AMBIENT WATER QUALITY CRITERIA FOR

THALLIUM

Prepared By
U.S. ENVIRONMENTAL PROTECTION AGENCY

Office of Water Regulations and Standards
Criteria and Standards Division
Washington, D.C.

Office of Research and Development
Environmental Criteria and Assessment Office
Cincinnati, Ohio

Carcinogen Assessment Group
Washington, D.C.

Environmental Research Laboratories
Corvalis, Oregon
Duluth, Minnesota
Gulf Breeze, Florida
Narragansett, Rhode Island

DISCLAIMER

This report has been reviewed by the Environmental Criteria and Assessment Office, U.S. Environmental Protection Agency, and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

AVAILABILITY NOTICE

This document is available to the public through the National Technical Information Service, (NTIS), Springfield, Virginia 22161.

FOREWORD

Section 304 (a)(1) of the Clean Water Act of 1977 (P.L. 95-217), requires the Administrator of the Environmental Protection Agency to publish criteria for water quality accurately reflecting the latest scientific knowledge on the kind and extent of all identifiable effects on health and welfare which may be expected from the presence of pollutants in any body of water, including ground water. Proposed water quality criteria for the 65 toxic pollutants listed under section 307 (a)(1) of the Clean Water Act were developed and a notice of their availability was published for public comment on March 15, 1979 (44 FR 15926), July 25, 1979 (44 FR 43660), and October 1, 1979 (44 FR 56628). This document is a revision of those proposed criteria based upon a consideration of comments received from other Federal Agencies, State agencies, special interest groups, and individual scientists. The criteria contained in this document replace any previously published EPA criteria for the 65 pollutants. This criterion document is also published in satisifaction of paragraph 11 of the Settlement Agreement in Natural Resources Defense Council, et. al. vs. Train, 8 ERC 2120 (D.D.C. 1976), modified, 12 ERC 1833 (D.D.C. 1979).

The term "water quality criteria" is used in two sections of the Clean Water Act, section 304 (a)(1) and section 303 (c)(2). The term has a different program impact in each section. In section 304, the term represents a non-regulatory, scientific assessment of ecological effects. The criteria presented in this publication are such scientific assessments. Such water quality criteria associated with specific stream uses when adopted as State water quality standards under section 303 become enforceable maximum acceptable levels of a pollutant in ambient waters. The water quality criteria adopted in the State water quality standards could have the same numerical limits as the criteria developed under section 304. However, in many situations States may want to adjust water quality criteria developed under section 304 to reflect local environmental conditions and human exposure patterns before incorporation into water quality standards. It is not until their adoption as part of the State water quality standards that the criteria become regulatory.

Guidelines to assist the States in the modification of criteria presented in this document, in the development of water quality standards, and in other water-related programs of this Agency, are being developed by EPA.

STEVEN SCHATZOW
Deputy Assistant Administrator
Office of Water Regulations and Standards

ACKNOWLEDGEMENTS

Aquatic Life Toxicity

William A. Brungs, ERL-Narragansett
U.S. Environmental Protection Agency

David J. Hansen, ERL-Gulf Breeze
U.S. Environmental Protection Agency

Mammalian Toxicology and Human Health Effects

Paul B. Hammond (author)
University of Cincinnati

Christopher DeRosa (doc. mgr.) ECAO-Cin
U.S. Environmental Protection Agency

Jerry F. Stara (doc. mgr.), ECAO-Cin
U.S. Environmental Protection Agency

Thomas Clarkson
University of Rochester

Karl L. Gabriel
Medical College of Pennsylvania

John W. Allis, HERL
U.S. Environmental Protection Agency

J.B. Lal
National Institute of Occupational Safety and Health

Gordon Newell
National Academy of Sciences

Rolf Hartung
University of Michigan

John Carroll
U.S. Environmental Protection Agency

S.M. Charbonneau
Health and Welfare, Canada

Patrick Durkin
Syracuse Research Corporation

David H. Groth
National Institute of Occupational Safety and Health

Terri Laird, ECAO-Cin
U.S. Environmental Protection Agency

Steven B. Lutkenhoff, ECAO-Cin
U.S. Environmental Protection Agency

William W. Sutton, EMSL-Las Vegas
U.S. Environmental Protection Agency

Technical Support Services Staff: D.J. Reisman, M.A. Garlough, B.L. Zwayer, P.A. Daunt, K.S. Edwards, T.A. Scandura, A.T. Pressley, C.A. Cooper, M.M. Denessen.

Clerical Staff: C.A. Haynes, S.J. Faehr, L.A. Wade, D. Jones, B.J. Bordicks, B.J. Quesnell , T. Highland, R. Rubinstein.

TABLE OF CONTENTS

	Page
Criteria Summary	
Introduction	A-1
Aquatic Life Toxicology	B-1
Introduction	B-1
Effects	B-1
Acute Toxicity	B-1
Chronic Toxicity	B-2
Plant Effects	B-2
Residues	B-3
Miscellaneous	B-3
Summary	B-3
Criteria	B-4
References	B-11
Mammalian Toxicology and Human Health Effects	C-1
Exposure	C-1
Ingestion from Water	C-1
Ingestion from Food	C-3
Inhalation	C-5
Dermal	C-6
Exposure to Thallium from Food, Water, and Air as a Basis for Estimating Daily Absorption	C-6
Pharmacokinetics	C-7
Absorption	C-8
Distribution	C-9
Excretion	C-11
Total Daily Excretion of Thallium as a Basis for Estimating Daily Absorption	C-18
Body Burden of Thallium as a Basis for Estimating Daily Absorption	C-22
Effects	C-23
Acute, Subacute and Chronic Toxicity	C-23
Synergism and/or Antagonism	C-32
Teratogenicity	C-33
Mutagenicity	C-34
Carcinogenicity	C-34
Criterion Formulation	C-35
Existing Guidelines and Standards	C-35
Current Levels of Exposure	C-35
Special Groups at Risk	C-37
Basis and Derivation of Criterion	C-38
References	C-42

TABLE 1

Water Solubilities of some Thallium Compounds[a]

Compound	Molecular Formula	Solubility (mg/l)	Temperature (°C)
Thallium sulfide	Tl_2S	220	20
Thallium bromide	TlBr	240	0
Thallium chromate	Tl_2CrO_4	300	60
Thallium chloride	TlCl	2,100	0
Thallium sulfate	Tl_2SO_4	27,000	0
Thallium carbonate	Tl_2CO_3	42,000	15
Thallium bromide	TlBr	160,000	20
Thallium hydroxide[b]	TlOH	259,000	0
		520,000	40
Thallium fluoride	TlF	780,000	15

[a]Source: Standen, 1967
[b]Weast, 1975

REFERENCES

Hampel, C.A. (ed.) 1968. The Encyclopedia of Chemical Elements. Reinhold Publishers, New York.

Lee, A.G. 1971. The Chemistry of Thallium. Elsevier Publisning Co., Amsterdam.

Standen, A. (ed.) 1967. Kirk-Othmer Encyclopedia of Chemical Technology. Interscience Publishers, New York.

U.S. Department of the Interior. 1977. Commodity data summaries. Bur. Mines.

Weast, R.C. (ed.) 1975. Handbook of Chemistry and Physics. 56th ed. CRC Press, Cleveland, Ohio.

Windholz, M. (ed.) 1976. The Merck Index. 9th ed. Merck and Co., Inc., Rahway, New Jersey.

Zitko, V. 1975. Toxicity and pollution potential of thallium. Sci. Total Environ. 4: 185.

Aquatic Life Toxicology*

INTRODUCTION

The data base for the effects of thallium on freshwater organisms does not permit any determination of the effects of water quality on toxicity. There are sufficient data to indicate that thallium is chronically toxic to fish and invertebrate species at concentrations as low as approximately 20 µg/l. Algae are also sensitive with effects occurring at concentrations as low as 100 µg/l.

There are a variety of results for thallium and saltwater organisms from tests conducted using static test procedures. No adverse acute effects were observed at concentrations lower than 2,130 µg/l. An embryo-larval test with the sheepshead minnow resulted in adverse effects at concentrations as low as 8,400 µg/l, a concentration about one-half of the 96-hour LC_{50} for that species.

EFFECTS

Acute Toxicity

Daphnia magna 48-hour 50 percent effect concentrations were 2,180 and 910 µg/l (Table 1). The fathead minnow was of similar sensitivity with a 96-hour LC_{50} of 1,800 µg/l (Table 1). Two 96-hour LC_{50} values for the bluegill were 132,000 and 121,000 µg/l which results indicate that this species is rather insensitive to thallium.

The saltwater shrimp species, *Mysidopsis bahia*, was more sensitive than the tested fish species with an LC_{50} value of 2,130 µg/l (Table 1). The

---

*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life and Its Uses in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are calculations for deriving various measures of toxicity as described in the Guidelines.

sheepshead minnow (U.S. EPA, 1978) and the tidewater silverside (Dawson, et al. 1977) are similarly sensitive with LC_{50} values of 20,900 and 24,000 µg/l, respectively (Table 1).

Chronic Toxicity

A life cycle test with Daphnia magna (Kimball, Manuscript) has been conducted and the chronic value was 130 µg/l (Table 2). The acute-chronic ratio for this species is 7.0.

An embryo-larval test has been conducted (U.S. EPA, 1978) with the fathead minnow and adverse effects were observed at the lowest tested thallium concentration of 40 µg/l (Table 2). Kimball (Manuscript) also conducted an embryo-larval test with the same species and observed adverse effects at 81 µg/l but not at 40 µg/l (Table 2). When the chronic value for this species (57 µg/l) is divided into the 96-hour LC_{50}, an acute-chronic ratio of 32 results.

The only chronic test with a saltwater species has been conducted with the sheepshead minnow (U.S. EPA, 1978). No adverse effects during an embryo-larval test were observed at 4,300 µg/l (Table 2). At 8,400 µg/l adverse effects were detected. The acute-chronic ratio for the sheepshead minnow is 3.5.

Species mean acute and chronic values are summarized in Table 3.

Plant Effects

There was a 40 percent inhibition of oxygen evolution by the freshwater alga, Chlamydomonas reinhardi, exposed to a concentration of 40,800 µg/l (Table 4). The 96-hour EC_{50} values for chlorophyll a inhibition and cell number of the alga, Selenastrum caporicornutum, was 110 and 100 µg/l, respectively (U.S. EPA, 1978).

There was a 50 percent inhibition of photosynthesis by two saltwater algal species at thallium concentrations of 4,080 and 51,200 µg/l (Table 4).

Residues

Muscle tissue of Atlantic salmon (Zitko, et al. 1975) bioconcentrated thallium to a concentration 130 times that in the water (Table 5). The bluegill (whole body) bioconcentrated thallium 34 times and the tissue half-life was greater than 4 days (U.S. EPA, 1978).

Zitko and Carson (1975) observed bioconcentration factors of 18 and 12 for the soft shell clam and blue mussel, respectively (Table 5). These results indicate that saltwater clams and mussels do not bioconcentrate thallium as much as freshwater fishes.

Miscellaneous

Zitko, et al. (1975) exposed Atlantic salmon for as long as 2,600 hours and observed 40 and 70 percent mortality at approximately 20 and 45 µg/l, respectively (Table 6). No effects were observed for other species at concentrations close to those affecting the salmon.

Early development of sea urchin eggs was inhibited at concentrations of thallium between 41,000 and 204,000 µg/l (Table 6).

Summary

Daphnia magna and the fathead minnow were of similar acute sensitivity to thallium with LC_{50} values in the range of concentrations from 910 to 2,180 µg/l. The bluegill LC_{50} values were about two orders of magnitude higher. The chronic values for *Daphnia magna* and the fathead minnow were also similar, 130 and 57 µg/l, respectively. There were 50 percent reductions in chlorophyll *a* and cell numbers of an alga at concentrations of 110 and 100 µg/l, respectively. The highest bioconcentration factor for fishes

Table 2. Chronic values for thallium

Species	Method*	Limits (µg/l)	Species Mean Chronic Value (µg/l)	Reference
		FRESHWATER SPECIES		
Cladoceran, *Daphnia magna*	LC	100-181	130	Kimball, Manuscript
Fathead minnow, *Pimephales promelas*	E-L	<40	-	U.S. EPA, 1978
Fathead minnow, *Pimephales promelas*	E-L	40-81	57	Kimball, Manuscript
		SALTWATER SPECIES		
Sheepshead minnow, *Cyprinodon variegatus*	E-L	4,300-8,400	6,000	U.S. EPA, 1978

* E-L = embryo-larval, LC = life cycle or partial life cycle

Acute-Chronic Ratios

Species	Chronic Value (µg/l)	Acute Value (µg/l)	Ratio
Cladoceran, *Daphnia magna*	130	910	7.0
Fathead minnow, *Pimephales promelas*	57	1,800	32
Sheepshead minnow, *Cyprinodon variegatus*	6,000	20,900	3.5

Table 3. Species mean acute and chronic values for thallium

Number	Species	Species Mean Acute Value* (µg/l)	Species Mean Chronic Value (µg/l)	Acute-Chronic Ratio**
		FRESHWATER SPECIES		
3	Bluegill, *Lepomis macrochirus*	126,000	-	-
2	Fathead minnow, *Pimephales promelas*	1,800	57	32
1	Cladoceran, *Daphnia magna*	1,400	130	7.0
		SALTWATER SPECIES		
3	Tidewater silverside, *Menidia beryllina*	24,000	-	-
2	Sheepshead minnow, *Cyprinodon variegatus*	20,900	6,000	3.5
1	Mysid shrimp, *Mysidopsis bahia*	2,130	-	-

* Rank from high concentration to low concentration by species mean acute value.

**See the Guidelines for derivation of this ratio.

REFERENCES

Dawson, C.W., et al. 1977. The acute toxicity of 47 industrial chemicals to fresh and saltwater fishes. Jour. Hazard. Mater. 1: 303.

Dilling, W.J. and C.W. Healey. 1926. Influence of lead and the metallic ions of copper, zinc, thorium, beryllium and thallium on the germination of frogs' spawn and on the growth of tadpoles. Ann. Appl. Biol. 13: 177.

Kimball, G. The effects of lesser known metals and one organic to fathead minnows (Pimephales promelas) and Daphnia magna. Manuscript.

Lallier, R. 1968. Investigation of the toxicity of thallium ions in the eggs of the sea urchin, Paracentrotus lividus. C.R. Acad. Sci. Paris 267: 962.

Nehring, D. 1962. Experiments on the toxicological effect of thallium ions on fish and fish-food organisms. Zeitz. Fisch. 11: 557.

Overnell, J. 1975a. Effect of some heavy metal ions on photosynthesis in a freshwater alga. Pest. Biochem. Physiol. 5: 19.

Overnell, J. 1975b. The effect of heavy meals on photosynthesis and loss of cell potassium in two species of marine algae, Dunaliella tertiolecta and Phaedoctylum tricornutum. Mar. Biol. 29: 99.

U.S. EPA. 1978. In-depth studies on health and environmental impacts of selected water pollutants. U.S. Environ. Prot. Agency, Contract No. 68-01-4646.

Zitko, V. and W.V. Carson. 1975. Accumulation of thallium in clams and mussels. Bull. Environ. Contam. Toxicol. 14: 530.

Zitko, V., et al. 1975. Thallium: Occurrence in the environment and toxicity to fish. Bull. Environ. Contam. Toxicol. 13: 23.

Mammalian Toxicology and Human Health Effects

EXPOSURE

Ingestion from Water

The major problem in assessing the amount of thallium ingested from water is the inadequate sensitivity of analytical methods for thallium. An almost equally serious problem is the limited amount of information available utilizing even the inadequate methodologies currently available. As a matter of fact, essentially all the information available is to be found in two reports. The first of these is a U.S. EPA study which was conducted in cooperation with the National Heart and Lung Institute and the National Center for Health Statistics. Its main purpose was to delineate the occurrence of inorganics in household tap water and relationships to cardiovascular mortality rates (Greathouse, 1978). The second study was not concerned with average or usual exposures. Rather, it was concerned with worse situations, namely the concentration of thallium in the run-off from slag heaps and holding ponds associated with ore processing and mining operations (U.S. EPA, 1977).

In the first study grab samples of tap water were taken from 3,834 homes. The study began in July 1974 and was completed in December 1975. Multi-elemental analyses were conducted using proton-induced x-ray emission (PIXE). The procedure and its characteristics of precision and sensitivity are described in a separate report (U.S. EPA, 1978a). The limit of detectability as applied to water was 0.3 ppb. Samples of tap water were collected from 3,834 households which were randomly selected from 35 geographic areas by

the Bureau of Census to provide a "representative" sample of the U.S. population. Thallium was detectable in only 0.68 percent of the samples. The average thallium concentration, when detectable, was 0.89 ppb. Assuming a water consumption of 2 l/d for the average adult, over 99 percent of adults would consume <1 µg Tl per day.

So far as worse situations are concerned, the so-called Calspan Report (U.S. EPA, 1978a) reviews in great detail the basis for concluding that the leaching of thallium from ore processing operations is the major source of elevated thallium concentrations in water. Thallium is a trace metal associated with copper, gold, zinc and cadmium. Thus, wherever these metals have been mined and processed, an enrichment of the environment with thallium was also suspected to occur. This led to analyses of run-offs from mining and smelting operations involving these other metals. The sensitivity of the analytical methodology for thallium was not as good as for the tap water studies referred to earlier. The overall limit of sensitivity was reported to be 10 ppb, but values as low as 3 ppb are reported. It is not clear how this apparent shift in sensitivity occurred. Mines and processing operations from Washington and California to New Jersey and Pennsylvania were studied. The highest concentrations reported were 30 ppb in slag run-off near Kellogg, Idaho and 21 ppb in the Colorado River just below the Big Williams River which drains the Planet Mine, an operation in which copper is extracted from iron ore. It is not at all clear as to how much of the Colorado River thallium came from that particular mine, since this was a generally ore-rich area. The only other source of information as to discharges from Canadian ore operations into

streams is a study by Zitko, et al. (1975) in which he indicates concentrations of 0.7-88 ppb.

Ingestion from Food

Data concerning the intake of thallium from food are sparse. So far as thallium in man's usual diet is concerned, only three studies are available. They provide only a limited indication as to what might constitute the total contribution of food to daily intake under normal circumstances. Vegetables (lettuce, red cabbage, green cabbage, leek, and endive) averaged 68.2 ppb dry weight (Geilmann, et al. 1960). Assuming 85 percent water content, this would amount to 10 ppb, wet weight. From the same study, bread contained 0.75 ppb, dry weight. The only data concerning thallium in meat report that the concentration in rib eye beef and veal is <0.5 ppm (Mitteldorf and Landon, 1952). Due to the poor analytical sensitivity, this study is not very helpful. It seems unlikely, however, that meats contribute as much thallium to the total diet as vegetables. This is based on two considerations: 1) vegetarians excrete in their urine four times as much thallium as non-vegetarians (Weinig and Zink, 1967); and 2) the concentration of thallium in human skeletal muscle is only approximately 1 ppb (Weinig and Zink, 1967). This raises the interesting question as to why vegetables should contain so much more thallium than meat. It is possible that this is related to the relatively high concentration of thallium in fertilizer. Geilmann, et al. (1960) found 37-230 µg Tl/kg in 4 samples of potash fertilizers containing 35 to 43 percent potassium. Since these studies were conducted on a very limited number of vegetables and fertilizer samples in Germany, it

is difficult to estimate just how representative these data are of the situation in the U.S. In any event, if one accepts that most dietary thallium is to be found in vegetables and that 10 ppb is the average fresh weight concentration, an estimate can be made as to the contribution of food to total intake of thallium in man. The average adult consumption of vegetables in the U.S. is estimated at 0.38 kg/d (Toscano, 1975), and the total food consumption is 1.6 kg/d (U.S. Dep. of Agric., 1968). Assuming the cited concentration figures are correct and they apply to the average diet of vegetables, the daily intake of thallium from vegetables would be (0.38) X (10 µg) or 3.8 µg. As will be shown in the section on Criterion Formulation, this is probably a high estimate. In all probability, the data cited as to concentrations of thallium in a few selected vegetables are really not representative of what is normally eaten in the category of vegetables. Based on the solubility characteristics of thallium, it is also possible that a good deal of thallium is leached out during food preparation.

A bioconcentration factor (BCF) relates the concentration of a chemical in aquatic animals to the concentration in the water in which they live. An appropriate BCF can be used with data concerning food intake to calculate the amount of thallium which might be ingested from the consumption of fish and shellfish. Residue data for a variety of inorganic compounds indicate that bioconcentration factors for the edible portion of most aquatic animals is similar, except that for some compounds bivalve molluscs (clams, oysters, scallops, and mussels) should be considered a separate group. An analysis (U.S. EPA, 1980) of data from a food survey was used to

estimate that the per capita consumption of freshwater and estuarine fish and shellfish is 6.5 g/day (Stephan, 1980). The per capita consumption of bivalve molluscs is 0.8 g/day and that of all other freshwater and estuarine fish and shellfish is 5.7 g/day.

Zitko, et al. (1975) reported a BCF of 130 for thallium in muscle of atlantic salmon, whereas Zitko and Carson (1975) found BCF values of 18 and 12 for the edible portions of the soft shell clam and blue mussel, respectively. If 130 and the geometric mean of 18 and 12 are used with the consumption data, the weighted average bioconcentration factor for thallium and the edible portion of all freshwater and estuarine aquatic organisms consumed by Americans is calculated to be 116.

Inhalation

The concentration of thallium in ambient urban air from six major U.S. cities was reported in a U.S. EPA study conducted by Battelle Columbus Laboratories (U.S. EPA, 1971). The concentrations of thallium were given as weighted averages from data from all cities: low, $\leq .02$; high, 0.1 and typical, < 0.04.

The concentration of thallium in fly ash has been estimated, however, and on this basis the ground level concentration of thallium near a coal-fired plant might be 700 ug/m^3 (Carson and Smith, 1977). This can hardly be used as a basis for judging usual exposure for the general population, but it does suggest a worse case situation. Assuming inhalation of 20 m^3/d and 35 percent retention of the thallium-bearing aerosol, 700 ng Tl/m^3 would result in the daily absorption of 4.9 ug Tl. The air level in Chadron, Nebraska is stated to be .04-.48 ng Tl/m^3. This may be the more typical level

of exposure (Carson and Smith, 1977). Assuming 20 m^3/d inhalation and 35 percent retention, 0.48 ng/m^3 = 3.4 ng Tl/d from air.

Inhalation of thallium in cigarette smoke may, on the other hand, be a very significant source. The urinary excretion of thallium in smokers is about twice that in non-smokers (Weinig and Zink, 1967) and the concentration in cigar stubs was shown to be 57-170 ng/g (Geilmann, et al. 1960), about 20 times the concentration estimated for the diet.

Dermal

The dermal absorption of thallium presumably would normally occur as a result of bathing and from contact with thallium in clothing. It is virtually impossible to estimate the contribution of these potential sources to total intake. Suffice it to say that the concentration of thallium in tap water is less than in body tissues ($<$0.3 µg/l vs. $\sim$ 1 µg/kg in tissues). From this it would seem that the net flux of thallium as a result of bathing would, if anything, be outward rather than inward. As to thallium in clothing, there does not appear to be any information.

Exposure to Thallium from Food, Water and Air as a Basis for Estimating Daily Absorption

In summary, this section on various sources of exposure provides only a very broad perspective as to the relative contributions of known environmental media to which the general population is exposed. The most reliable data, fortuitously, concern thallium in drinking water. It is possible to state with reasonable assurance that $>$99 percent of Americans probably absorb $<$1 µg Tl per day from this medium. Vegetables may contribute as much as

3.8 µg/day (see Ingestion from Foods) and air is probably an insignificant source, being probably no more than 3.4 ng/day (see Inhala tion). If foods other than vegetables are assumed to have a concentration of 1 µg/kg, then their contribution at approximate consumption levels of 1.2 kg (total daily consumption of 1.6 kg minus daily vegetable consumption of 0.38 kg) would be 1.2 µg/day, i.e. (1.2 kg/day x 1 µg Tl/kg in non-vegetable food). Thus, the total daily input based on data reviewed above is $\leq$1 µg (water) + 3.8 µg (vegetables) + .0034 µg (air) + 1.2 µg (non-vegetable food) $\leq$6.0 µg/day. In all of the above, 100 percent absorption is assumed for food and water sources.

PHARMACOKINETICS

Very little is known about the disposition of thallium in man, and most of the limited information concerns cases of clinical poisoning. The reasons for this are twofold. First, thallium has not been thought of as a significant environmental pollutant; therefore, little effort has been made to characterize its metabolism under usual conditions of human exposure. Secondly, the concentration of thallium in biological media is so low that metabolic studies are extremely difficult to conduct with generally available analytical methods. This latter hindrance applies to man, but not to experimental studies in animals since there exists a very convenient radioisotopic form ^{204}Tl, which has a radiological half-life of approximately 3 years, a readily detectable beta emission, and a 70 keV photon owing to K-electron capture.

Since the primary concern of this document is with regard to possible subtle health effects from the low level of thallium to

which man is exposed via water, attention will be drawn wherever possible to the distinction between the pharmacokinetics of massive doses and the pharmacokinetics of small doses. Unfortunately, such distinctions can be drawn only from consideration of animal data.

Absorption

The only study of gastrointestinal absorption in man was conducted in a middle-aged woman with terminal osteogenic carcinoma (Barclay, et al. 1953). Following oral administration of a single tracer dose of ^{204}Tl, only approximately 0.5 percent of the dose was excreted in the feces during the succeeding 72 hours, while urinary excretion rose dramatically. This suggests that no bolus of ^{204}Tl passed unabsorbed. Complete absorption of tracer doses of ^{204}Tl administered orally in rats is suggested by the data of Lie, et al. (1960). They found approximately the same fraction of a single tracer dose of ^{204}Tl in various organs at 1, 2 and 7 days regardless of whether the dose was given orally or by any one of four parenteral routes. There is no information available concerning the deposition and clearance of inhaled thallium aerosols. As with almost all metallic salts, the pattern of deposition of thallium aerosols would depend upon particle size (aerodynamic); and the rate of clearance would depend upon the solubility of the salt. From the report of the Task Group on Lung Dynamics it would be predicted, however, that all salts of thallium (oxide, hydroxide and halide excepted) would be cleared rapidly (days) and that none would be cleared slowly (years) (ICRP, 1966).

The skin as a route of absorption has not received much attention, as is the case with most metallic salts. At one time thallium

was applied to the skin as an ointment containing 3 to 8 percent thallous acetate. Numerous cases of systemic poisoning have been documented to result from this practice (Munch, 1934). This does not mean that skin is a significant portal of entry under usual exposure conditions however. The net movement of thallium through the skin is dependent on the concentration gradient, and the concentration of thallium to which the skin is normally exposed is miniscule in comparison to the concentration under which significant absorption has been demonstrated.

As a summary statement it may be said with reasonable confidence that thallium is completely absorbed from all the usual portals of entry, with the possible exception of the skin.

Distribution

Thallium is widely distributed in the body. It is distributed preferentially to the intracellular space. Based on tracer studies in rats, the apparent volume of distribution has been calculated to be 20 l/kg (Rauws, 1974). This indicates a high degree of concentration in one or more parts of the body. To some extent at least, this preferential intracellular distribution is analogous and related to mechanisms which favor the intracellular localization of potassium. Active transport of thallium into erythrocytes, mediated by (Na-K)ATPase, has been demonstrated by a number of investigators (Gehring and Hammond, 1964; Cavieres and Ellroy, 1974). In spite of the considerable avidity of erythrocytes for thallium, Rauws (1974) estimated that, in rats at least, under steady state conditions 61 percent was distributed to the blood cells as compared to 39 percent in the plasma. Gibson and Becker (1970)

similarly reported a cell-plasma ratio of 1.5-2 in rats. The very minor degree of preferential thallium distribution to blood cells is probably due to the very high concentration of potassium in the blood, which competes with thallium for active transport. Factors other than active transport into cells must be operative in the localization of thallium in various organs and systems, since there does exist some organ-specific concentration. Thus, in both conditions of normal thallium exposure and fatal exposure in man, there is a tendency for thallium to concentrate in the kidneys, colon and hair (Weinig and Zink, 1967; Cavanagh, et al. 1974). In other respects the distribution of thallium is not remarkable.

Thallium distributes rather freely from the maternal circulation to the fetus. The fetal-maternal ratios of tracer doses of ^{204}Tl in rats and mice are reported to be, respectively, 0.84 and 0.46 under steady state conditions (Gibson, et al. 1967). These observations were made on gestation days 18 and 19 for mice and rats respectively. It was also found that thallium administered on days 1 and 7 postnatally was distributed in a manner quite similar to that for adult animals. In a later publication, Gibson and Becker (1970) reported that simultaneous thallium ratios in whole fetuses and in maternal rat blood plasma were approximately 0.07 over a wide range of thallium infusion rates (0.2-6.4 mg/min/kg), indicating that dosage does not seem to alter the kinetics of distribution from mother to fetus. The fetal-maternal ratio in this instance is not contradictory to the authors' earlier observation, cited above, that fetal-maternal ratios in rats and mice are 0.84 and 0.46, respectively, since steady state conditions did not

prevail in the latter study. Low dietary potassium did not significantly alter fetal-maternal distribution of thallium.

So far as distribution of thallium to the human fetus is concerned, there is essentially no quantitative data. One report indicates that no thallium was found in the 5-month fetus of a woman who died of thallium poisoning. Thallium was demonstrated in various tissues of the mother (Neal, et al. 1935). Absence of detectable thallium in this fetus does not rule out its presence, even at abnormally high concentrations since the spectrographic method used probably was neither very sensitive nor very precise. It is only possible to surmise that fetal concentrations were lower than maternal concentrations. Richeson (1958) cites one report in which thallium was found in the tissues of a baby whose mother had taken 1.2 g thallium at term. The infant died five days after birth.

Excretion

There have been numerous reports of the characteristics of thallium excretion in animals using both tracer doses of ^{204}Tl and rather large (up to 10 mg/kg) carrier doses. By contrast, there are only two studies reported of thallium excretion in man from which may be derived any useful kinetic constants. Worse, each of these two studies involved only a single subject. This serious limitation must be remembered in judging the reliability of the safety assessment which ultimately must be made in this document.

The first study traced the fate of an orally-administered tracer dose of ^{204}Tl given to a middle-age woman with osteogenic carcinoma metastatic to the lungs (Barclay, et al. 1953). The dose of thallium given was 0.5 mci, containing 2.3 mg total

thallium. In addition, single oral doses of 45 mg non-radioactive thallium sulfate (presumably = 8.7 mg Tl) were also given every 3 days until 225 mg had been administered. Excretion of radioactivity in the urine and feces was determined for the succeeding 5.5 days. It is evident that fecal excretion was inconsequential as compared to urinary excretion (Figure 1). Based on these data, a first order rate constant of 0.032 day^{-1} was estimated for excretion. The $t_{\frac{1}{2}}$ for rate of excretion of the dose would therefore be 21.7 days. Based on a rate constant of 0.032 day^{-1}, the amount of thallium remaining in the body at the time of death (24 days after administration of ^{204}Tl) would have been 46.3 percent of the dose from:

$$A = A_o \cdot e^{-kt}$$

where:

A = percent dose in body at 24 d

A_o = 100 percent

k = 0.032

t = 24 d

The amount actually recovered in the body at the time of death was stated to be 45 percent. It is not clear how this figure was obtained. The cumulative urinary excretion of ^{204}Tl, illustrated in Figure 1 has a hyperbolic form during the first 48 hours, consistent with a first order rate process. Subsequently, the cumulative urinary excretion is linear with time. This is inconsistent with animal studies and with the only other human study discussed. In these studies a first order rate process prevails, even months following dosing. The supplementary doses of thallium sulfate

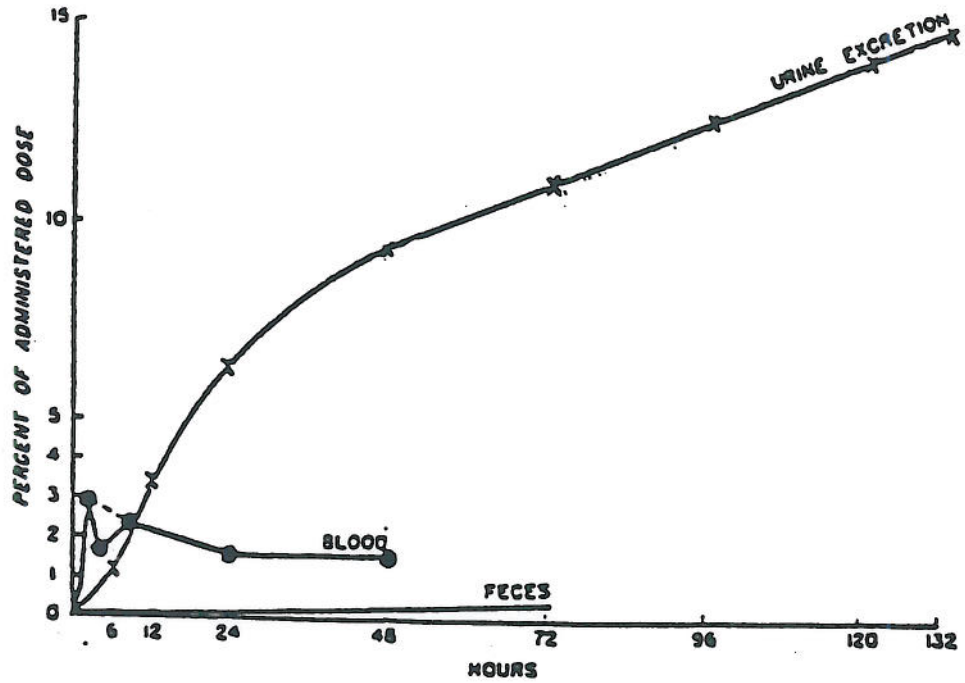

FIGURE 1

The excretion of ^{204}Tl by a human after oral administration of 500 µc of activity plus five 45 mg doses of thallous sulfate orally. The level of ^{204}Tl in the blood at 2, 4, 8, 24, and 48 hour intervals after administration of the radioactive isotope is also included.

Source: Barclay, et al. 1953

given subsequent to the single dose of ^{204}Tl would not likely have altered the form of the excretion curve. These supplementary doses no doubt increased total thallium excretion, but this would not affect the rate of ^{204}Tl excretion since dilution of the ^{204}Tl pool with "cold" thallium would precisely cancel any enhancement of ^{204}Tl excretion resulting from the increased total thallium concentration presented to the kidney.

The only other paper which sheds light on the kinetics of thallium excretion in man was a report of a single case of poisoning (Innis and Moses, 1978). Approximately four weeks following the time of intoxication a series of urine analyses for thallium were performed. These data are presented in graphic form (Figure 2). The estimated $t_{\frac{1}{2}}$ for urinary excretion was 30 days ($k = .023\ day^{-1}$).

The discrepancy in rate of urinary loss of the body burden in the two above-described cases ($k = .032$ vs. $k = .023$) is not remarkable. The rate constant calculated for the first subject was based on excretion data which behaved in a kinetically anomalous fashion. On the other hand, the rate constant calculated for the second subject may have been influenced by the fact that she was experiencing clinical manifestations of thallium poisoning. It is known from experimental studies in rats that the rate of body clearance of thallium is considerably slower following a toxic dose than following a tracer dose. Thus, Gehring and Hammond (1967) reported a rate constant for total thallium excretion of $0.0353\ day^{-1}$ in rats receiving a single iv injection of 10 mg Tl/kg as compared to a rate constant of $0.0790\ day^{-1}$ in rats receiving a tracer dose

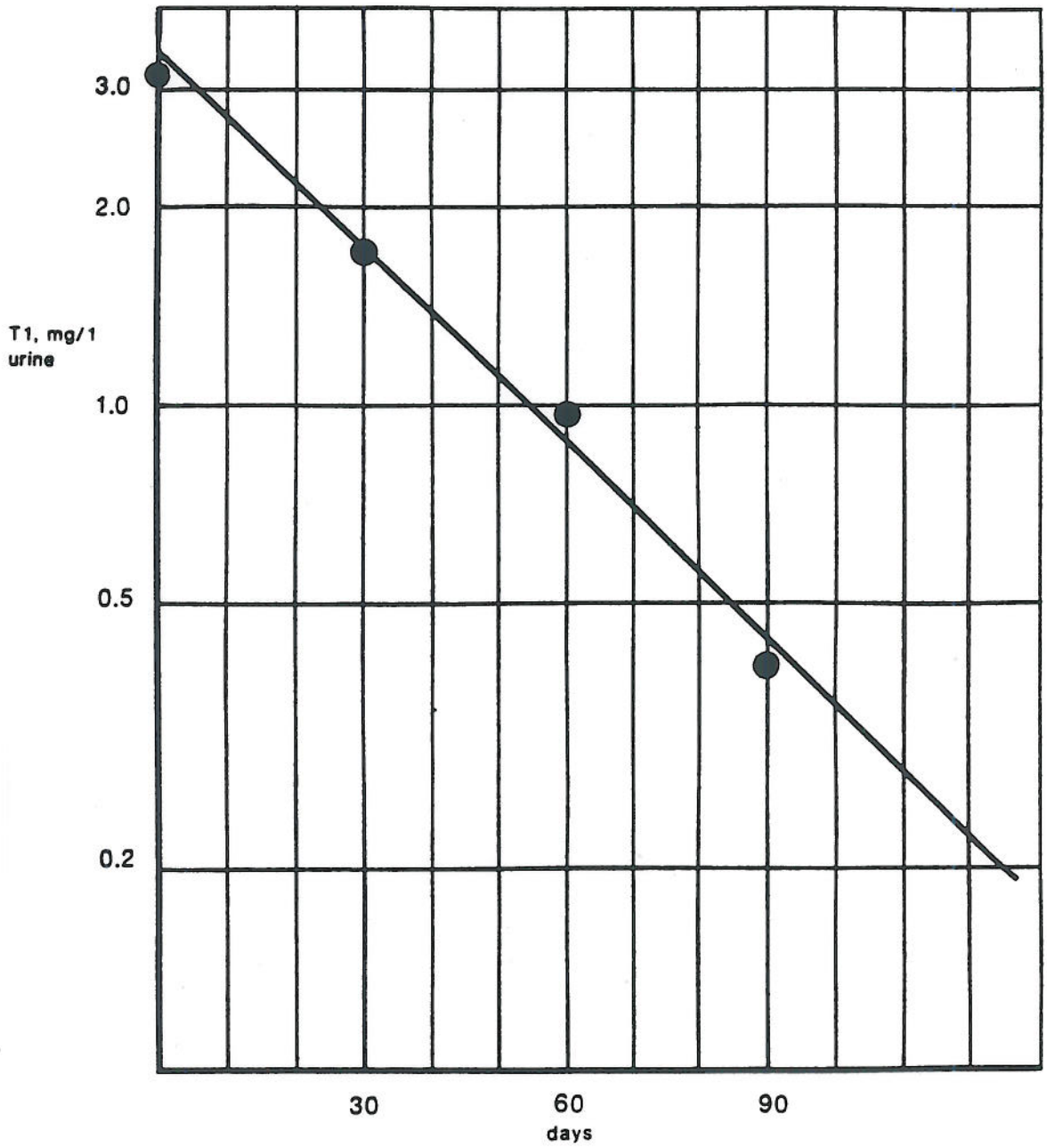

FIGURE 2

The Excretion of Thallium in the Urine of a Patient, Beginning Approximately Four Weeks after Thallium Intoxication.

Source: Innis and Moses, 1978

($<$0.1 mg Tl/kg). These constants were for animals on low dietary potassium. When dietary potassium was high, tracer doses were more rapidly excreted ($k = 0.146\ day^{-1}$). In summary, for people not experiencing overt signs of thallium poisoning, it seems that the appropriate rate constant lies between 0.032 and 0.023 day^{-1}. The slower rate constant (0.023) will be assumed in the criteria formulation for purposes of calculating the accumulation of thallium in man, since this represents the more conservative approach.

It should be noted that excretion of thallium in animals differs from excretion in man in two respects. The rate of excretion is much more rapid in animals. For example, in Gehring and Hammond (1967) the rate constant for total excretion in rats on a high potassium diet was 0.146 day^{-1}. Lie, et al. (1960) calculated a rate constant of 0.210 day^{-1} for rats receiving single tracer doses and Rauws (1974) calculated a rate constant of 0.173 day^{-1} in rats receiving single doses of 10 mg/kg. The average rate from these three studies was 0.18 day^{-1}. Another major difference between man and animals is the relative contribution of fecal and urinary excretion. Whereas the gastrointestinal tract seems to be a very minor excretory pathway in man, the rate of fecal excretion is about 3 to 4 times the rate of urinary excretion in the rat (Gehring and Hammond, 1967; Lie, et al. 1960). In the rabbit the contribution of the two routes of excretion is about equal (Truhaut, 1952).

The rate of urinary excretion under steady state conditions of intake should reflect accurately the rate of total thallium absorption. This proves to be an extremely important consideration in light of the fact that reliable estimates of intake based on known

concentrations in food, air and water are virtually non-existent. The only published estimate of total dietary intake is < 2 µg/d (Hamilton and Minski, 1972/1973).

Four groups of investigators have reported reasonably useful data regarding the concentration of thallium in the urine of persons with no known unusual exposure. Williams and Riegert (1971) reported urinary thallium in a group of workmen suspected of having thallium poisoning. Their analytical method was not described and probably was not very sensitive. The range of urinary thallium was 3-15 µg/l, but half of the samples were registered as negative (presumably < 3 µg/l). Unaffected workers had similar levels. This study is of very limited use because of uncertainties regarding the reliability of the analytical method, and because it is not at all certain that the unaffected workers had essentially normal thallium exposure. The second study was performed using an organic solvent extraction procedure and atomic absorption spectrometry (Kubasik and Volosin, 1973). The limit of detection was 1.5 µg Tl/l of urine. Twenty samples of urine from normal subjects were all negative for thallium. It would seem from these results that the "usual" value for thallium in the urine of normal people is < 1.5 µg/l.

The last two papers in this series are the most significant in that methodologic sensitivity was sufficiently good to yield finite numbers for the concentration of thallium in urine. In the first of these two investigations (Weinig and Zink, 1967), the subjects were categorized according to dietary and smoking habits. It appeared that both smoking and vegetarian dietary habits tended to

increase thallium excretion and perhaps dietary intake (Table 1). In the second study (Goenechea and Sellier, 1967) no such distinction is made, and the average urinary concentration of thallium is somewhat lower though similar (Table 2). From the data in the last three papers it seems safe to assume that the concentration of thallium in urine seldom exceeds 1.5 µg/l. The discrepancy between the data in the last two studies, 0.81 vs. 0.23 µg/l, cannot be explained. Even if one assumes that the higher of the two figures is correct and that average daily urinary excretion is 1.5 µg/l, average daily thallium excretion in the urine would be 1.2 µg (0.81 µg/l x 1.5 l).

Total Daily Excretion of Thallium as a Basis for Estimating Daily Absorption

It is useful to estimate total daily excretion of thallium since this can reasonably be assumed to be the same as total daily absorption, at least under steady state conditions. To the daily excretion via the urine must be added the following miscellaneous routes:

1) gastrointestinal excretion (including cell exfoliation)
2) hair
3) exfoliating epithelium of the skin
4) sweat

The contribution of gastrointestinal excretion is probably very minor in man, at least based on the data of Barclay, et al. (1953). From Figure 1, it can be estimated that cumulative fecal excretion was 0.5 percent of the dose of ^{204}Tl at 72 hours, whereas cumulative urinary excretion at the same time was approximately 11 percent of the dose. On this basis, one might add to the average

TABLE 1

Thallium Concentration in the Morning Urine of Vegetarians, Smokers and Non-smokers with Normal Diets*

Subject	Sex	Years of Age	Urine sp.g.[a]	Tl, ng/g	Ave. Tl, µg/l for group[b]
Vegetarian	F	40	1.024	1.34	
"	M	43	1.034	1.69	1.28
"	M	12	1.032	0.92	
Smoker	M	28	1.019	1.42	
"	M	25	1.023	0.40	0.82
"	M	24	1.018	0.69	
Non-smoker	M	26	1.008	0.13	
"	F	60	1.025	0.39	0.34
"	F	48	1.030	0.53	
				overall average	0.81

*Source: Weinig and Zink, 1967

[a]urine specific gravity

[b]calculated from the authors' data in the table

TABLE 2

Naturally-Occurring Thallium Concentration in the Urine and Feces of Humans Under Physiological Conditions*

Case	Urine, µg/kg	Feces, µg/kg
1	0.1 0.4	0.6 3.0
2	0.1	b
3	0.2	b
4	0.1	b
5	0.1	b
6	0.3	0.1
7	1.0	b
8	0.2	b
9	a	a
10	a	0.1
average[c]	0.23	

*Source: Goenechea and Sellier, 1967

[a]below detectable limit, which is 0.02

[b]not determined

[c]assumes urine samples below detectable limit = 0.02 µg/kg

urinary excretion an additional increment of 1.2 x 0.5/11 = 0.06 µg/d.

So far as excretion via hair is concerned, it was reported by Barclay, et al. (1953) that at autopsy 7 percent of the original dose of ^{204}Tl was localized in scalp hair. During this same period 55 percent of the original dose had been lost by other excretory routes. Minor loss of ^{204}Tl via hair was also reported in rats (Lie, et al. 1960). Seven days following a pulse dose of ^{204}Tl, approximately 75 percent of the radioactivity had been excreted in the urine and feces. Only 1.56 percent of the residual amount was localized in hair. Assuming that total excretion via hair = 2X scalp hair excretion, 14 percent could conceivably have been removed from the body in this manner. An additional increment of 1.26 µg x 14/55 or 0.32 µg results.

Exfoliation of skin and sweat probably do not contribute significantly to total thallium excretion, at least probably not more so than the gastrointestinal tract which has a larger surface area than the skin, a very rapid turnover rate of epithelium, and a high rate of secretory activity. It would seem conservative to assign the skin an excretory role similar to the role of the gastrointestinal tract. In summary, total excretion of thallium per day in adults not exposed to unusual sources of thallium is probably as follows:

Excretory route		µg Tl/d
urine		1.20
feces		0.06
hair		0.32
skin and sweat		0.06
	Total	1.64

Body Burden of Thallium as a Basis for Estimating Daily Absorption

There is an alternate basis for estimating daily absorption of thallium. It begins with certain assumptions. First, it is assumed that the excretory process is essentially first-order, wherein the rate of excretion is proportional to the amount in the body at that time. Second, it assumes that input is fairly constant - essentially zero order. For the steady state condition, the following relationship exists:

$A_B = \frac{A_d}{k}$ where:

A_B = amount in the body

A_d = amount absorbed per day

k = elimination constant (day^{-1})

The amount of thallium in the body (A_B) of persons not unduly exposed has been estimated to be 100 ug per 75 kg (Weinig and Zink, 1967). Using the elimination constant of Innis and Moses (1978), k = 0.023, the daily absorption of thallium to attain a steady state body burden of 100 ug would be:

$100\ \mu g = \frac{x}{.023}$ or $x = 2.3\ \mu g$.

That is approximately 1.4X the value obtained using the estimated sum of excretion by all pathways, and approximately 0.4 times the

intake value derived from estimates of input from food, water, and air. Since the estimated body burden is based on data from only two cadavers, the small difference in estimated daily absorption is not surprising. Order-of-magnitude agreements using two different approaches to the problem of intake are about all one can expect given the small amount of hard data available.

EFFECTS

Acute, Subacute, and Chronic Toxicity

The vast majority of the cases of adult human poisoning have been acute, usually involving single doses, taken by reason of homicidal or suicidal intent. Acute poisoning in children has resulted from ingestion of thallium-containing rat and ant bait or from thallium's therapeutic use as a depilatory agent. It is possible to estimate at least roughly the minimum lethal dose. As for the minimally toxic dose, the former practice of using thallium as a depilatory agent makes it possible to make an estimate, at least for children.

Cavanagh, et al. (1974) investigated a homicidal attempt on three men, two of whom died after being given 930 mg thallous acetate (721 mg Tl). The third man survived a dose of 310 mg (240 mg Tl). In another series of seven cases of suicidal attempts, four survived the consumption of one tube of Zelio Paste (263 mg Tl) with signs of poisoning, two survived after eating two tubes of Zelio Paste (526 mg Tl), and one died after eating five tubes of Zelio Paste (Grunfeld and Hinostroza, 1964). Assuming an average weight of 70 kg, the average toxic, non-fatal dose for adults is about 4-8 mg/kg and the minimal fatal dose is probably somewhat

less than 10 mg/kg. The minimal acute lethal dose is quite similar for a variety of animal species and the range from the highest non-lethal dose to the lowest lethal dose also is quite narrow (Table 3) (Downs, et al. 1960).

Based on the limited data available, children seem to be no more sensitive to the acute toxic or lethal effects of thallium than adults. In a series of 8,006 children estimated to have been given single oral doses of 3.1-7.8 mg Tl per kilogram body weight of thallous acetate as a depilatory, 447 (6 percent) became ill and eight (0.1 percent) died (Munch, 1934). Given the imprecise nature of reports as to incidence of toxic effects, it is of course quite possible that substantially more than 6 percent of the children in this series experienced signs or symptoms of poisoning. It is not even known how consistently the therapeutic objective of alopecia was attained in this series of cases.

Acute thallium poisoning is a disease entity which has been widely described. The initial signs and symptoms involve primarily the gastrointestinal tract and peripheral nervous system. Alopecia does not generally occur until several weeks following intoxication. Indeed, in fatal cases death may supervene before alopecia occurs. The detailed description of three cases of acute poisoning by Cavanagh, et al. (1974) is rather typical of what has been described by many other investigators (see, for example, Paulson, et al. 1972; Papp, et al. 1969). Initially, the subject experiences gastrointestinal pains, diarrhea, and vomiting. This is followed by paresthesia of the upper and lower limbs, dizziness, and facial weakness. These signs first appear in 2-5 days. A frequent

TABLE 3

Acute Toxicity of Thallium Compounds*

Route	Species	Thallous Acetate #	Thallous Acetate Sex	Thallous Acetate lethal range** mg Tl/kg	Thallic Oxide #	Thallic Oxide Sex	Thallic Oxide lethal range** mg Tl/kg
iv	rabbit	7	F	12-20	3	F	24-39
ip	rabbit	9	F	8-13	3	M	30-60
	guinea pig	25	M,F	4-7	3	F	10-30
	rat	41	F	13-20	41	F	62-92
po	rabbit	4	F	12-19	3	M	10-30
	guinea pig	4	M	8-12	10	M,F	3-5
	rat	37	F	18-29	42	F	9-20
	dog	3	M,F	10-20	3	M	20-30

*Source: Downs, et al. 1960

**lethal range = highest non-lethal dose - lowest dose showing any lethality during 14-day period.

complaint is pain and tenderness of the lower limbs, particularly of the knees. Dysphagia and dyspnea also are commonly reported. Sensory impairment occurs frequently. The cranial nerves as well as the spinal nerves are affected. The central nervous system also is affected to varying degrees. Attention span is reduced; somnolence and delerium or coma may occur. Various abnormalities of cardiac function have been reported, including sinus tachycardia and flattening or inversion of the T-wave. These and other cardiac effects have been variously attributed to vagus involvement and to myocardial damage. The electroencephalogram is frequently abnormal (Cavanagh, et al. 1974). These effects and others occur in various combinations. Chamberlain, et al. (1958) summarized the incidence of effects in their series of 14 cases in children (Figure 3), as did Grunfeld and Hinostroza (1964) in a series of adult cases (Figure 4).

Although acute poisoning is a somewhat protracted disease, with effects lingering for several months, the prognosis for full recovery in adults seems to be good. Such does not appear to be the case in children. In a follow-up study of 72 cases, Reed, et al. (1963) found that 26 of 48 had neurologic abnormalities when they were followed up for an average of 4 years. The neurologic abnormalities found at follow-up usually represented persistence of signs found during the initial stages of the disease (Table 4). It should be noted that mental abnormalities and muscle weakness or paralysis actually increased in incidence during the follow-up period.

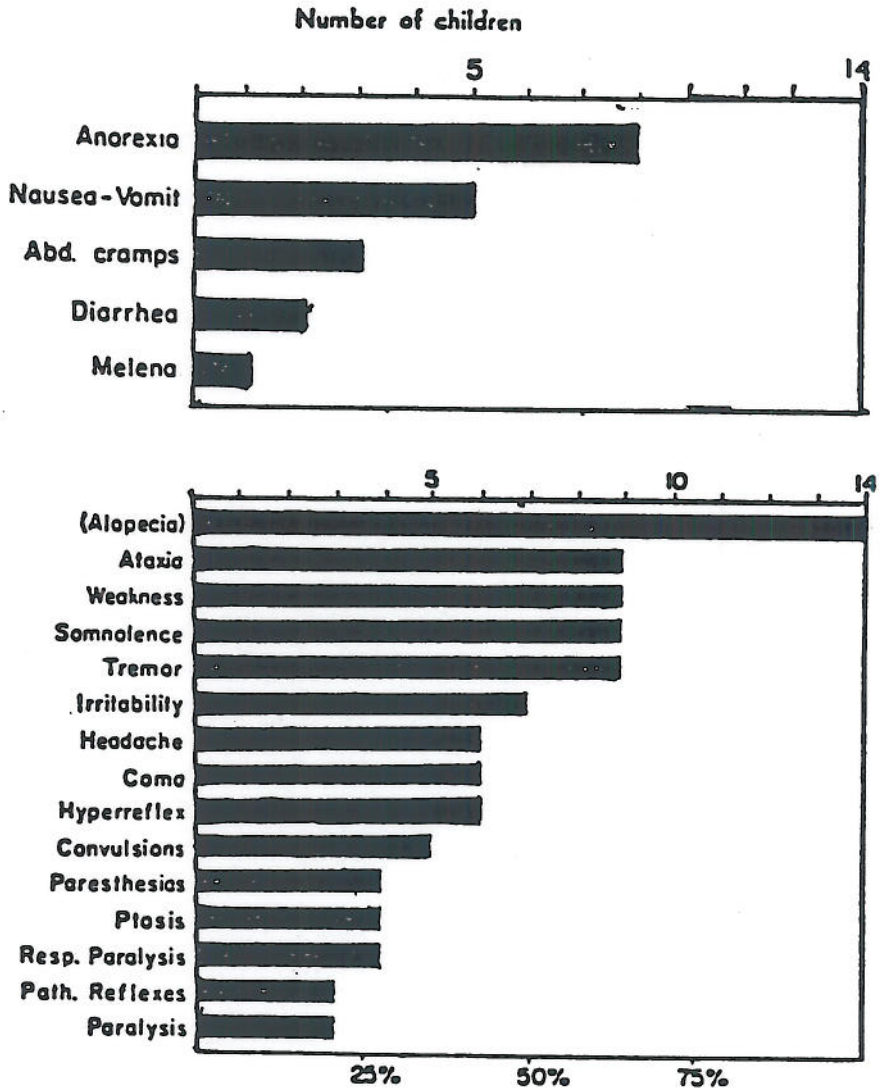

FIGURE 3

Incidence of Gastrointestinal (Top) and Neurologic Signs and Symptoms of Thallotoxicosis in Children

Source: Chamberlain et al., 1958

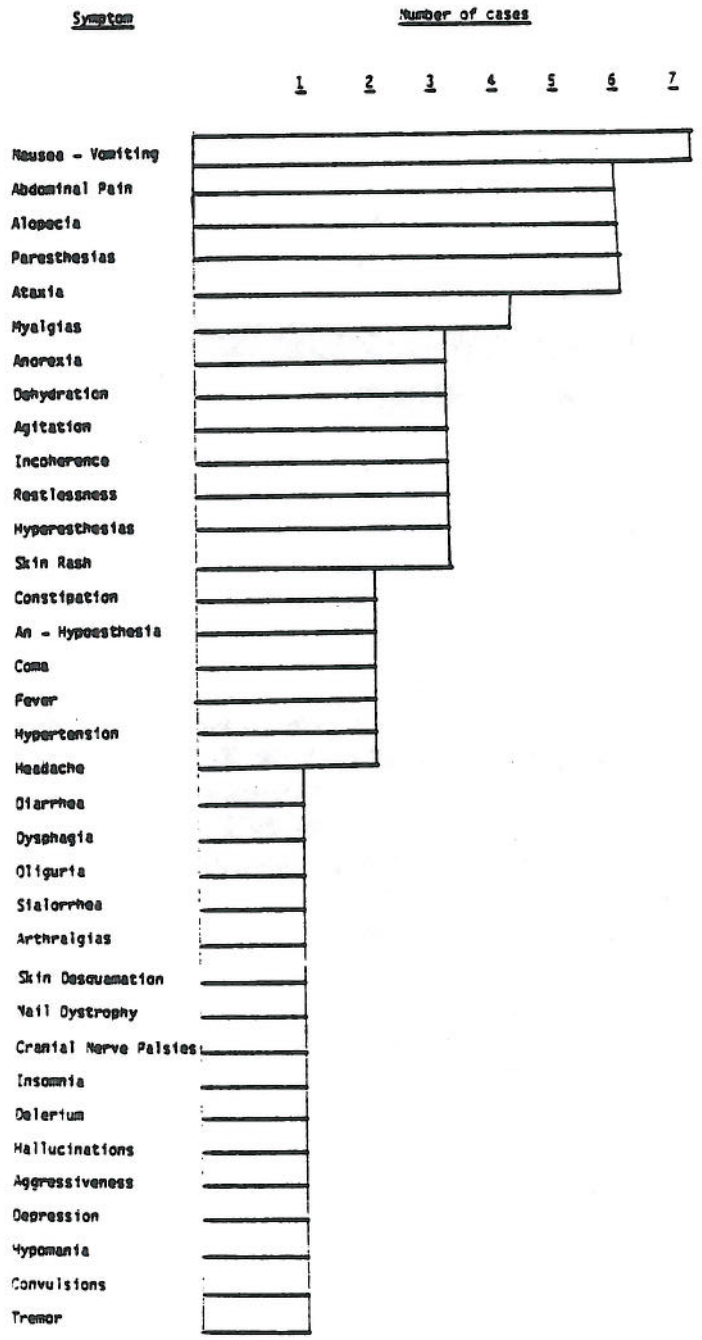

FIGURE 4

Signs and Symptoms in Seven Cases of Thallotoxicosis

Source: Grunfeld and Hinostroza, 1964

TABLE 4

Percent of 26 Patients with Abnormalities at Follow-up Stage (Southern Texas Thallotoxicosis Study, 1954-1959)*

Symptoms	Acute Stage of Illness, %	Follow-up Stage, %
ataxia	81	23
tremor	57	19
abnormal reflexes	62	38
convulsions	27	15
abnormal vision	15	4
mental abnormalities	15	58
abnormal movements	15	8
muscle weakness or paralysis	4	15

*Source: Reed et al., 1963

It is not surprising that acute thallium poisoning should lead to irreversible damage, or at least to only slowly-reversible damage to the central and peripheral nervous system. Degeneration of peripheral nerve fibers and chromatolysis of motor nerve cells were frequently reported in man (Munch, et al. 1933; Gettler and Weiss, 1943), and in animals (Zook and Gilmore, 1967; Zook, et al. 1968).

So far as subacute and chronic thallium poisoning in man are concerned, there are very few reports of any kind and those which are available provide little information as to duration of exposure, level of exposure as reflected in thallium concentrations, or doses in either the external environment or in the affected subjects. In one brief report concerning 13 men exposed 3-4 months, the signs and symptoms were pains in the legs, weariness, loss of hair, disturbance of sensation, psychic trouble, albuminuria and nephritis (Meyer, 1928). Generally speaking, these findings correspond to the usual description of acute poisoning. The author also reports that lymphocytosis was a constant finding. Gettler and Weiss (1943) reported that in two cases of chronic poisoning the only symptoms observed were pain in the legs, mild symptoms resembling those of encephalitis, alopecia, and oliguria. The suggestion that renal damage is a feature of chronic poisoning is not surprising. In the description of acute cases of poisoning, frequent reference is made to manifestations of renal damage (Fischl, 1966). Postmortem evidence of renal damage, at least in acute poisoning, also has been reported (Gettler and Weiss, 1943). Finally, there also is one report of a case of chronic intoxication in a man

exposed 24 years. The main effects were loss of hair, ascending polyneuritis and disturbances of speech and vision (Egen, 1955).

Rats fed thallous acetate in their diet for 105 days experienced no reduction in weight gains at concentrations of 5 and 15 ppm. Doses of 30 ppm for 105 days proved fatal to approximately half of the animals. The only toxic effect noted at 15 ppm was loss of hair (Downs, et al. 1960). It was first noted at two weeks. It must be recognized, however, that there has been very little effort to search for more subtle effects at exposure levels below those causing alopecia. A study of the toxic effects of chronic administration of thallium in animals (>90 days) was reported by Tikhonova (1967). In this instance, thallium administration in rabbits resulted in paralysis and pathological changes in the liver, kidneys and stomach mucosa.

It seems from the limited number of reports that regardless of whether thallium intake occurs in one dose or over several months, the effects are qualitatively very similar, if not identical. It is not possible to state with any degree of certainty which of the many effects reported is the one to which man is most sensitive. It would seem that in cases of acute poisoning in man alopecia is the most consistent effect among those surviving more than two weeks. In the series of children studied by Chamberlain, et al. (1958), this was clearly the case. In the series of adult cases reviewed by Grunfeld and Hinostroza (1964), (see Figure 4), nausea and vomiting occurred in one case where alopecia did not occur. That subject survived only 5 days after ingesting thallium. Among documented cases of chronic poisoning no specification as to the frequency of

various signs and symptoms has been recorded. In summary, the most consistently reported effect is alopecia. Unfortunately, consistency cannot be equated a priori with sensitivity.

Synergism and/or Antagonism

Potassium has long been known to exhibit significant interactions with thallium, both in the pharmacokinetic sense and in toxic interactions. Lund (1956) first demonstrated that potassium increases the renal clearance of thallium. Mullins and Moore (1960) demonstrated that the influx and efflux patterns of thallium in frog muscle were quite similar to the fluxes of potassium. Gehring and Hammond (1967) extended these earlier observations to show that potassium markedly enhanced the rate of thallium excretion in both rats and dogs. The excretion occurred for the most part in the urine. Salivary secretion of potassium, when stimulated with deoxycorticosterone, was accompanied by a corresponding increase in thallium excretion. Potassium also increased somewhat the acute LD_{50} of thallium, suggesting that mobilization from the receptor sites is responsible for the toxic effects.

As a result of these studies in animals, the use of potassium was instituted in the management of thallotoxicosis in man. Results have been somewhat equivocal. The use of potassium in the management of thallotoxicosis does result in some increase in the urinary excretion of thallium, but this mobilization is accompanied by a temporary accentuation of the neurological signs and symptoms (Innis and Moses, 1978; Papp, et al. 1969).

Several other interactions have been reported, but their significance is difficult to evaluate. Levkovitch (1938) reported

that ambient temperature had an effect on thallium toxicity in sheep and rabbits, and that confinement and dietary restriction enhanced toxicity. Levander and Argrett (1969) observed that thallium reduced the exhalation of volatile selenium metabolites, an action shared with mercury and arsenic. Unlike arsenic, however, neither thallium nor mercury increased biliary excretion concomitantly.

Teratogenicity

There are two reports in the literature which suggest a teratogenic effect of thallium. The first was a study of the effect on chick embryos (Karnofsky, et al. 1950) in which Tl_2SO_4 (0.4 - 0.7 mg/egg) was administered during incubation. The primary defect produced was achondroplasia. Thallium also produced early embryonic death and reduced embryonic size. Thus, the study did not fulfill the usual criteria for teratogenesis wherein the effect must be evident at doses not otherwise grossly toxic.

Only one study of thallium teratogenesis in mammalian species has been reported. Gibson and Becker (1970) studied the teratogenic effects of thallium in rats under conditions of both low and normal dietary potassium. Thallium administered intraperitoneally to the mothers early (d. 8,9,10) at 2.5 mg/kg/dose, or late (d. 12,13,14) at 2.5 and 10 mg/kg, resulted in reduced fetal weight and in increased incidence of teratologic effects (hydronephrosis and missing or non-ossification of vertebrae). It was observed that at both dosage levels thallium caused maternal toxicity as manifested by diarrhea, lethargy, irritability, poor hair luster and body hair loss. One interesting aspect of this study was in regard to the

effects of dietary potassium deficiency. A low-potassium diet increased the toxicity of thallium to the dams and was of itself teratogenic, but it did not potentiate the teratogenic effect of thallium. Given the types of malformation reported, the evidence of maternal toxicity and the reduced fetal weights, it is quite likely that these effects were due to delayed fetal maturation (see, for example, Kimmel and Wilson, 1973). In both studies thallium was administered by a parenteral route and in both cases general fetotoxic effects were apparent. Thus, it is impossible to distinguish teratogenicity from a more general toxic effect.

Mutagenicity

No pertinent information could be found in the available literature concerning the mutagenicity of thallium.

Carcinogenicity

There are no available published reports on the carcinogenicity of thallium; however, there are two carcinogenicity studies on-going at the time of this document's preparation. Carcinogenicity/mutagenicity/teratogenicity evaluations of thallium sulfate are being conducted by Litton Bionetics under EPA contract; Sprague-Dawley rats are being fed thallium sulfate in the diet at three dose levels. The National Institute for Occupational Safety and Health (NIOSH) in Cincinnati, Ohio is investigating the carcinogenicity of thallic oxide by inhalation in rodents.

Without any implications as to non-carcinogenicity it is of interest to note that thallium has mild anti-carcinogenic effects, along with other metals of Group IIIa (Adamson, et al. 1975).

CRITERION FORMULATION

Existing Guidelines and Standards

There is a threshold limit value (TLV) of 0.1 mg/m^3 for thallium in workplace air (ACGIH, 1971). This value is based on analogy to other highly toxic metals. This standard has been adopted by the Occupational Safety and Health Administration (OSHA), and is the same as that for East Germany and West Germany (Winell, 1975). The U.S.S.R. standard is 0.01 mg/m^3. No criteria have been developed for thallium in irrigation water, drinking water, fresh water or other media.

Current Levels of Exposure

It is extremely difficult to specify current levels of exposure for either man or animals because of the scarcity of good data. This is due to the fact that analytical methods which have been applied to the problem have generally not been sufficiently sensitive for determination of thallium in major media (air, food, water) or in normal man. This is not to say that adequate methods do not exist. For example, the mass spectroscopic-isotope dilution procedure used by Weinig and Zink (1967) could detect thallium in urine in the range of .01-0.1 ng/g. There probably has not been sufficient motivation to develop alternate sensitive methodology to define human exposure adequately in the normal range.

Certain approximations as to usual human exposure are possible. Thus, based on one extensive study it seems that tap water seldom exceeds 0.3 µg Tl/l (Greathouse, 1978). Assuming that the average adult consumes 2 liters of water per day, total input would be somewhat less than 1 µg/d.

Even in the worst conditions of water pollution, the concentration of thallium probably seldom exceeds 30 µg/l (U.S. EPA, 1977). These conditions occur in the immediate vicinity of ore processing operations and possibly in streams draining ore-rich soils, e.g. the Colorado River as it courses through western Arizona.

Limited data on thallium in vegetables suggest that, as a class of food, these may have considerably higher concentrations of thallium, perhaps 10 µg/kg wet weight, than other classes of foods (Geilmann, et al. 1960). Bread and muscle, for example, contain 1 µg/kg or less. This may explain the observation that vegetarians excrete considerably more thallium in the urine than non-vegetarians. Assuming that total food consumption is 1.6 kg/d, (USDA, 1968), that 0.38 kg is in the form of vegetables, and that the remainder has a concentration of only 1 µg/kg, total daily thallium intake would be (0.38) (10) + (1.2) (1) = 5 µg. This estimate probably is on the high side since prepared vegetables would likely have less thallium than raw vegetables due to leaching of thallium into water during cooking.

So far as ambient air as a source is concerned, the single largest anthropogenic source of thallium is considered to be stack emissions from coal-fired plants. It has been estimated that flue gas would contain about 0.7 mg/m^3, with a likely ground level concentration of 0.7 $\mu g/m^3$. Given that a large factor of dilution would result by dispersion from the base of a stack, it seems unlikely that the contribution of coal combustion to thallium in ambient air would be significant. The highest measurement of

thallium reported in ambient air indicated a range of 0.04-0.48 ng/m^3 (Carson and Smith, 1977).

Inhalation of thallium in cigarette smoke may, on the other hand, be a very significant source. The urinary excretion of thallium in smokers is about twice that in non-smokers (Weinig and Zink, 1967) and the concentration in cigar stubs was shown to be 57-170 ng/g (Geilmann, et al. 1960), about 20 times the concentration estimated for the diet.

Total intake in the general non-smoking adult population calculated on the basis of exposure data thus would consist of no more than 1.0 ug/d from water and no more than 5 ug/d from food, even assuming that virtually all ingested thallium is absorbed.

The total daily assimilation of thallium by adults in the general population has also been arrived at by consideration of excretion data and estimated body burden. The estimated daily intake arrived at by consideration of food and water exposure and by these other two methods is as follows:

Basis	Estimated Daily Adult Intake
Food, air and water exposure	$\lesssim$ 6 µg/d
Excretion data	1.64 µg/d
Body burden data	2.30 µg/d

Special Groups at Risk

From the standpoint of age, there is no basis for believing that children are more susceptible to thallium intoxication than adults. Children, however, experience neurological sequelae, while adults do not. There is no reason for suspecting that the fetus is unusually sensitive. Essentially nothing is known regarding sex

differences in susceptibility. One study in rats indicated that females are more resistant to sub-chronic toxicity than males. From the standpoint of exposure hazard, it would seem that smokers may have twice as great a level of thallium intake as non-smokers. This suggestion is based solely on data concerning urinary thallium excretion in six people and on very limited information concerning thallium in cigars. Obviously, people occupationally exposed to thallium may constitute a special risk category. This matter has received little attention because the total annual industrial production of about 0.5 tons of thallium is so small. In the U.S., the main source of poisoning, thallium-containing rodenticides and insecticides, has been terminated. The manufacture and distribution of these products is no longer permitted.

Basis and Derivation of Criteria

The proposed criterion for thallium in water is derived from 1) estimated least toxic level on chronic intake in man, 2) introduction of a margin of safety, and 3) relative contribution of water and other media to total daily intake in the general population.

In estimating the least toxic level of intake, the effect to which man is most sensitive is probably alopecia. Loss of scalp hair in man and of body fur in animals seems to occur at somewhat lower levels of intake than any other known effects. This is not so clearly the case in adults as in children and animals. There is, however, no great difference between the acute or chronic dose causing alopecia and the dose causing neurologic effects. The least daily amount of thallium which, when taken for a lifetime, will cause alopecia can only be estimated on the basis of sub-chronic

animal exposure data combined with some kinetic considerations. In the Downs, et al. (1960) study alopecia occurred in 2 weeks as a result of the administration of thallium at 12 ppm in the diet. At this dose level, either effects occurred within two weeks or they did not occur with continued intake. This is consistent with the rapid turnover of thallium in rats and the consequently rapid attainment of a steady state level of thallium in the body. Within two weeks, a steady state is virtually achieved since 14 days represents more than three half-lives for thallium clearance from the body. Rats at the next lowest dose (5 ppm thallous acetate or 4 ppm thallium) fed for 105 days showed no alopecia or other toxic effects. Therefore, the highest no observable adverse effect level (NOAEL) would be 4 ppm (4 µg/g) of thallium.

In the following calculation the average weight of rats, 0.075 kg, is derived from inspection of Figure 1 (male rats) in the author's report; the average daily food intake is assumed to be 10 g at that weight. Therefore, the "safe" ADI for rats can be calculated as:

$$(4.0\ \mu g/g)\ (10\ g) = 40\ \mu g/0.075\ kg = 533\ \mu g/kg.$$

Conversion to an acceptable daily intake (ADI) for man would be as follows:

$$ADI = \frac{533\ \mu g/kg \times 70\ kg}{1{,}000} = 37.1\ \mu g$$

where:

70 kg = average weight of man

1,000 =safety factor as recommended by NAS (1977) for compounds where there are: "No long term or acute human data. Scanty results on experimental animals. No indication of carcinogenicity."

For the purpose of establishing a water quality criterion, human exposure to thallium is considered to be based on ingestion of 2 liters of water and 6.5 g of fish/day. The bioaccumulation factor for thallium has been established to be 119.

The criterion (C) is derived from this data as follows:

$$(C \times 2 \text{ liters}) + (C \times 119 \times 0.0065) = 37.3\ \mu g.$$

Solving for C gives: C = 13.4 µg/liter. Thus, the recommended water quality criterion for thallium is 13.4 µg/liter. The criterion can alternatively be expressed, if exposure is assumed to be only from ingestion of contaminated fish and shellfish, as 48 µg/l.

It is interesting to note the similarity between the minimal body burden causing alopecia in rats (on chronic administration) and the single dose causing alopecia, with moderate incidence of other effects, in children. For the rat:

$$\frac{1.6 \text{ mg/kg/d}}{0.18 \text{ day}^{-1}} = 8.88 \text{ mg Tl/kg}$$

For children, the average acute dose associated with alopecia is 3.1 to 7.8 mg/kg (Munch, 1934).

So far as a safe level of thallium in drinking water is concerned, there does not seem to be any reasonable possibility that even the most thallium-polluted waters would have a toxic effect. In the worst case identified by Zitko, et al. (1975), the concentration of thallium was 88 µg/l. Assuming that this were a human water supply, the daily input at 2 liters per day would be only 176 µg Tl, 4.74 times the ADI calculated for man in the document and well within the 1,000-fold safety factor.

The great difference between estimated minimally toxic exposures and current total exposure in the general population is

reassuring. One cannot be totally sanguine, however, since there is a paucity of chronic data, including information on mutagenicity, teratogenicity and carcinogenicity. For that reason it seems prudent to keep levels of exposure at or below their present levels. From the data available, it would seem that few if any public water supplies would ever contain more than 4 μg/l. Thus, the criterion of 13 μg/l is approximately threefold greater than the likely maximum in public water supplies.

In summary form, the dose and exposure parameters for man are estimated to be:

minimally lethal single dose	4-10 mg/kg
recommended criterion	13 μg/l water
ADI for 70 kg/man	37.3 μg/kg
probable limit for $>$ 99 percent of U.S. tap waters	1 μg/l
probable current level of daily adult thallium consumption from drinking water	$\leq$1 μg/d

REFERENCES

Adamson, R.H., et al. 1975. Studies on the anti-tumor activity of gallium nitrate (NSC-15200) and other Group IIIa metal salts. Cancer Chemo. Rep. 59: 599.

American Conference of Governmental Industrial Hygienists. 1971. Documentation of threshold limit values for substances in workroom air. 3rd ed.

Barclay, R.K., et al. 1953. Distribution and excretion of radioactive thallium in the chick embryo, rat and man. Jour. Pharmacol. Exp. Ther. 107: 178.

Carson, B.L. and I.C. Smith. 1977. Thallium. An appraisal of environmental exposure. Tech. Rep. No. 5, Contract No. NO1-ES-2-2090. Natl. Inst. Environ. Health Sci.

Cavanagh, J.B., et al. 1974. The effects of thallium salts with particular reference to the nervous system changes. Jour. Med. 43: 293.

Cavieres, J.D. and J.C. Ellroy. 1974. Thallium and the sodium pump in human red cells Jour. Physiol. 243: 243.

Chamberlain, P.H., et al. 1958. Thallium poisoning. Pediatrics. p. 1170.

Downs, W.L., et al. 1960. Acute and subacute toxicity studies of thallium compounds. Am. Jour. Ind. Hyg. Assoc. Jour. 21: 399.

Egen, B. 1955. Gewerbliche thalliumvergiftung. Zentralblatt Arbeitsmed. Arbeitsschutz. 5: 141.

Fischl, J. 1966. Aminoaciduria in thallium poisoning. Am. Jour. Med. Sci. 251: 40.

Gehring, P.J. and P.B. Hammond. 1964. The uptake of thallium by rabbit erythrocytes. Jour. Pharmacol. Exp. Ther. 145: 215.

Gehring, P.J. and P.B. Hammond. 1967. The interrelationship between thallium and potassium in animals. Jour. Pharmacol. Exp. Ther. 155: 187.

Geilmann, W., et al. 1960. Thallium ein regelmassig vorhandenes spurenelement im tierschen und pflanzlichen organismus. Biochem. Zeit. 333: 62.

Gettler, A.O. and C.A. Weiss. 1943. Thallium poisoning. III. Clinical toxicology of thallium. Am. Jour. Clin. Pathol. 13: 422.

Gibson, J.E. and B.A. Becker. 1970. Placental transfer, embryo toxicity and teratogenicity of thallium sulfate in normal and potassium-deficient rats. Toxicol. Appl. Pharmacol. 16: 120.

Gibson, J.E., et al. 1967. Placental transport and distribution of thallium-204 sulfate in newborn rats and mice. Toxicol. Appl. Pharmacol. 10: 408 (Abst.)

Goenechea, S. and K. Sellier. 1967. Uber die naturlichen thalliumgehalt des menschlichen korpers. Deutsche Zeit. Gericht. Med. 60: 135.

Greathouse, D.G. 1978. Personal communication.

Grunfeld, O. and Y. Hinostroza. 1964. Thallium poisoning. Arch. Int. Med. 114: 132.

Hamilton, E.I. and M.J. Minski. 1972/1973. Abundance of the chemical elements in man's diet and possible relations with environmental factors. Sci. Total Environ. 1: 375.

Innis, R. and H. Moses. 1978. Thallium poisoning. Johns Hopkins Med. Jour. 142: 27.

International Cancer Research Program. 1966. Deposition and retention models for internal dosimetry of the human respiratory tract. Health Phys. 12: 173.

Karnofsky, D.A., et al. 1950. Production of achondroplasia in the chick embryo with thallium. Proc. Soc. Exp. Biol. Med. 73: 255.

Kimmel, C.A. and J.G. Wilson. 1973. Skeletal deviations in rats: malformations or variations? Teratology. 8: 309.

Kubasik, N.P. and M.T. Volosin. 1973. A simplified determination of urinary cadmium, lead and thallium, with use of carbon rod atomization and atomic absorption spectrometry. Clin. Chem. 19: 954.

Levander, O.A. and L.C. Argrett. 1969. Effects of arsenic, mercury, thallium and lead on selenium metabolism in rats. Toxicol. Appl. Pharmacol. 14: 308.

Levkovitch, L.I. 1938. The influence of external temperature, diet and emotion on the pharmacological action of thallium. Bull. Biol. Med. Exp. USSR. Chem. Abst. 34: 2461[8] (1940).

Lie, R., et al. 1960. The distribution and excretion of thallium-204 in the rat, with suggested MPC's and a bio-assay procedure. Health. Phys. 2: 334.

Lund, A. 1956. Distribution of thallium in organisms and its elimination. Acta Pharmacol. Toxicol. 12: 251.

Meyer, S. 1928. Changes in the blood as reflecting industrial damage. Jour. Ind. Hyg. 10: 29.

Mitteldorf, A.J. and D.O. Landon. 1952. Spectrochemical determination of the mineral-element content of beef. Anal. Chem. 24: 469.

Mullins, L.J. and R.D. Moore. 1960. The movement of thallium ions in muscle. Jour. Gen. Physiol. 43: 759.

Munch, J.C. 1934. Human thallotoxicosis. Jour. Am. Med. Assoc. 102: 1929.

Munch, J.C., et al. 1933. The 1932 thallotoxicosis outbreak in California. Jour. Am. Med. Assoc. 100: 1315.

National Academy of Science. 1977. Drinking Water and Health. Washington, D.C.

Neal, J.B., et al. 1935. An unusual occurrence of thallium poisoning. N.Y. Med. Jour. 35: 657.

Papp, J.P., et al. 1969. Potassium chloride treatment in thallotoxicosis. Ann. Intern. Med. 71: 119.

Paulson, G., et al. 1972. Thallium intoxication treated with dithizone and hemodialysis. Arch. Intern. Med. 129: 100.

Rauws, A.G. 1974. Thallium pharmacokinetics and its modification by Prussian Blue. Naunyn Schmiedeberg's Arch. Pharmacol. 284: 295.

Reed, D., et al. 1963. Thallotoxicosis. Acute manifestations and sequelae. Jour. Am. Med. Assoc. 183: 516.

Richeson, E.M. 1958. Industrial thallium intoxication. Ind. Med. Surg. 2: 607.

Stephan, C.E. 1980. Memorandum to J. Stara. U.S. EPA. July 3.

Tikhonova, T.S. 1967. Toxicity of thallium and its compounds in workers. Nov. Dannye Toksikol. Redk. Metal. Ikh Soedin. Chem. Abst. 71: 53248j, 1969.

Toscano, V.A. 1975. In: Nutrients in Processed Foods. Publishing Sciences Group, Inc., Acton, Massachusetts. pp. 111-123.

Truhaut, R. 1952. Les effets biologiques du thallium. Ph.D. Thesis. Faculty of Sciences. University of Paris.

U.S. Department of Agriculture. 1968. Food consumption of households in the United States, spring, 1965. U.S. Gov. Printing Off., Washington, D.C.

U.S. EPA. 1971. Identification and estimation of ions, molecules and compounds in particulate matter collected from ambient air. Contract CPA-70-159, Air Programs by Battelle Columbus Lab.

U.S. EPA. 1977. Heavy metal pollution from spillage at ore smelters and mills. EPA-600/2-77-171. Washington, D.C.

U.S. EPA. 1978a. The multielemental analysis of drinking water using proton-induced x-ray emission (PIXE). EPA-600/1-78-058. Washington, D.C.

U.S. EPA. 1978b. In-depth studies on health and environmental impacts of selected water pollutants. Contract No. 68-01-4646. Washington, D.C.

U.S. EPA. 1980. Seafood consumption data analysis. Stanford Research Institute International. Menlo Park, California. Final Report, Task 11. Contract No. 68-01-3887.

Weinig, E. and P. Zink. 1967. Uber die quantitative massenspektrometrische bestimmung des normalen thallium-gehalts im menschlichen organismus. Arch. f. Toxikol. 22: 255.

Williams, N. and A.L. Riegert. 1971. Epidemic alopecia areata. An outbreak in an industrial setting. Jour. Occup. Med. 13: 535.

Winell, M. 1975. An international comparison of hygienic standards for chemicals in the work environment. Ambio. 4: 34.

Zitko, V. and W.V. Carson. 1975. Accumulation of thallium in clams and mussel. Bull. Environ. Contam. Toxicol. 14: 530.

Zitko, V., et al. 1975. Thallium: occurrence in the environment and toxicity to fish. Bull. Environ. Contam. Toxicol. 13: 23.

Zook, B.C. and C.E. Gilmore. 1967. Thallium poisoning in dogs. Jour. Am. Vet. Med. Assoc. 151: 206.

Zook, B.C., et al. 1968. Thallium poisoning in cats. Jour. Am. Vet. Med. Assoc. 153: 285.

☆ U. S. GOVERNMENT PRINTING OFFICE : 1980 720-016/4396