6−10.3 mg/kg-day (180−720 mg/day) and used a standardized survey on treatment-related symptoms, reported several symptoms that led to downward dosage adjustment or termination of treatment. These symptoms included weight gain (in 8/31 patients), diarrhea (7/31), nausea/vomiting (2/31), polyuria (2/31), confusion (4/31), and excitement/agitation (4/31). In a related study, biomarkers of kidney dysfunction were not changed in 10 patients receiving oral doses of 5.1 mg/kg-day (360 mg/day) rubidium chloride for 15 days (Tuoni et al., 1987).

Placidi et al. (1988)

The clinical trial conducted by Placidi et al. (1988) included the largest number of patients of any of the identified studies (31 women who had been treated with antidepressive therapies in the past). Patients were examined using standardized psychometric tests before and after 3 weeks of daily dosing with one to four capsules containing 180 mg rubidium chloride each. The trial was conducted without blinding, and treatment was preceded by a 1-week period without pharmacological therapy. The average doses were 5.3, 5.8, and 5.6 mg/kg-day (370, 407, and 390 mg/day)[1] in Weeks 1, 2, and 3, respectively. Information about side effects was collected using standardized surveys on a weekly basis or when dosage was changed. In addition, blood was collected before and after treatment for determining plasma rubidium concentration, blood cell counts, and aspartate aminotransferase (AST; formerly called serum glutamic-oxaloacetic transaminase [SGOT]), blood urea nitrogen (BUN), glucose, γ-glutamyl transferase (GGT), alkaline phosphatase (ALP), bilirubin, and electrolytes. Among these blood endpoints, the report only mentioned results for plasma rubidium concentrations, which ranged between 0.15 and 0.37 mEq/L (mmol/L) and did not correlate with clinical improvement. The mean duration of treatment was 14.3 days, as only 52% of the patients received the complete schedule of treatment. Premature terminations were due to adverse reaction (n = 2), inefficacy (n = 7), mania (n = 1), and patient requests for termination due to significant improvement (n = 5). By Week 2, about two-thirds of patients showed statistically significant clinical improvement in the standardized psychometric measures. Reported symptoms (n = number of patients reporting) that led to downward dosage adjustment or interruption of treatment were

[1]Adult human standard body weight of 70 kg was used for all dosimetric conversions in human studies throughout unless study-specific body weights were reported. Doses were calculated as follows: reported dose (mg/day) ÷ standard body weight (70 kg) = single, average daily, or average weekly dose (mg/kg-day). Sample calculations presented using weekly dose data from Placidi et al. (1988): 370 mg/day ÷ 70 kg = 5.3 mg/kg-day; 407 mg/day ÷ 70 kg = 5.8 mg/kg-day; 390 mg/day ÷ 70 kg = 5.6 mg/kg-day.

weight gain (n = 8), diarrhea (n = 7), nausea/vomiting (n = 2), polyuria (n = 2), confusion (n = 4), and excitement/agitation (n = 4). It is not clear from the Placidi et al. (1988) study report whether each individual was administered the same dose throughout the study or what the individual average daily doses of rubidium chloride were for each patient. Only the weekly average daily doses (ADDs) consumed by all the remaining subjects (at least 16 patients) in Weeks 1, 2, and 3 were reported. The Week 1 ADD of 5.3 mg/kg-day is identified as the lowest-observed-adverse-effect level (LOAEL) because it was the lowest ADD reported where patients exhibited adverse effects such as diarrhea, vomiting/nausea, body-weight gain, excitation/agitation, confusion, and polyuria. A no-observed-adverse-effect level (NOAEL) could not be identified.

Tuoni et al. (1987)

Measures of kidney function were within normal ranges after 10 women with bipolar emotional disturbances received 5.1 mg/kg-day (360 mg/day)[1] rubidium chloride for 15 days (Tuoni et al., 1987). This study appears to have been conducted at the same institution as the Placidi et al. (1988) clinical trial. Kidney function was the focus because it is a side effect from repeated treatment for bipolar emotional disturbances with lithium, a Group 1A alkali metal like rubidium. One week prior to the start of rubidium chloride treatment, patients received no pharmacological therapies. The following endpoints were examined, before and after treatment: urea clearance, creatinine clearance, uric acid clearance, plasma and urinary electrolytes, BUN, and urinary levels of α-glucuronidase, N-acetyl-β-D-glucosaminidase (NAG), muramidase, and GGT. Mean values of these endpoints (before and after treatment) were reported to be within normal ranges. No statistically significant adverse changes were found for any of the endpoints after treatment. A NOAEL of 5.1 mg/kg-day is identified based on the absence of any adverse side effects. No LOAEL is identified.

Torta et al. (1993)

An English language abstract reported "slight adverse effects" in the form of diarrhea and skin rashes among 20 depressed patients (18 females and 2 males) who were given oral doses of 5.1 or 10.3 mg/kg-day (360 or 720 mg/day)[1] rubidium chloride for 60 days (Torta et al., 1993). The treatment was reported to elicit a "marked and rapid antidepressive action." The full report of this trial is in Italian and was not translated for this assessment. A LOAEL of 5.1 mg/kg-day (the lowest dose tested) is identified based on skin rashes and diarrhea, described as "slight adverse effects," and no NOAEL is identified.

Brundusino and Cairoli (1996)

A "lack of side effects" and "therapeutic efficacy" were reported in the English language abstract of a trial in which oral doses of 7.7 mg/kg-day (540 mg/day)[1] rubidium chloride were given to 15 depressed patients for 3 weeks (Brundusino and Cairoli, 1996). The full report of this study is in Italian, and was not translated for this assessment. A NOAEL of 7.7 mg/kg-day is identified based on "lack of side effects." No LOAEL can be identified because only one dose was tested.

Paschalis et al. (1978)

No "severe side effects" were noted in a trial of two female patients with chronic bipolar emotional disturbance who received unspecified volumes of a solution containing 50 g/L (410 mmol/L) rubidium chloride intermittently over a 35- or 44-day period, achieving peak rubidium erythrocyte concentrations of 9.4 and 10.5 mmol/L, respectively

(Paschalis et al., 1978). In these patients, rubidium chloride treatment was associated with positive changes in mood and prolongation of mania periods. Three other chronic bipolar patients received an unspecified volume of the same rubidium chloride solution once each, without experiencing changes in mood. No severe side effects were reported by these patients. No NOAEL or LOAEL can be identified because no adverse effects were reported at any of the doses tested.

Fieve et al. (1971); Fieve and Meltzer (1974); Fieve et al. (1973); Meltzer and Fieve (1975)

Oral doses of 8.2 or 12.4 mmol (~1 or 1.5 g)[2] rubidium chloride (given as single dose of 8.2 mmol or split into two doses of 4.1 or 6.2 mmol given 4 hours apart; resulting adjusted daily doses are 14.3 or 21.4 mg/kg-day)[3] were reported to produce a minimal or moderate increase in the proportion of lower frequency signals in electroencephalographs, a transient decrease in pulse rate, and no detectable changes in clinical state in four volunteer subjects, including two patients hospitalized with depression and two normal subjects (Fieve et al., 1971). One of the depressed patients was given unspecified oral doses of rubidium chloride intermittently for 86 days for a cumulative administered dose of 268 mEq (32.4 g)[4]. No adverse side effects were reported or observed during the treatment period and during 4 months after treatment. No "meaningful gross therapeutic effects" were reported by the patient, and no changes were observed in the frequency or duration of manic and depressive cycles. Plasma concentrations of rubidium were determined at numerous times during treatment. The maximum concentration, about 0.16 mEq/L, was measured on Day 75 (Meltzer and Fieve, 1975; Fieve and Meltzer, 1974; Fieve et al., 1973).

No "immediate or long-term side effects" were observed in five hospitalized depression patients given oral doses of rubidium chloride intermittently for 15 to 86 days, achieving plasma rubidium concentrations as high as 0.35 mEq/L (Fieve and Meltzer, 1974; Fieve et al., 1973). No "mood changes" were noted in four of these patients showing maximum plasma concentrations of about 0.28 mEq/L in 40 days of treatment, 0.35 mEq/L in 23 days of treatment, 0.3 mEq/L in 20 days of treatment, or 0.1 mEq/L in 44 days of treatment (Fieve and Meltzer, 1974). One patient with a maximum plasma concentration of about 0.3 mEq/L showed recovery from depression (i.e., positive changes in mood) within about 15 days of treatment (Fieve and Meltzer, 1974). In a later report of this clinical trial, a total of 15 patients with bipolar disturbances were treated with rubidium chloride, achieving maximum plasma rubidium concentrations as high as 0.4 mEq/L (Meltzer and Fieve, 1975). Three patients experienced marked increase in mood, two experienced slight increase in mood, five experienced no change in mood, and one experienced a decrease in mood. Four patients did not meet the criteria of retaining at least 200 mEq and achieving greater than or equal to 0.25 mEq/L of rubidium in plasma. No NOAEL or LOAEL can be identified because no adverse effects were reported at any of the doses tested.

[2]Sample calculation: 8.2 mmol × 120.92 mg/mmol = 992 mg = ~1 g.
[3]Sample calculations: 1 g/day (or 1,000 mg/day) ÷ 70 kg = 14.3 mg/kg-day;
1.5 g/day (or 1,500 mg/day) ÷ 70 kg = 21.4 mg/kg-day.
[4]Sample calculation: 268 mEq = 268 mmol; 268 mmol × 120.92 mg/mmol = 32,406 mg = 32.4 g.

Inhalation Exposures

No studies examining possible associations between health effects in humans and repeated inhalation exposure to rubidium have been identified.

ANIMAL STUDIES

Oral Exposure

Short-Term-Duration Studies

Stolk (1974)

Preliminary results were reported from a study in which groups of Beagles were given encapsulated doses of rubidium chloride for 30 days: three control dogs; three dogs given 0.4 mEq/kg-day (~48 mg/kg-day); and four dogs given 1.2 mEq/kg (~145 mg/kg-day)[5]. Results from necropsy, hematology, and blood chemistry were presented, but histology of tissues was not completed when the report was prepared. No follow-up report of this study was located in the literature search for this assessment. Evidence presented for gastrointestinal irritation was frequent emesis after dose administration in 1/3 low-dose and 2/4 high-dose dogs, and generalized congestion of the colonic mucosa was noted in 2/3 low-dose and 4/4 high-dose dogs. Necropsy showed no gross effects in the kidney, liver, or heart in exposed dogs. No exposure-related changes were found in red blood cell (RBC) or white blood cell (WBC) counts, hemoglobin, hematocrit, or blood chemistry variables (calcium, inorganic phosphate, glucose, creatinine, BUN, uric acid, cholesterol, total protein, albumin, and total bilirubin). The lowest dose tested of 48 mg/kg-day appears to be a LOAEL for gross signs of gastrointestinal tract irritation without changes in hematological or blood chemistry variables. The small number of dogs per group and the lack of histological examination limit the reliability of this LOAEL determination. A NOAEL cannot be identified.

Alexander et al. (1980); Alexander and Meltzer (1975)

Repeated exposure of mice to high concentrations of rubidium chloride in drinking water has been shown to increase the incidence of animals susceptible to audiogenic seizures (Alexander et al., 1980; Alexander and Meltzer, 1975). These studies were conducted because earlier studies noted that some rats receiving repeated oral doses of rubidium chloride had convulsive seizures induced by the noise from the release of compressed air.

In the Alexander et al. (1980) study, male Swiss-Webster mice (10 per group) were treated with 0 or 896 mg/kg-day[6] (0.03 Eq/L) rubidium chloride in drinking water for 3 weeks. About 45% of exposed mice exhibited convulsive seizures when stimulated with sound signals of 22 kHz and 74 dbA (40% in one group and 50% in another group) (Alexander et al., 1980).

In the same study, male Swiss-Webster mice (10 per group, except 20 in high-dose group) were exposed to 0, 299, 597, or 896 mg/kg-day[6] (0, 0.01, 0.02, or 0.03 Eq/L) rubidium chloride in drinking water for 3 weeks. Incidences of audiogenic-convulsive seizures were 2/10 in the 597-mg/kg-day dose group and 7/20 in the 896-mg/kg-day dose group (Alexander and Meltzer, 1975).

[5]Sample calculation for converting mEq/kg-day to mg/kg-day throughout: 0.4 mEq/kg-day = 0.4 mmol/kg-day; 0.4 mmol/kg-day × 120.92 mg/mmol = 48 mg/kg-day.

[6]An estimated dose of 896 mg/kg-day is calculated using U.S. EPA (1988) reference values for body weight (0.0316 kg) and water consumption (0.0078 L/day) for subchronically exposed male mice ($B6C3F_1$) as follows: 0.03 Eq/L = 0.03 mol/L × 120.92 g/mol = 3.63 g/L × 1,000 mg/g ×0.0078 L/day ÷ 0.0316 kg = 896 mg/kg-day.

The available data indicate that rubidium-induced susceptibility to audiogenic seizures is a high-dose phenomenon. In these mouse studies, a LOAEL (also a frank effect level [FEL]) of 597 mg/kg-day is identified for audiogenic convulsive seizures. A corresponding NOAEL of 299 mg/kg-day is also identified.

Abdollahi et al. (1998)

Exposure of male Sprague-Dawley (S-D) rats to 167 mg/kg-day rubidium chloride in drinking water (1,200 mg/L [~0.01 Eq/L]) for 10 days caused decreased saliva flow rate from submandibular glands, increased saliva concentrations of protein and Ca^{2+}, and increased activity of NAG in saliva, compared with control rats (Abdollahi et al., 1998). Saliva was collected from anesthetized (60 mg/kg pentobarbital, intraperitoneal [i.p.]) exposed and control rats fitted with cannulas in both submandibular ducts. Secretion was stimulated by pilocarpine (6 mg/kg, i.p.), which reportedly does not stimulate secretion of NAG.

Allain et al. (1974)

Reduced pentobarbital-induced sleeping time was observed in male Swiss mice (10 mice/dose group) exposed to 747 or 1,494 mg/kg-day (0.025 or 0.05 M [or Eq/L])[7] rubidium chloride in drinking water for up to 10 days, compared with controls given drinking water with equimolar concentrations of sodium chloride. Following 10 days of exposure, duration of phenobarbital-induced sleep was decreased by 34 and 60% in low- and high-dose mice, respectively, compared with controls. In high-dose mice, the decreases were dependent on duration of exposure: 9, 24, and 60% decrease in sleep duration after 2, 5, and 10 days of exposure, respectively. In mice exposed to 1,494 mg/kg-day (0.05 M) rubidium chloride for 10 days, the mean cerebral concentrations of pentobarbital 8, 16, or 24 minutes after pentobarbital injection were not statistically significantly different from control values, providing evidence that rubidium chloride did not influence the metabolism of pentobarbital. From the results, the study authors proposed that rubidium chloride may have similar pharmacological properties to amphetamine.

Chow and Cornish (1979)

Increased general motor activity and brainstem levels of cyclic adenosine monophosphate (cAMP) were found in groups of 5−8 male S-D rats provided 834 mg/kg-day rubidium chloride (0.05 M [~6 g/L]) in drinking water for 4 weeks compared with control rats. This dose is identified as a LOAEL, and no NOAEL is identified. No additional study details were provided.

Subchronic-Duration Studies

Tomizawa et al. (1974), as cited by Stolk (1974)

Groups of Wistar rats (10/sex/dose) were given daily gavage doses of 0, 500, 1,000, or 2,000 mg/kg-day rubidium chloride in water (0, 4.13, 8.26, or 16.5 mEq/kg-day) for up to 30 days. Deaths occurred in 2 males and 2 females between Days 18 and 30 in the 500-mg/kg-day group, 4 males and 5 females between Days 15 and 30 in the 1,000-mg/kg-day group, and 10 males and 9 females between Days 10 and 25 in the 2,000-mg/kg-day group. The rats died while crouching quietly with lowered spontaneous motor activity. Hematological findings were reported qualitatively as decreased RBC counts in males and females in all exposed groups and decreased hemoglobin levels in females in all exposed groups, with no changes in hematocrit, relative to control values. No exposure-related changes in blood

[7]Note that for rubidium chloride, 1 M = 1 Eq/L because the valence state = 1.

chemistry endpoints (Na^+ and K^+, glucose, creatinine, BUN, total protein, SGOT, alanine aminotransferase [ALT; formerly called serum glutamic pyruvic transaminase, or SGPT], and ALP) were found. Changes in urinalysis endpoints from control values were also reported qualitatively: decreased urine volume in low- and middle-dose males at 2 weeks and middle-dose females at 2−4 weeks, and increased urine levels of Na^+ and K^+ in males and females in the 1,000- and 2,000-mg/kg-day groups, generally at Weeks 1−4. Necropsy findings were reported qualitatively (without incidence data) as congestive edema of the lung, pneumonitis, pulmonary abscess formation, and cloudy swelling of the kidney in exposed animals, and pneumonitis in one control rat.

Histopathology was also reported qualitatively without incidence data for all lesions. Histologic evaluation of spleen, pituitary gland, thymus, adrenal glands, pancreas, testis, and ovary were reported to be "benign," whereas adverse changes were described for the liver, lung, heart, and kidney in exposed groups compared with control groups. Histopathology in the 500-mg/kg-day group was described as consisting of slightly congested liver, bronchitis or bronchopneumonia with thickened alveolar walls and cellular infiltration in all male rats (but not females), and mild kidney congestion without major alterations in glomeruli or tubules. In the 1,000-mg/kg-day group, histopathology was described as: degeneration of liver cells without necrosis: endocardial thrombus with mild degeneration of the heart muscle and neutrophilic infiltration in two dead animals: congestive pulmonary edema with exudative cells and yellowish-brown pigmentation, which was prominent in dead animals; and markedly degenerated or destructed renal tubules in animals of both sexes, especially noted in dead animals. Histopathology in the 2,000-mg/kg-day group was described as: degeneration of liver cells without necrosis, myocardial degeneration and inflammatory cell infiltration in one animal, severe congestive pulmonary edema with hemorrhage and pneumonitis, especially in animals with marked kidney lesions; and markedly degenerated or destructed renal tubules in animals of both sexes, especially noted in dead animals.

The lowest dose (500 mg/kg-day) in this 30-day study appears to be a FEL with premature deaths occurring in 20% of the rats. At higher dose levels (1,000 and 2,000 mg/kg-day), greater percentages of rats had premature deaths, with marked histopathological changes in the lungs and kidneys. Decreased RBC counts and hemoglobin were reported for all exposed groups, but further details were not available. A NOAEL is not identified.

Alexander and Meltzer (1975)

As in mice, repeated exposure of rats to high concentrations of rubidium chloride in drinking water has been shown to increase the incidence of animals susceptible to audiogenic seizures (Alexander et al., 1980; Alexander and Meltzer, 1975).

In a study by Alexander and Meltzer (1975), male S-D rats were exposed to 0 (10 rats), 167 (10 rats), 333 (10 rats), or 500 mg/kg-day (60 rats) (0, 0.01, 0.02, or 0.03 Eq/L, respectively) rubidium chloride in drinking water for up to 8 weeks. Upon stimulation with sound signals of 22 kHz and 74 dbA, the incidence of convulsive seizures was 1/10 (treatment terminated on Day 56) and 17/60 (treatment terminated on Day 31) in animals treated with 333 or 500 mg/kg-day rubidium chloride, respectively. Deaths were observed only in 4/60 rats treated with 500 mg/kg-day and none in 333-mg/kg-day treated rats. No audiogenic effects were observed in rats treated with 167 mg/kg-day.

In the same study by Alexander and Meltzer (1975), male Wistar rats (up to 60 per group) were exposed to 0, 176, 353, or 529 mg/kg-day rubidium chloride in drinking water for up to 8 weeks. Unlike the S-D rats, no convulsions or deaths were observed in the Wistar rats.

The rate of development of this susceptibility to sound was dose-related, and less rubidium chloride was needed to induce susceptibility if dietary levels of potassium and magnesium were deficient (Alexander and Meltzer, 1975). Variability between S-D and Wistar rat strains was also evident. At similar doses, Wistar rats did not show convulsive behavior in any of the doses when exposed for up to 8 weeks. Tissue rubidium levels were not significantly different in audiosensitive and audioresistant rats exposed to rubidium chloride (Alexander and Meltzer, 1975). The available data indicate that rubidium-induced susceptibility to audiogenic seizures is a high-dose phenomenon. In these rat studies, a LOAEL (also an FEL) of 333 mg/kg-day is identified for audiogenic convulsive seizures. A corresponding NOAEL of 167 mg/kg-day is also identified.

Glendening et al. (1956)

To test whether rubidium is an essential element, rats were treated with varying levels of Rb, Na^+, and K^+. Four rats per group (two females and two males) were fed diets containing 0, 0.01, 0.1, 0.2, 0.3, or 0.4% rubidium with constant K^+ and Na^+ levels in feed (equivalent to 0, 14.1, 141, 282, 423, or 564 mg/kg-day[8] of rubidium chloride, respectively) in the absence or presence of 0.2% sodium (added as sodium chloride) in a synthetic custom basal diet for up to 300 days. Body weight was recorded on Days 10, 20, 40, 80, and 120 of treatment. Rubidium chloride at 282 mg/kg-day and higher doses decreased survival time. Excitement from handling caused convulsions, often leading to death. Postmortem findings were not conclusive. Lungs, heart, liver, kidney, and brain were weighed and preserved for analysis. A dose of 282 mg/kg-day rubidium chloride appears to be the lowest dose that caused death, and is thus identified as a FEL, and 141 mg/kg-day appears to be a NOAEL. The reduction in body weight was present in the 282-, 423-, and 564-mg/kg-day dose groups beginning on Day 40. Body weight was reduced compared to controls in the 141-mg/kg-day dose group beginning on Day 80. Conversely, rats treated with 14.1 mg/kg-day exhibited increased body weight compared to controls from Days 40−120. However, because there are only four rats per group (two per sex), the biological relevance of the changes in body weight following rubidium chloride exposure is unclear. One of the major shortcomings of this study is that the synthetic diet has half the content of Na^+ and K^+ (compared to laboratory chow from the same study), and lower levels of Na^+ and K^+ have been shown to enhance the effects of rubidium. Therefore, the interpretation of the effects observed in this study may be confounded by the reduced levels of Na^+ and K^+.

Männistö and Saarnivaara (1976); Saarnivaara and Männistö (1976)

These studies examined counteraction of the antinociception effects (i.e., pain diminishment in a hot plate test) of antipsychotic drugs and narcotic analgesic drugs in male mice exposed to 247 mg/kg-day rubidium chloride in drinking water (as 1 g/L [~0.008 Eq/L]) for up to 21 days (Männistö and Saarnivaara, 1976; Saarnivaara and Männistö, 1976). However, the

[8]Rubidium chloride consists of 70.68% of Rb element. Rat (Fischer 344) rat default food intake factor default for subchronic duration study is 0.1. Dosimetry calculation:0.01% rubidium in feed = 0.01/0.7068 = 141 ppm of rubidium chloride; 141 ppm × 0.1 [waterfood intake factor calculated using average Fischer 344 rat body weight (BW) and average water food intake according to U.S. EPA (1988)] = 14.1 mg/kg day.

reports had apparent errors in tables reporting the results, discrepancies between results in the tables and conclusions in the text, and inconsistencies of effects with duration of exposure to rubidium chloride and across drugs of the same class. These reports were considered to be unreliable sources of information for the purposes of identifying health hazards from subchronic or chronic durations of exposure to rubidium and deriving provisional reference doses (p-RfDs) for rubidium chloride.

Inhalation Exposures

No studies have been identified examining any toxicologically pertinent endpoints following inhalation exposure of laboratory animals to rubidium or rubidium compounds.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Tests Evaluating Genotoxicity and/or Mutagenicity

Rubidium chloride did not induce deoxyribonucleic acid (DNA) damage in the rec assay with *Bacillus subtilis* (Kanematsu et al., 1980). Other tests of rubidium genotoxicity in short-term in vitro or in vivo tests have not been identified.

Other Supporting Human Studies

Severe dermatitis of the face, eyelids, and periorbital areas occurred in a 70-year-old man following 5 months of treatment with ophthalmic preparations containing rubidium chloride for the treatment of cataracts (Cameli et al., 1990). Skin patch tests with a 1% rubidium chloride solution were strongly positive for this subject, whereas patch testing with 10% rubidium chloride in 20 healthy human subjects produced negative results. Other supporting human studies identifying possible adverse effects of rubidium chloride have not been identified.

Supporting Animal Toxicity Studies

Reported acute oral lethality values for rubidium compounds in rats are median lethal dose (LD_{50}) values of 586 mg/kg for rubidium hydroxide and 4,708 mg/kg for rubidium iodide (Johnson et al., 1975; Johnson et al., 1972). The LD_{50} values for rubidium chloride are 4,440 mg/kg in rats and 3,800 mg/kg in mice (ChemIDplus, 2016).

A number of studies of animals parenterally exposed for short time periods to rubidium chloride reported changes in behavior and associated endpoints. Observations of rubidium-induced changes in general activity include the following.

- Increased low frequency changes in electroencephalograms and increased locomotor activity in monkeys following intravenous (i.v.) injection with 2 mEq of rubidium chloride. In another experiment, monkeys were given oranges injected with increasing concentrations of rubidium chloride up to the point where the monkeys refused to eat them. One monkey retreated instantly after consuming 4 mmol. A second monkey, originally aggressive, became hyperactive and more aggressive after consuming increasing once-a-week doses of 0.5, 1.0, 2.0, 4.0 mmol rubidium and trace amounts in the fifth week. The monkeys that were administered rubidium chloride in oranges orally showed none of the toxic effects noted after i.v. injection (Meltzer et al., 1969).
- Increased shock-elicited aggressive behaviors in rats given single i.p. injections of 0.3 or 0.6 mEq/kg rubidium chloride, compared with rats given 6 mEq/kg potassium chloride (Stolk et al., 1971).

- Increased motor activity in rats given 14 daily i.p. injections of 3 mEq/kg rubidium chloride, compared with rats given injections with 3 mEq/kg sodium chloride (Acobettro et al., 1979).
- Increased rearing activity in rats over a period of 6 hours after i.p. administration of 3 or 6 mEq/kg BW rubidium chloride (Ribas et al., 1979). This report also noted that statistically significant elevations of serotonin concentrations were found in the hypothalamus of rats given daily i.p injections of 1 mEq/kg body weight (BW) rubidium chloride for 14 days, but not in rats given three or six daily injections.
- Decreased immobility times in forced swimming test (FST) and tail suspension test (TST) in male NMRI mice tested 60 minutes after i.p. administration of 30 mg/kg rubidium chloride (FST) and 30 and 50 mg/kg (TST). No effects were observed at 10 mg/kg. In a time-course evaluation, decreased immobility time in FST was also observed 30 minutes and 120 minutes after i.p. administration of 30 mg/kg rubidium chloride, but only 30 minutes after administration for TST. In separate i.p experiments, noneffective doses of L-NAME (10 mg/kg) and aminoguanidine (50 mg/kg), coadministered with 30 mg/kg rubidium choride, reversed decreased immobility time in FST and TST, while 7-nitroindazole (25 mg/kg) could not prevent decreased immobility time. Conversely, coadministration of a noneffective L-arginine dose (750 mg/kg) with 10 mg/kg rubidium chloride decreased immobility time in FST and TST (Kordjazy et al., 2015) (Kordjazy et al., 2015).

Other studies found equivocal or no evidence for rubidium-induced general activity in animals.

- Spontaneous locomotor activities were not statistically elevated in male ddY mice given single or 16 repeated (every other day) subcutaneous doses of 50, 150, or 450 mg/kg rubidium, compared with sodium chloride controls (Furukawa and Tokuda, 1976).
- Mice that were repeatedly injected subcutaneously with 150 mg/kg rubidium chloride showed greater activity in response to methamphetamine than sodium chloride controls, but this apparent potentiation of methamphetamine-induced increased activity was not as pronounced with the higher dose of rubidium chloride, 450 mg/kg (Furukawa and Tokuda, 1976).
- No exposure-related effects on immobility time in a forced swimming test were found in male Wistar rats following single or repeated (once daily for 14 days) i.p. injections of 1 or 3 mEq/kg rubidium chloride (Sugihara et al., 1989).
- S-D rats administered 10 mmol of rubidium chloride plus potassium chloride or 20 mmol of potassium chloride only in drinking water for three generations did not show adverse effects compared to control animals, except that the rats in the group receiving rubidium plus potassium were more excitable (Meltzer and Lieberman, 1971).

Wistar rats administered 30 mg/100 g BW-day of rubidium chloride by i.p. injection for 21 days showed degenerative changes in the morphology of liver cells including hypertrophy of hepatocytes with condensed picnotic nuclei, and increased mitochondrial glutamate oxaloacetate transaminase (GOT) levels in the serum. In the kidneys, rubidium chloride treatment caused detachment of the glomerulus from the Bowman's capsule as well as degeneration of the

glomerulus. The activities of both cholinesterase and inorganic pyrophosphatase in the brain were decreased significantly compared to control (Chatterjee et al., 1979). Additionally, isolated rat kidneys perfused with 3 or 6 mEq/L rubidium for an unspecified period of time developed tubular dilations, degeneration, and necrosis, similar in severity to that produced in kidneys perfused with 3 mEq/L lithium (Bertelli et al., 1985).

Metabolism/Toxicokinetic Studies

As reviewed by Williams et al. (1987), orally ingested rubidium chloride is rapidly and completely absorbed by the gastrointestinal tract. It is expected to distribute widely to tissues throughout the body and be excreted predominantly through the kidneys (Williams et al., 1987). On a biochemical and physiological basis, rubidium is considered to resemble potassium; whereas, lithium (another Group 1A alkali metal) is considered to resemble sodium (Williams et al., 1987). Following administration of single oral doses of rubidium chloride (180 mg) to human subjects, peak rubidium concentrations in RBCs were reached within about 3 hours and maintained for 24 hours (del Vecchio et al., 1979). In contrast, peak plasma concentrations were attained within about 60–90 minutes and declined through 24 hours after dose administration (del Vecchio et al., 1979). Paschalis et al. (1978) reported similar blood kinetics in a few patients given oral doses of rubidium chloride at an unspecified level. More than 90% of rubidium in whole blood is contained in RBCs, and rubidium concentrations in RBCs are typically 20- to 30-fold higher than plasma concentrations (Williams and Leggett, 1987). Monitoring of urinary excretion of rubidium in human subjects following oral administration of single doses of rubidium chloride ranging from about 500−1,000 mg found fairly long whole-body half-times of 21−55 days (Fieve et al., 1971). Usuda et al. (2014) reported a recovery of 8−10.5% rubidium in the urine of rats 24 hours after administration of single dose of rubidium as an acetate, bromide, carbonate, chloride, or fluoride. Observed differences in liver and kidney toxicity were attributable to the type of anion rather than rubidium itself (Usuda et al., 2014).

Mode-of-Action/Mechanistic Studies

As reviewed by Williams et al. (1987), the use of rubidium as an antidepressant was suggested by findings indicating that rubidium has biological effects opposite to those of lithium, an agent used to treat patients with bipolar emotional disturbances (i.e., manic depression). Description of a few of these findings follows.

- Rubidium chloride increased shock-induced aggressive behaviors in rats (Stolk et al., 1971), while lithium decreased shock-induced aggressive behaviors in rats (Sheard, 1970).
- Rubidium increased the release and turnover of brain stem norepinephrine (Stolk et al., 1970), while lithium decreased the release of norepinephrine from brain neurons (Schanberg et al., 1967).
- Rubidium increased electroencephalogram frequency in monkeys (Meltzer et al., 1969), while lithium slowed electroencephalograms in manic and nonmanic patients (Mayfield and Brown, 1966).

DERIVATION OF PROVISIONAL VALUES

Tables 4 and 5 present a summary of noncancer and cancer reference values, respectively, for rubidium chloride. IRIS data are indicated in the table, if available.

Table 4. Summary of Noncancer Reference Values for Rubidium Chloride (CASRN 7791-11-9)

Toxicity Type (units)	Species/Sex	Critical Effect	p-Reference Value	POD Method	POD	UF_C	Principal Study
Screening subchronic p-RfD (mg/kg-d)	Human/F	Adverse side effects (weight gain, diarrhea, nausea/vomiting, polyuria, confusion, and excitement/agitation)	5×10^{-3}	LOAEL	5.3	1,000	Placidi et al. (1988)
Chronic p-RfD (mg/kg-d)	Not derived due to inadequate data						
Subchronic p-RfC (mg/m^3)	Not derived due to inadequate data						
Chronic p-RfC (mg/m^3)	Not derived due to inadequate data						

F = female(s); LOAEL = lowest-observed-adverse-effect level; p-RfC = provisional reference concentration; p-RfD = provisional reference dose; POD = point of departure; UF_C = composite uncertainty factor.

Table 5 Summary of Cancer Values for Rubidium Chloride (CASRN 7791-11-9)

Toxicity Type (units)	Species/Sex	Tumor Type	Cancer Value	Principal Study
p-OSF $(mg/kg\text{-}d)^{-1}$	Not derived due to inadequate data			
p-IUR $(mg/m^3)^{-1}$	Not derived due to inadequate data			

p-IUR = provisional inhalation unit risk; p-OSF = provisional oral slope factor.

DERIVATION OF ORAL REFERENCE DOSES

Human and animal data are not completely adequate, and the lack of a comprehensive database does not provide a suitable basis for deriving a p-RfD for rubidium chloride. The specific associated shortcomings are listed below. However, hazards from rubidium chloride exposure have been identified in human and animal studies. Therefore, a screening subchronic p-RfD was derived (see Appendix A).

The available human studies are small clinical trials designed to test the efficacy of rubidium chloride for treating depression in a few patients. The studies' shortcomings are as follows.

- The trials with the greatest number of subjects were those by Placidi et al. (1988) with 31 patients and Torta et al. (1993) with 20 patients, but neither study had an untreated control group for comparison.
- Durations of exposure were mostly on the order of 2−3 weeks. The trial reported by Torta et al. (1993) treated 20 patients with rubidium chloride for 60 days, and reported "slight adverse effects" similar to those reported in the Placidi et al. (1988) study. However, the full report of this trial is in Italian and was not translated for this assessment. Moreover, the half-life of rubidium in humans in more than 20 days [21−55 days; Fieve et al. (1971)], which means approximately 80−100 days (4−5 half-lives) would be required to reach a steady state (Ito, 2011). The duration of 2−3 weeks or 60 days of rubidium treatment in the available human studies is not long enough for rubidium to reach steady-state levels in the body, and may not be long enough to capture all of the effects of rubidium chloride following longer duration exposure.
- Many of the studies did not report clinical chemistry or hematological data to assess effects on different organs and tissue (e.g., liver, kidney, and blood). They mainly mentioned self-reported or clinically observed side effects (weight gain, diarrhea, nausea/vomiting, skin rash, or polyuria) that were noted in the trials (Torta et al., 1993; Placidi et al., 1988).
- A clinical trial (with 10 patients) reported by Tuoni et al. (1987) included objective tests for possible side effects, specifically biomarkers for kidney dysfunction. No effects on these endpoints were found.

A number of studies of animals given oral doses of rubidium chloride for 10−30 days, and one study in rats exposed for 12−300 days (Glendening et al., 1956) are available, but these are not useful for the purposes of deriving a p-RfD for several reasons that are detailed below.

- The most comprehensive study is a 30-day gavage rat toxicity study with an adequate design (e.g., control and three dose groups, and 10 rats/sex/group) and a relatively comprehensive set of toxicity endpoints (e.g., hematology, blood chemistry, urinalysis, and histopathology). However, the lowest dose level, 500 mg/kg-day, caused early mortality in 20% of the low-dose animals (Tomizawa et al., 1974 as cited by Stolk, 1974). A FEL is not a suitable basis for p-RfD derivation. The qualitatively reported hematological and histological findings indicate that the toxicity targets were RBCs, lungs, and kidneys, but it is unknown if these targets would be affected at nonfatal doses.
- A study of Beagles orally exposed for 30 days to encapsulated rubidium chloride at two nonfatal dose levels included necropsy, hematology, and blood chemistry endpoints, but results of histological examinations are not available and exposure groups only contained 3−4 dogs (Stolk, 1974). Both low and high doses induced gross signs of gastrointestinal tract irritation without changes in hematological or blood chemistry variables. This study, however, is not a suitable basis for developing a p-RfD, because of the small number of dogs per group and the lack of histological examination of a comprehensive set of tissues.

- The subchronic-duration oral exposure study in rats by Glendening et al. (1956), which examined rubidium chloride exposure for 12−300 days, had inadequate study design (e.g., only four rats per group, controls were not included in an experiment to study reproductive outcomes). Rubidium toxicity is variable in relation to the amount of sodium and/or potassium present in the body or administered to rats (Glendening et al., 1956). In this study, rubidium chloride effects were demonstrated with restricted sodium and potassium intake (with 0.2% sodium and 0.29% potassium in diet) confounding the effects observed.
- Other available animal studies involving ten 30-day oral exposures are inadequate to serve as a principal study for a p-RfD because they were focused on limited endpoints and did not include more general assessment of toxicity (Abdollahi et al., 1998; Alexander et al., 1980; Chow and Cornish, 1979; Alexander and Meltzer, 1975; Allain et al., 1974).
- Induction of frank effects such as convulsive seizures necessitates a comprehensive neurotoxicity study, which is missing in the current database.
- Although animal studies were relatively more comprehensive than human studies, the lowest dose used in animal studies (Stolk, 1974) was at least nine times higher than the lowest dose that induced effects in human subjects. Hence, animal studies were not useful to derive a p-RfD.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

Suitable data for deriving subchronic or chronic p-RfCs for rubidium or rubidium compounds have not been identified.

CANCER WEIGHT-OF-EVIDENCE (WOE) DESCRIPTOR

Table 6 identifies the cancer WOE descriptor for rubidium.

Table 6. Cancer WOE Descriptor for Rubidium and Rubidium Compounds

Possible WOE Descriptor	Designation	Route of Entry (oral, inhalation, or both)	Comments
"Carcinogenic to Humans"	NS	NA	No human data are available.
"Likely to Be Carcinogenic to Humans"	NS	NA	No adequate chronic-duration animal cancer bioassays are available.
"Suggestive Evidence of Carcinogenic Potential"	NS	NA	No adequate chronic-duration animal cancer bioassays are available.
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Both**	**No adequate chronic-duration animal cancer bioassays are available. No studies are available assessing the carcinogenic potential of rubidium or rubidium compounds in humans or animals following oral or inhalation exposure.**
"Not Likely to Be Carcinogenic to Humans"	NS	NA	No evidence of noncarcinogenicity is available. No adequate chronic-duration animal cancer bioassays are available.

NA = not applicable; NS = not selected.

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

Derivation of a Provisional Oral Slope Factor (p-OSF)

Not derived due to inadequate data.

Derivation of a Provisional Inhalation Unit Risk (p-IUR)

Not derived due to inadequate data.

APPENDIX A. SCREENING PROVISIONAL VALUES

For reasons noted in the main provisional peer-reviewed toxicity value (PPRTV) document, it is inappropriate to derive provisional toxicity values for rubidium chloride. However, information is available for this chemical which, although insufficient to support derivation of a provisional toxicity value under current guidelines, may be of limited use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information in an appendix and develops a "screening value." Appendices receive the same level of internal and external scientific peer review as the PPRTV documents to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of an appendix screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the Superfund Health Risk Technical Support Center.

DERIVATION OF ORAL REFERENCE DOSES

Derivation of a Screening Subchronic Provisional Reference Dose (p-RfD)

Placidi et al. (1988), a peer-reviewed, short-term-duration study in human patients, is selected as the principal study to derive a screening subchronic p-RfD for rubidium chloride.

Limitations

Including Placidi et al. (1988), each of the human studies in the database had limitations with respect to design, duration of treatment, outcomes observed, and dosing. Specifically, Placidi et al. (1988) did not include a control/placebo group for comparison, had only 16/31 patients remaining by the end of the third week, and used subjects who were treated chronically with a variety of antidepressants until 1 week before the start of the rubidium chloride treatment.

Justification for the study

Placidi et al. (1988) had the most number of patients (n = 31 females) in the study and they were exposed to rubidium chloride up to 3 weeks. Only the study by Torta et al. (1993) had a longer exposure duration (60 days) and similar exposure doses, but the detailed study report was not available for review. Neither of these studies are comprehensive. Lower doses of rubidium chloride were tested in Placidi et al. (1988) as well as all other human studies when compared to the animal studies. Although the rat study by Tomizawa et al. (1974) as summarized in Stolk (1974) and the dog study by Stolk (1974) were more comprehensive studies than Placidi et al. (1988), a true no-observed-adverse-effect level (NOAEL) could not be established in these animal studies as all the doses tested produced adverse and frank effects. Based on this information from the database, the Placidi et al. (1988) study in humans was selected to derive a screening subchronic p-RfD.

Justification of adverse effects

Adverse effects such as diarrhea, body-weight gain, vomiting/nausea, excitation/agitation, confusion, and polyuria (Placidi et al., 1988) were considered as critical effects to derive points of departure (PODs). Taken together, all the human studies describe rubidium chloride treatment-related outcomes as producing no adverse effects (Tuoni et al., 1987; Fieve et al., 1971) or lack of side effects (Brundusino and Cairoli, 1996), no severe

adverse effects (Paschalis et al., 1978; Meltzer and Fieve, 1975; Fieve and Meltzer, 1974; Fieve et al., 1973), or adverse effects (Torta et al., 1993; Placidi et al., 1988). Gastrointestinal effects such as vomiting, nausea, and diarrhea in humans were reported by both Placidi et al. (1988) and Torta et al. (1993). Dogs treated with rubidium chloride also exhibited gastrointestinal irritation, emesis, and colonic congestion (Stolk, 1974) concurring with gastrointestinal effects observed in humans.

The POD for derivation of the screening subchronic p-RfD from Placidi et al. (1988) is a **lowest-observed-adverse-effect level (LOAEL) of 5.3 mg/kg-day** for adverse effects such as diarrhea, vomiting/nausea, body-weight gain, excitation/agitation, confusion, and polyuria in human patients. This POD represents the Week 1 average daily dose of 5.3 mg/kg-day, which was the lowest average daily dose (ADD) reported where patients exhibited the aforementioned adverse effects in the Placidi et al. (1988) study. The screening subchronic p-RfD is derived as follows:

$$\begin{aligned} \textbf{Screening Subchronic p-RfD} &= \text{LOAEL} \div UF_C \\ &= 5.3 \text{ mg/kg-day} \div 1{,}000 \\ &= \mathbf{5 \times 10^{-3} \text{ mg/kg-day}} \end{aligned}$$

Table A-1 summarizes the uncertainty factors for the screening subchronic p-RfD for rubidium chloride.

Table A-1. Uncertainty Factors for the Screening Subchronic p-RfD for Rubidium Chloride

UF	Value	Justification
UF_A	1	A UF_A of 1 is applied because a human study is selected as the principal study.
UF_H	10	A UF_H of 10 is applied for intraspecies variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of rubidium chloride in humans.
UF_D	10	A UF_D of 10 is applied to account for deficiencies and uncertainties in the database. The database lacks a proper long-term exposure study, as well as reproductive and developmental toxicity studies in either humans or animals. Additionally, convulsive seizures is one of the common hazards identified in animal studies necessitating a need for a neurotoxicity study in the database.
UF_L	10	A UF_L of 10 is applied for LOAEL-to-NOAEL extrapolation because the POD is a LOAEL.
UF_S	1	A UF_S of 1 is applied because although the POD is based on a short-term-duration study, the severity of adverse side effects in human subjects does not appear to increase following a longer treatment duration (60 d) with an equivalent dose of rubidium chloride.
UF_C	1,000	Composite UF = $UF_A \times UF_H \times UF_D \times UF_L \times UF_S$.

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure.

Derivation of a Screening Chronic Provisional Reference Dose (p-RfD)

Placidi et al. (1988) and other human studies were short-term-duration studies and are not considered appropriate for deriving a screening chronic p-RfD. This is because the half-life of rubidium in humans is 21−55 days (Fieve et al., 1971), and approximately 80−100 days (4−5 half-lives) is required to reach a steady state (Ito, 2011). Accordingly, the durations of 2−3 weeks or 60 days of rubidium exposure in the available human studies is not enough to reach steady-state levels of rubidium in the body and may not be enough to capture all of the effects of rubidium chloride following chronic-duration exposures. Furthermore, the Glendening et al. (1956) study in rats indicated that lower doses of rubidium chloride exposure takes a longer time to develop toxicity, suggesting that severity of toxicity increases with an increase in exposure duration. Hence, a screening chronic p-RfD was not derived from the available short-term-duration studies.

Derivation of Screening Subchronic p-RfDs for Other Rubidium Compounds

The screening subchronic p-RfD derived for rubidium chloride is used as the basis for calculating screening subchronic p-RfDs for additional rubidium compounds. Because the toxicity of the various rubidium salts is expected to be due to rubidium itself, the toxicity of such salts would be directly related to the fraction of the molecular weight contributed from rubidium. Thus, based on molecular-weight adjustments to the screening subchronic p-RfD derived for rubidium chloride (molecular weight = 120.92 g/mol) in this PPRTV assessment, the resulting screening subchronic p-RfDs for other rubidium compounds are summarized in Table A-2 (see calculations below).

Screening Subchronic p-RfD Calculations for Rubidium Compounds[9]

Screening Subchronic p-RfD for Rubidium Hydroxide

= Screening Subchronic p-RfD for Rubidium Chloride × (MW of Rubidium Hydroxide ÷ MW of Rubidium Chloride)
= 5×10^{-3} mg/kg-day × (102.48 g/mol ÷ 120.92 g/mol)
= **4×10^{-3} mg/kg-day**

Screening Subchronic p-RfD for Rubidium Iodide

= Screening Subchronic p-RfD for Rubidium Chloride × (MW of Rubidium Iodide ÷ MW of Rubidium Chloride)
= 5×10^{-3} mg/kg-day × (212.37 g/mol ÷ 120.92 g/mol)
= **9×10^{-3} mg/kg-day**

Screening Subchronic p-RfD for Rubidium

= Screening Subchronic p-RfD for Rubidium Chloride × (MW of Rubidium ÷ MW of Rubidium Chloride)
= 5×10^{-3} mg/kg-day × (85.4678 g/mol ÷ 120.92 g/mol)
= **4×10^{-3} mg/kg-day**

Table A-2. Molecular Weights and Screening Subchronic p-RfDs for Rubidium Compounds

Compound	Fraction as Rubidium (%)	Molecular Weight (g/mol)	Screening Subchronic p-RfD (mg/kg-d)
Rubidium Hydroxide	83.4	102.48	4×10^{-3}
Rubidium Iodide	40.2	212.37	9×10^{-3}
Rubidium	100	85.4678	4×10^{-3}

[9]MW = molecular weight.

APPENDIX B. REFERENCES

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