ZINC

Ambient Water Quality Criteria

Criteria and Standards Division
Office of Water Planning and Standards
U.S. Environmental Protection Agency
Washington, D.C.

CRITERION DOCUMENT

ZINC

CRITERIA

Aquatic Life

For zinc the criterion to protect freshwater aquatic life as derived using the Guidelines is "$e^{(0.67 \cdot \ln(\text{hardness}) + 0.67)}$" as a 24-hour average (see the figure "24-hour average zinc concentration vs. hardness") and the concentration should not exceed "$e^{(0.64 \cdot \ln(\text{hardness}) + 2.46)}$" (see the figure "maximum zinc concentration vs. hardness") at any time.

For saltwater aquatic life no criterion for zinc can be derived using the Guidelines, and there are insufficient data to estimate a criterion using other procedures.

Human Health

For the prevention of adverse effects due to the organoleptic properties of zinc, the current standard for drinking water of 5 mg/l was adopted for ambient water criterion.

Introduction

Zinc is a bluish-white metal which dissolves readily in strong acids. Its principal uses include electroplating and the production of alloys. Zinc is never found free in nature, but occurs as the sulfide, oxide, or carbonate (Lange, 1956).

In the aquatic environment zinc is acutely toxic to freshwater organisms at concentrations as low as 90 µg/l (Rabe and Sappington, 1970) and the lowest reported chronic effects lie between 26 and 51 µg/l (Spehar, 1976). In marine waters comparable values are 141 µg/l in acute tests (Calabrese, et al. 1977) and 220 µg/l in chronic tests (Reish, et al. 1976).

Water quality has been shown to affect zinc toxicity. The best-studied of these is the protective effect exerted by water hardness, which has been incorporated into the freshwater criterion for the protection of aquatic life.

Because zinc is an element it can be expected to persist in the environment indefinitely in some form.

In humans zinc ingestion has produced no clinical symptoms at daily intakes of 150 mg/day for as long as six months (Greaves and Sillen, 1970). Brown, et al. (1964) reported food poisoning from ingestion of a meal estimated to contain nearly 1,000 ppm of zinc and another case among people who had drunk punch containing zinc at a concentration of 2,200 ppm.

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AQUATIC LIFE TOXICOLOGY*

FRESHWATER ORGANISMS

Introduction

Zinc is one of the most commonly occurring heavy metals in natural waters, and is an essential element for most plants and animals. Zinc is used principally for alloys and galvanizing.

Predicting the toxicity of a given total zinc concentration in water is complicated by numerous physical-chemical factors which alter the form of the zinc and hence change its availability, rate of uptake, and toxicity. Seasonally and locally, toxicity may be altered by the presence of naturally occurring chelating, complexing, and precipitating agents. While there are many such factors which may alter zinc toxicity, the only factor for which the effect is well documented is hardness. Therefore the criterion for zinc is expressed as a function of water hardness. However, as evidenced by the criteria derived herein, concentrations required for survival, growth, and reproduction of the more sensitive aquatic species may at time be below ambient total zinc concentrations in some surface waters of the United States

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life [43 FR 21506 (May 18, 1978) and 43 FR 29028 (July 5, 1978)] 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 the calculations for deriving various measures of toxicity as described in the Guidelines.

This results, in large part, from the current inability to correlate quantitatively the effects on zinc toxicity of physical-chemical factors other than hardness.

Acute Toxicity

One hundred and thirty 96-hour LC50 values for 21 species of freshwater fish are listed in Table 1, including 34 for the rainbow trout, 31 for the fathead minnow, and 20 for the bluegill. The 96-hour LC50 values for all species ranged from 90 to 40,900 µg/l. Approximately one-half of the values were based on flow-through tests with measured zinc concentrations; the range of values from these tests was 93 to 35,500 µg/l.

Because there are no studies which directly compare static and flow-through results, the Guideline factors for converting static to flow-through LC50 values are used. Similarly, the Guideline factors for adjusting unmeasured to measured values and less than 96-hour to 96-hour values were used. The resultant adjusted acute values ranged from 49 to 48,266 µg/l. The use of the Guideline factors did not produce an appreciable change in the range of 96-hour LC50 values.

Data on interspecific variability in zinc sensitivity are provided by several studies. Holcombe and Andrew (1978) found that rainbow trout are two- to four-times more sensitive to zinc and six to seven times less sensitive than the fathead minnow.

Following the Guidelines, the mean intercept, adjusted by the species sensitivity factor, for all 20 fish species is 3.93. Since results of flow-through tests with measured concentrations for chinook salmon are lower than this, the data for chinook salmon are used to derive the Final Fish Acute Value which is

$e^{(0.67 \cdot \ln(\text{hardness}) + 3.63)}$.

The effect of hardness on zinc toxicity is not as well documented with invertebrate species as with fish; however, the data of Cairns and Scheier (1958) and Wurtz and Bridges (1961) indicate that zinc is more toxic to the snail, Physa heterostropha, in soft water than in hard water.

Sufficient data are available for Physa heterostropha to fit a hardness regression equation. The slope (0.64) is similar to that for fish thus lending additional support to this approach. The calculated mean intercept for the 16 invertebrate species is 5.50, indicating that invertebrate species are slightly less sensitive than fish. The range (1,937 times) of adjusted LC50 values for invertebrate species (33 to 63,910 µg/l) is somewhat greater than that for fish, with cladocerans being more sensitive than any fish.

Daphnia hyaline, the most sensitive species (intercept = + 1.49), is approximately 55 times more sensitive to zinc than indicated by the mean sensitivity. At least 3 invertebrate species are more sensitive than chinook salmon. The most resistant adult insects, however, have not been tested in hardnesses higher than 40-50 µg/l.

Using the Guidelines, the adjusted mean intercept is 2.46, which is adequate to protect all species except possibly Daphnia hyalina. Only a single acute value, run under static conditions with unmeasured zinc concentrations, is available for this species. The adjusted mean intercept thus appears adequate for invertebrate species. The Final Invertebrate Acute Value is $e^{(0.64 \cdot \ln(\text{hardness}) + 2.46)}$. Since this value is lower than that for fish, it becomes the Final Acute Value.

Chronic Toxicity

Chronic toxicity values for five fish species ranged from 36 to 852 µg/l (Table 3). All chronic tests were conducted in soft water (25-46 mg/l as $CaCO_3$); no acceptable hard water chronic tests are found in the literature to compare with the soft water data. A life-cycle test with the fathead minnow in hardwater (Brungs, 1969) observed adverse effects at all exposure concentrations (as low as 180 µg/l) (Table 7). However, it is felt to be inappropriate to estimate a chronic value using that concentration and the much lower average control concentration of 30 µg/l.

Since no other appropriate fish data were available to establish a significant relationship between chronic toxicity values and hardness, a relationship was estimated by using the slope (0.67) from fish acute values. Calculated intercepts for the five species tested ranged from 1.05 for flagfish to 4.20 for brook trout, with a mean of 2.57. The adjusted mean intercept (0.67) is below that for all species. Thus the Final Fish Chronic Value is obtained from $e^{(0.67 \cdot \ln(\text{hardness}) + 0.67)}$.

Only one invertebrate chronic test result is available (Table 4). This test with Daphnia magna was conducted in soft water, and the resulting chronic value is 3.3 times lower than the acute value (280 µg/l) for the same species in the same water. Daphnids are the most sensitive invertebrate organisms tested in the acute exposures; therefore, it seems reasonable to assume that the chronic zinc value for Daphnia magna would be equal to or lower than most other invertebrate chronic values. Thus, it would appear to be inappropriate to use the species sensitivity factor

(5.1) with the chronic data for Daphnia magna, since it is one of the most sensitive invertebrate species. Consequently the sensitivity factor was not used in the calculations to derive the Final Invertebrate Chronic Value. It is also interesting to note that the Daphnia magna chronic value for zinc is relatively close to the fish chronic value (Table 3). Even though invertebrate chronic tests have not been conducted in hard water, it again seems logical to assume that a similar relationship probably exists between chronic zinc toxicity and water hardness for invertebrate species as is demonstrated for acute and chronic exposures of fish.

Since appropriate invertebrate data are not available to establish a relationship between chronic toxicity values and hardness, a relationship is estimated by using the slope (0.64) from invertebrate acute values and the zinc value and water hardness from the Daphnia magna chronic test. Thus the Final Invertebrate Chronic Value is from $e^{(0.64 \cdot \ln(\text{hardness}) + 2.00)}$.

Since the Final Fish Chronic Value is lower than that for invertebrate species, it becomes the Final Chronic Value.

Plant Effects

Tests with five species of plants, including four species of algae, are listed in Table 5. Zinc concentrations from 30 to 21,600 µg/l have been shown to reduce the growth of various plant species. The significance of short-term growth inhibition in algae has not been established; however, since many algal tests are conducted in artificial media which may complex zinc more

than most natural waters, the existence of low effect levels should be considered as a potential important ecological effect.

The lowest plant value (30 µg/l) is similar to the chronic values for fish and invertebrate species, so sensitive algal species will probably be protected by criteria for the protection of other sensitive freshwater organisms.

Residues

Table 6 contains the zinc bioconcentration factors for two fish species and two invertebrate species. The bioconcentration factors for fish are low (8 and 12.2), whereas the factors for invertebrate species are one or two orders of magnitude greater (106 and 1,130).

Dietary zinc at a level of 2,000 mg/kg has been shown to produce stillbirths and inhibition of postnatal growth in rats (Ketcheson, et al. 1969). Assuming a diet of invertebrate organisms which could bioconcentrate zinc by a factor of 1,130, it would require a zinc water concentration of 1,800 µg/l (the Residue Limited Toxicant Concentration) to produce this effect. This concentration is well above chronically toxic levels for freshwater fish and invertebrate species; therefore bioconcentration does not seem to be a critical factor in establishing a freshwater criterion for zinc.

Miscellaneous

Table 7 contains other data on the effects of zinc on freshwater organisms. With the exception of the avoidance data of Sprague (1968), no data are found which would appear to influence the criterion for zinc. Sprague (1968) found that rainbow trout

would avoid a zinc concentration of 5.6 µg/l in a laboratory behavior test in water with a hardness of 14 mg/l as $CaCO_3$. The final chronic value for zinc at a water hardness of 14 mg/l is 7.6 µg/l (Figure 1), and may or may not protect against significant avoidance behavior.

CRITERION FORMULATION

Freshwater-Aquatic Life

Summary of Available Data

All concentrations herein are expressed in terms of zinc.

Final Fish Acute Value = $e^{(0.67 \cdot \ln(\text{hardness}) + 3.63)}$

Final Invertebrate Acute Value = $e^{(0.64 \cdot \ln(\text{hardness}) + 2.46)}$

Final Acute Value = $e^{(0.64 \cdot \ln(\text{hardness}) + 2.46)}$

Final Fish Chronic Value = $e^{0.67 \cdot \ln(\text{hardness}) + 0.67)}$

Final Invertebrate Chronic Value = $e^{(0.64 \cdot \ln(\text{hardness}) + 2.00)}$

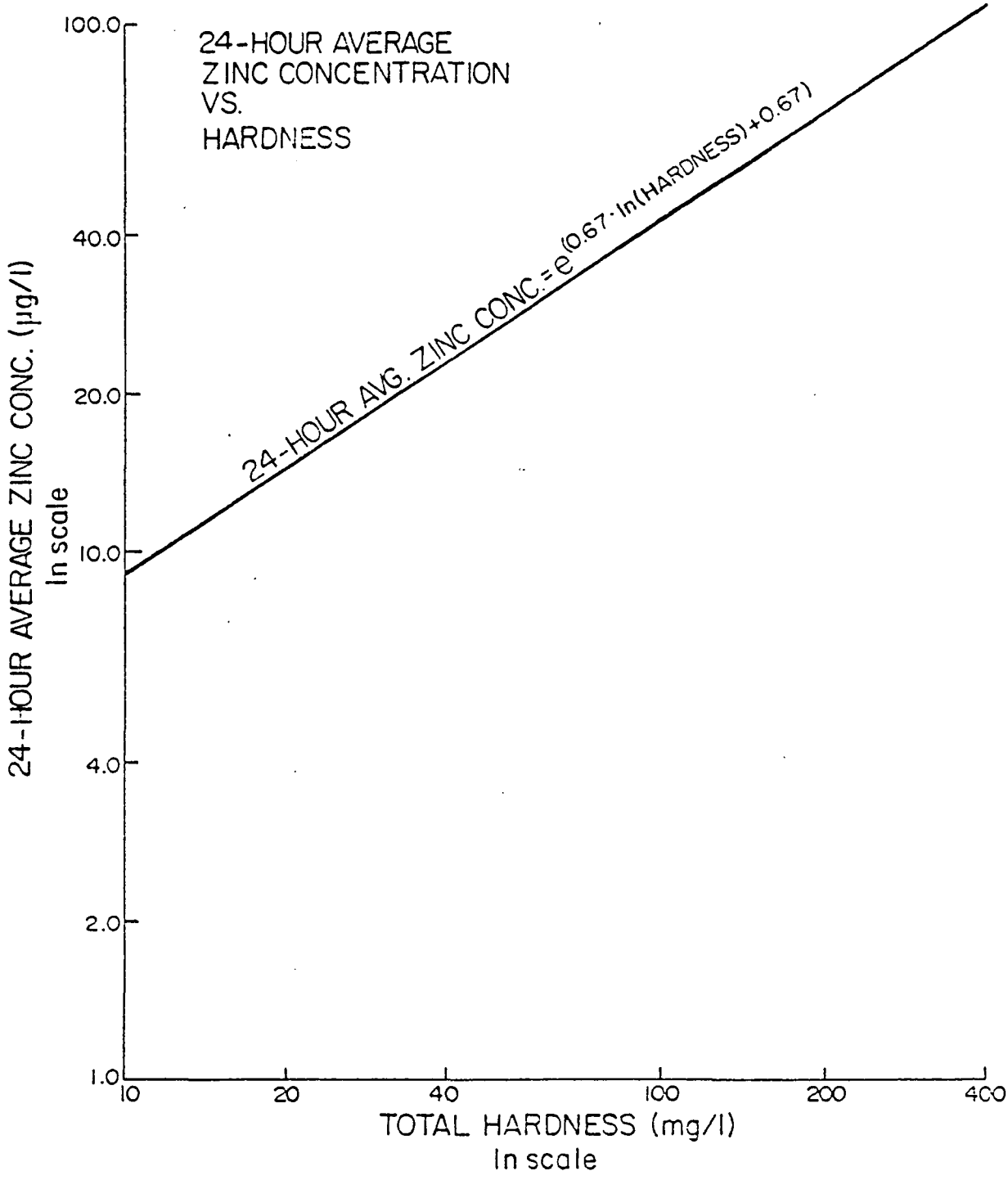
Final Plant Value = 30 µg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = $e^{(0.67 \cdot \ln(\text{hardness}) + 0.67)}$

The maximum concentration of zinc is the Final Acute Value of $e^{(0.64 \cdot \ln(\text{hardness}) + 2.46)}$ and the 24-hour average concentration is the Final Chronic Value of $e^{(0.67 \cdot (\text{hardness}) + 0.67)}$. No important adverse effects on freshwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For zinc the criterion to protect freshwater aquatic life as derived using the Guidelines is "$e^{(0.67 \cdot \ln(\text{hardness}) + 0.67)}$" as a 24-hour average (see the figure "24-hour average zinc concentration vs. hardness") and the concentration should not exceed "$e^{(0.64 \cdot \ln(\text{hardness}) + 2.46)}$" (see the figure "maximum zinc concentration vs. hardness") at any time.


24-HOUR AVERAGE
ZINC CONCENTRATION
VS.
HARDNESS
24-HOUR AVG. ZINC CONC. = e^(0.67·ln(HARDNESS)+0.67)
24-HOUR AVERAGE ZINC CONC. (µg/l)
ln scale
100.0
40.0
20.0
10.0
4.0
2.0
1.0
10
20
40
100
200
400
TOTAL HARDNESS (mg/l)
ln scale

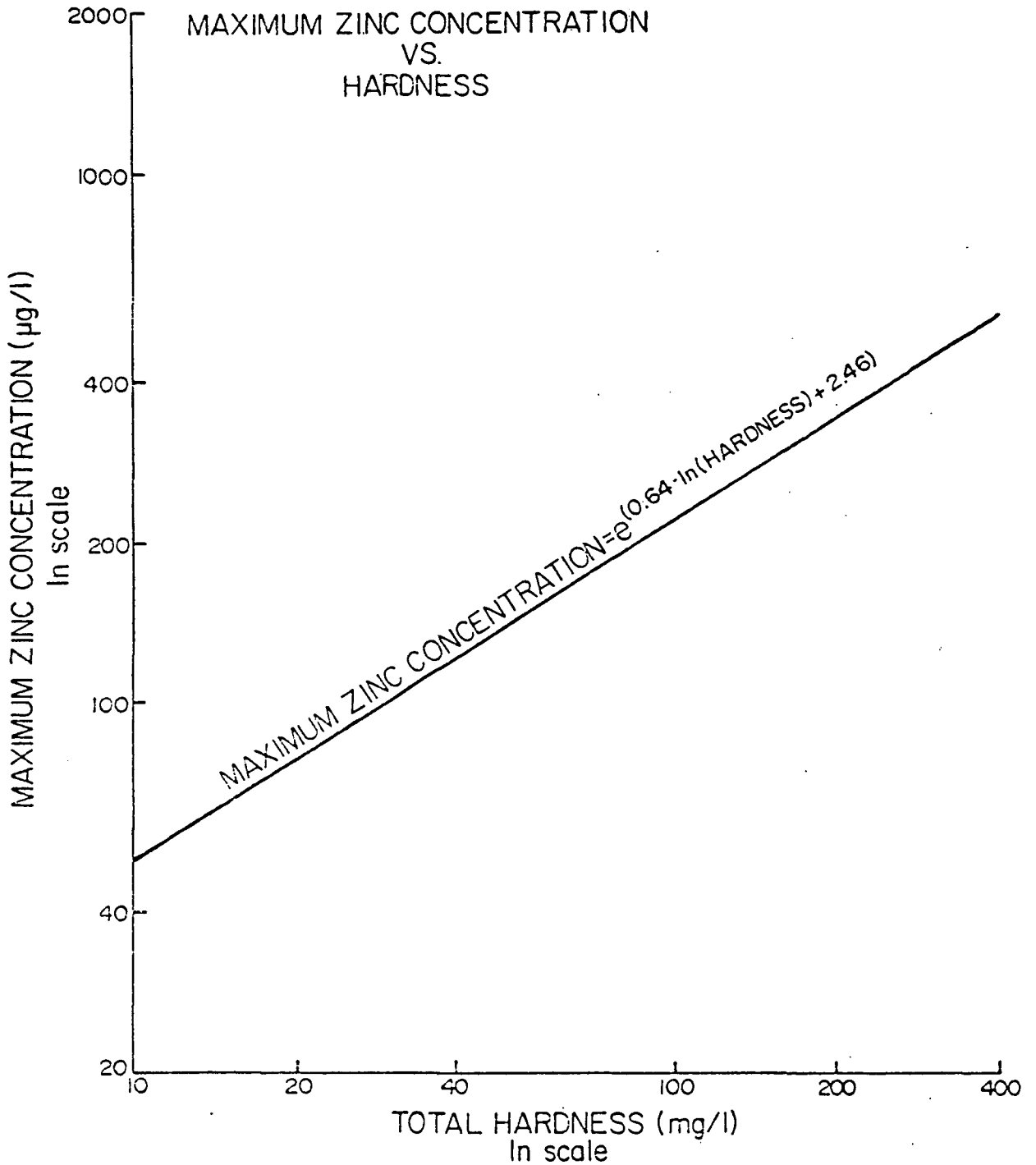

MAXIMUM ZINC CONCENTRATION
VS.
HARDNESS
MAXIMUM ZINC CONCENTRATION (µg/l)
ln scale
2000
1000
400
200
100
40
20
MAXIMUM ZINC CONCENTRATION=e^(0.64·ln(HARDNESS)+2.46)
10
20
40
100
200
400
TOTAL HARDNESS (mg/l)
ln scale

Table 1. Freshwater fish acute values for zinc

Organism	Bioassay Method*	Test Conc**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
American eel, Anguilla rostrata	S	M	53	96	14,600	10,366	Rehwoldt, et al 1971
American eel, Anguilla rostrata	S	M	55	96	14,500	10,295	Rehwoldt, et al. 1972
Coho salmon, Oncorhynchus kisutch	FT	M	89-99	96	4,600	4,600	Lorz & McPherson, 1976
Coho salmon, Oncorhynchus kisutch	FT	M	25	96	905	905	Chapman & Stevens 1978
Sockeye salmon, Oncorhynchus nerka	FT	M	34	96	749	749	Chapman, 1978a
Sockeye salmon, Oncorhynchus nerka	FT	U	13	96	1,000	770	Boyce & Yamada, 1977
Chinook salmon, Oncorhynchus tshawytscha	FT	M	24	96	97	97	Chapman, 1978b
Chinook salmon, Oncorhynchus tshawytscha	FT	M	24	96	701	701	Chapman, 1978b
Chinook salmon, Oncorhynchus tshawytscha	FT	M	24	96	463	463	Chapman, 1978b
Cutthroat trout, Salmo clarki	S	M	24	96	90	49	Rabe & Sappington, 1970
Cutthroat trout, Salmo clarki	FT	M	24	24	420	277	Rabe & Sappington, 1970
Rainbow trout, Salmo gairdneri	S	M	320	48	3,500	2,012	Brown, 1968
Rainbow trout, Salmo gairdneri	FT	M	500	48	4,700	3,807	Solbé, 1974
Rainbow trout, Salmo gairdneri	S	U	5	96	280	153	McLeay, 1976
Rainbow trout, Salmo gairdneri	FT	M	-	96	550	550	Hale, 1977

Table 1. (Continued)

Organism	Bioassay Method *	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Rainbow trout, Salmo gairdneri	FT	M	333	96	7,210	7,210	Sinley, et al. 1974
Rainbow trout, Salmo gairdneri	FT	M	26	96	430	430	Sinley, et al. 1974
Rainbow trout, Salmo gairdneri	R	M	240	48	4,000	2,300	Brown & Dalton, 1970
Rainbow trout, Salmo gairdneri	S	M	36	24	2,800	1,312	Cairns, et al. 1978
Rainbow trout, Salmo gairdneri	S	M	36	24	1,560	731	Cairns, et al. 1978
Rainbow trout, Salmo gairdneri	S	M	36	24	2,100	984	Cairns, et al. 1978
Rainbow trout, Salmo gairdneri	S	U	320	48	2,460	1,089	Herbert & Van Dyke, 1964
Rainbow trout, Salmo gairdneri	FT	M	83	96	1,755	1,755	Chapman & Stevens, 1978
Rainbow trout, Salmo gairdneri	S	U	320	72	3,500	1,760	Lloyd, 1961
Rainbow trout, Salmo gairdneri	FT	M	47	96	370	370	Holcombe & Andrew, 1978
Rainbow trout, Salmo gairdneri	FT	M	47	96	517	517	Holcombe & Andrew, 1978
Rainbow trout, Salmo gairdneri	FT	M	44.4	96	756	756	Holcombe & Andrew, 1978
Rainbow trout, Salmo gairdneri	FT	M	178	96	2,510	2,510	Holcombe & Andrew, 1978
Rainbow trout, Salmo gairdneri	FT	M	179	96	2,960	2,960	Holcombe & Andrew, 1978

Table 1. (Continued)

Organism	Bioassay Method*	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Rainbow trout, Salmo gairdneri	FT	M	170	96	1,910	1,910	Holcombe & Andrew, 1978
Rainbow trout, Salmo gairdneri	FT	M	333	96	4,520	4,520	Goettl, et al. 1972
Rainbow trout, Salmo gairdneri	FT	M	333	96	1,190	1,190	Goettl, et al. 1972
Rainbow trout, Salmo gairdneri	FT	M	26	96	560	560	Goettl, et al. 1972
Rainbow trout, Salmo gairdneri	FT	M	26	96	240	240	Goettl, et al. 1972
Rainbow trout, Salmo gairdneri	FT	M	26	96	810	810	Goettl, et al. 1972
Rainbow trout, Salmo gairdneri	FT	M	26	96	410	410	Goettl, et al. 1972
Rainbow trout, Salmo gairdneri	FT	M	26	96	830	830	Goettl, et al. 1972
Rainbow trout (yearling), Salmo gairdneri	FT	M	365	96	5,340	5,340	Watson, 1975
Rainbow trout (fingerling), Salmo gairdneri	FT	U	320	48	3,860	2,407	Herbert & Shurben, 1964
Rainbow trout (fingerling), Salmo gairdneri	S	U	320	48	2,400	1,063	Herbert & Shurben, 1964
Rainbow trout (fingerling), Salmo gairdneri	S	U	44	48	910	403	Herbert & Shurben, 1964
Rainbow trout, Salmo gairdneri	FT	M	23	96	93	93	Chapman, 1978b
Rainbow trout, Salmo gairdneri	FT	M	23	96	136	136	Chapman, 1978b

Table 1. (Continued)

Organism	Bioassay Method*	Test Conc. **	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Rainbow trout, Salmo gairdneri	FT	M	23	96	815	815	Chapman, 1978b
Atlantic salmon, Salmo salar	FT	M	14	96	740	740	Carson & Carson, 1972
Atlantic salmon, Salmo salar	FT	M	352	96	3,130	3,130	Hodson & Sprague, 1975
Atlantic salmon, Salmo salar	FT	M	20	96	~600	~600	Sprague, 1964
Atlantic salmon, Salmo salar	FT	M	14	96	~420	~420	Sprague & Ramsey, 1965
Brook trout, Salvelinus fontinalis	FT	M	47	96	1,550	1,550	Holcombe & Andrew, 1978
Brook trout, Salvelinus fontinalis	FT	M	47	96	2,120	2,120	Holcombe & Andrew, 1978
Brook trout, Salvelinus fontinalis	FT	M	44	96	2,420	2,420	Holcombe & Andrew, 1978
Brook trout, Salvelinus fontinalis	FT	M	178	96	6,140	6,140	Holcombe & Andrew, 1978
Brook trout, Salvelinus fontinalis	FT	M	179	96	6,980	6,980	Holcombe & Andrew, 1978
Brook trout, Salvelinus fontinalis	FT	M	170	96	4,980	4,980	Holcombe & Andrew, 1978
Goldfish, Carassius auratus	S	M	36	24	103,000	48,266	Cairns, et al. 1978
Goldfish, Carassius auratus	S	M	36	24	40,000	18,744	Cairns, et al. 1978
Goldfish, Carassius auratus	S	M	36	24	24,000	11,246	Cairns, et al. 1978
Goldfish, Carassius auratus	S	U	20	96	6,440	3,521	Pickering & Henderson, 1966

Table 1. (Continued)

Organism	Bioassay Method*	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (µg/l)	Adjusted LC50 (µg/l)	Reference
Goldfish, Carassius auratus	S	U	50	96	7,500	4,100	Cairns, et al. 1969
Carp, Cyprinus carpio	S	M	53	96	7,800	5,538	Rehwoldt, et al. 1971
Carp, Cyprinus carpio	S	M	55	96	7,800	5,538	Rehwoldt, et al. 1972
Golden shiner, Notemigonus crysoleucus	S	M	36	24	11,400	5,342	Cairns, et al. 1978
Golden shiner, Notemigonus crysoleucus	S	M	36	24	7,760	3,636	Cairns, et al. 1978
Golden shiner, Notemigonus crysoleucus	S	M	36	24	8,330	3,903	Cairns, et al. 1978
Golden shiner, Notemigonus crysoleucus	S	U	50	96	6,000	3,280	Cairns, et al. 1969
Fathead minnow, Pimephales promelas	FT	M	50	96	12,500	12,500	Mount, 1966
Fathead minnow, Pimephales promelas	FT	M	50	96	13,800	13,800	Mount, 1966
Fathead minnow, Pimephales promelas	FT	M	100	96	18,500	18,500	Mount, 1966
Fathead minnow, Pimephales promelas	FT	M	100	96	25,000	25,000	Mount, 1966
Fathead minnow, Pimephales promelas	FT	M	200	96	29,000	29,000	Mount, 1966
Fathead minnow, Pimephales promelas	FT	M	200	96	35,500	35,500	Mount, 1966
Fathead minnow, Pimephales promelas	FT	M	50	96	13,700	13,700	Mount, 1966
Fathead minnow, Pimephales promelas	FT	M	50	96	6,200	6,200	Mount, 1966

Table 1. (Continued)

Organism	Bioassay Method*	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Fathead minnow, Pimephales promelas	FT	M	100	96	12,500	12,500	Mount, 1966
Fathead minnow, Pimephales promelas	FT	M	100	96	12,500	12,500	Mount, 1966
Fathead minnow, Pimephales promelas	FT	M	200	96	19,000	19,000	Mount, 1966
Fathead minnow, Pimephales promelas	FT	M	200	96	13,600	13,600	Mount, 1966
Fathead minnow, Pimephales promelas	FT	M	50	96	4,700	4,700	Mount, 1966
Fathead minnow, Pimephales promelas	FT	M	50	96	5,100	5,100	Mount, 1966
Fathead minnow, Pimephales promelas	FT	M	100	96	8,100	8,100	Mount, 1966
Fathead minnow, Pimephales promelas	FT	M	100	96	9,900	9,900	Mount, 1966
Fathead minnow, Pimephales promelas	FT	M	200	96	8,200	8,200	Mount, 1966
Fathead minnow, Pimephales promelas	FT	M	200	96	15,500	15,500	Mount, 1966
Fathead minnow, Pimephales promelas	FT	M	203	96	8,400	8,400	Brungs, 1969
Fathead minnow, Pimephales promelas	FT	M	203	96	10,000	10,000	Brungs, 1969
Fathead minnow, Pimephales promelas	S	U	203	96	12,000	6,560	Brungs, 1969
Fathead minnow, Pimephales promelas	S	U	203	96	13,000	7,107	Brungs, 1969
Fathead minnow, Pimephales promelas	FT	M	46	96	600	600	Benoit & Holcombe, 1978

Table 1. (Continued)

Organism	Bioassay Method*	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Fathead minnow (embryo), Pimephales promelas	FT	M	174-198	96	1,850	1,850	Pickering & Vigor, 1965
Fathead minnow (embryo), Pimephales promelas	FT	M	174-198	96	1,820	1,820	Pickering & Vigor, 1965
Fathead minnow (fry), Pimephales promelas	FT	M	174-198	96	870	870	Pickering & Vigor 1965
Fathead minnow, Pimephales promelas	S	U	20	96	960	525	Pickering & Henderson, 1966
Fathead minnow, Pimephales promelas	S	U	20	96	780	426	Pickering & Henderson, 1966
Fathead minnow, Pimephales promelas	S	U	20	96	880	481	Pickering & Henderson, 1966
Fathead minnow, Pimephales promelas	S	U	360	96	33,400	18,260	Pickering & Henderson, 1966
Fathead minnow, Pimephales promelas	S	U	166	96	7,630	4,171	Rachlin & Perlmutter, 1968
Banded killifish, Fundulus diaphanus	S	M	55	96	19,200	13,632	Rehwoldt, et al. 1972
Banded killifish, Fundulus diaphanus	S	M	53	96	19,100	13,561	Rehwoldt, et al. 1971
Flagfish, Jordanella floridae	FT	M	44	96	1,500	1,500	Spehar, 1976
Guppy, Poecilia reticulatus	S	U	20	96	1,270	694	Pickering & Henderson, 1966
Southern platyfish, Xiphophorus maculatus	S	U	166	96	12,000	6,560	Rachlin & Perlmutter, 1968
White perch, Morone americana	S	M	53	96	14,300	10,153	Rehwoldt, et al. 1971
White perch, Morone americana	S	M	55	96	14,400	10,224	Rehwoldt, et al. 1972

Table 1. (Continued)

Organism	Bioassay Method*	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Striped bass, Morone saxatilis	S	M	55	96	6,800	4,828	Rehwoldt, et al. 1972
Striped bass, Morone saxatilis	S	M	53	96	6,700	4,757	Rehwoldt, et al. 1971
Striped bass (embryo), Morone saxatilis	S	M	137	96	1,850	1,313	O'Rear, 1972
Striped bass (fry), Morone saxatilis	S	M	137	96	1,180	837	O'Rear, 1972
Striped bass, Morone saxatilis	S	U	--	96	100	54	Hughes, 1973
Pumpkinseed, Lepomis gibbosus	S	M	53	96	20,000	14,200	Rehwoldt, et al. 1971
Pumpkinseed, Lepomis gibbosus	S	M	55	96	20,100	14,271	Rehwoldt, et al 1972
Bluegill, Lepomis macrochirus	FT	M	46	96	9,900	9,900	Cairns, et al. 1972
Bluegill, Lepomis macrochirus	S	U	10	48	5,200	2,302	Cairns, et al. 1965
Bluegill, Lepomis macrochirus	S	U	--	96	7,450	4,072	Cairns & Scheier, 1959
Bluegill, Lepomis macrochirus	S	U	--	96	7,200	3,936	Cairns & Scheier, 1959
Bluegill, Lepomis macrochirus	S	U	--	96	6,910	3,777	Cairns & Scheier, 1959
Bluegill, Lepomis macrochirus	S	M	36	24	23,000	10,778	Cairns, et al. 1978
Bluegill, Lepomis macrochirus	S	M	36	24	19,100	8,950	Cairns, et al. 1978
Bluegill, Lepomis macrochirus	S	M	36	24	8,850	4,147	Cairns, et al. 1978

Table 1. (Continued)

Organism	Bioassay Method*	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Bluegill, Lepomis macrochirus	S	U	43	96	2,860-3,780	1,564-2,067	Patrick, et al. 1968
Bluegill, Lepomis macrochirus	S	U	20	96	5,460	2,985	Pickering & Henderson, 1966
Bluegill, Lepomis macrochirus	S	U	20	96	4,850	2,651	Pickering & Henderson, 1966
Bluegill, Lepomis macrochirus	S	U	20	96	5,820	3,182	Pickering & Henderson, 1966
Bluegill, Lepomis macrochirus	S	U	20	96	5,370	2,936	Pickering & Henderson, 1966
Bluegill, Lepomis macrochirus	S	U	360	96	40,900	22,360	Pickering & Henderson, 1966
Bluegill, Lepomis macrochirus	S	U	45	96	8,020	4,385	Cairns & Scheier, 1957a
Bluegill, Lepomis macrochirus	S	U	45	96	4,900	2,679	Cairns & Scheier, 1957a
Bluegill, Lepomis macrochirus	S	U	44	96	2,860-3,780	1,560-2,067	Cairns & Scheier, 1957b
Bluegill, Lepomis macrochirus	S	U	44	96	1,930-3,630	1,055-1,985	Cairns & Scheier, 1957b
Bluegill, Lepomis macrochirus	S	U	171	96	10,130-12,500	5,538-6,834	Cairns & Scheier, 1957b
Bluegill, Lepomis macrochirus	S	U	171	96	10,150-12,300	5,549-6,724	Cairns & Scheier, 1957b

* S = static, R = renewal, FT = flow-through

** M = measured, U = unmeasured

Table 1. (Continued)

Adjusted LC50 vs. hardness

Rainbow trout: slope = 0.71, intercept = 3.79, r = 0.82, p = 0.01, N = 32

Atlantic salmon: slope = 0.54, intercept = 4.85, r = 0.96, p = 0.05, N = 4

Brook trout: slope = 0.82, intercept = 4.46, r = 0.96, p = 0.01, N = 6

Fathead minnow: slope = 0.86, intercept = 4.74, r = 0.54, p = 0.01, N = 31

Bluegill: slope = 0.49, intercept = 6.50, r = 0.58, p = 0.05, N = 17

Geomerric mean slope = 0.67

Mean intercept for 20 fish species = 5.29

Adjusted mean intercept = 5.29 - ln(3.9) = 3.93

Intercept for chinook salmon = 3.63

Final Fish Acute Value = $e^{(0.67 \cdot \ln(\text{hardness}) + 3.63)}$

Table 2. Freshwater invertebrate acute values for zinc

Organism	Bioassay Method*	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Worm, Nais sp.	S	M	50	96	18,400	20,240	Rehwoldt, et al. 1973
Snail (egg), Amnicola sp.	S	M	50	96	20,200	22,220	Rehwoldt, et al. 1973
Snail (adult), Amnicola sp.	S	M	50	96	14,000	15,400	Rehwoldt, et al. 1973
Snail, Goniobasis livescens	S	U	137-171	48	13,500	4,916	Cairns, et al. 1976
Snail, Lymnea emarginata	S	U	137-171	48	4,150	1,511	Cairns, et al. 1976
Snail, Physa heterostropha	S	U	44	96	790	669	Cairns & Scheier, 1958
Snail, Physa heterostropha	S	U	44	96	1,270	1,075	Cairns & Scheier, 1958
Snail, Physa heterostropha	S	U	44	96	620	525	Cairns & Scheier, 1958
Snail, Physa heterostropha	S	U	44	96	780	660	Cairns & Scheier, 1958
Snail, Physa heterostropha	S	U	171	96	2,660	2,253	Cairns & Scheier, 1958
Snail, Physa heterostropha	S	U	171	96	5,570	4,717	Cairns & Scheier, 1958
Snail, Physa heterostropha	S	U	171	96	2,360	1,998	Cairns & Scheier, 1958
Snail, Physa heterostropha	S	U	171	96	6,360	5,386	Cairns & Scheier, 1958
Snail, Physa heterostropha	S	U	100	96	14,000	11,860	Wurtz & Bridges, 1961
Snail, Physa heterostropha	S	U	20	96	4,900	4,150	Wurtz & Bridges, 1961

Table 2. (Continued)

Organism	Bioassay Method*	Test Conc**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Snail, Physa heterostropha	S	U	43	96	790-1,270	669-1,075	Patrick, et al. 1968
Snail, Physa integra	S	U	137-171	48	4,400	1,602	Cairns, et al. 1976
Cladoceran, Daphnia hyalina	S	U	23	48	40	33	Baudouin & Scoopa, 1974
Cladoceran, Daphnia magna	S	U	~20	48-64	71.9	60.9	Anderson, 1948
Cladoceran, Daphnia magna	R	M	45.3	48	100	110	Biesinger & Christensen, 1972
Cladoceran, Daphnia magna	R	M	45.3	48	280	308	Biesinger & Christensen, 1972
Cladoceran, Daphnia magna	S	U	-	48	1,800	1,524	Bringmann & Kuhn, 1959
Copepod, Cyclops abyssorum predpinus	S	U	23	48	5,500	2,003	Baudouin & Scoopa, 1974
Copepod, Eudiaptomus padanus padanus	S	U	23	48	500	182	Baudouin & Scoopa, 1974
Sowbug, Asellus communis	S	U	100	96	38,500	32,610	Wurtz & Bridges, 1961
Scud, Gammarus sp.	S	M	50	96	8,100	8,910	Rehwoldt, et al. 1973
Damselfly, Unidentified	S	M	50	96	26,200	28,820	Rehwoldt, et al. 1973
Midge, Chironomus sp.	S	M	50	96	18,200	20,020	Rehwoldt, et al. 1973
Caddisfly, Unidentified	S	M	50	96	58,100	63,910	Rehwoldt, et al. 1973

Table 2. (Continued)

Organism	Bioassay Method*	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Rotifer, Philodia acuticornus	S	U	81	24	4,100	902	Buikema, et al. 1974
Rotifer, Philodia acuticornus	S	U	25	96	1,500	1,270	Buikema, et al. 1974
Rotifer, Philodia acuticornus	S	U	25	96	1,200	1,016	Buikema, et al. 1974

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* S = static, R = renewal

** U = unmeasured, M = measured

Adjusted LC50 vs. hardness:

Snail, Physa heterostropha: slope = 0.64, intercept = 4.80, r = 0.48, Not significant, N = 11

Geometric mean slope = 0.64 (only value available)

Mean intercept for 16 species = 5.50

Adjusted mean intercept = 5.50 - ln(21) = 2.46

Final Invertebrate Acute Value = $e^{(0.64 \cdot \ln(\text{hardness}) + 2.46)}$

Table 3. Freshwater fish chronic values for zinc

Organism	Test*	Limits (ug/l)	Chronic Value (ug/l)	Hardness (mg/l as $CaCO_3$)	Reference
Chinook salmon, Oncorhynchus tshawytscha	E-L	280-500	187	22	Chapman, Manuscript
Rainbow trout, Salmo gairdneri	E-L	140-260	95	26	Sinley, et al. 1974
Brook trout, Salvelinus fontinalis	LC	534-1,360	852	45	Holcombe, et al. 1978
Fathead minnow, Pimephales promelas	LC	78-145	106	46	Benoit & Holcombe, 1978
Flagfish, Jordanella floridae	LC	26-51	36	44	Spehar, 1976

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

Chronic Value vs. hardness:

No hardness relationship could be derived for any fish species.

Slope = 0.67 from Fish Acute Values

Mean intercept for 5 species = 2.57

Adjusted mean intercept = 2.57 - ln(6.7) = 0.67

Final Fish Chronic Value = $e^{(0.67 \cdot \ln(\text{hardness}) + 0.67)}$

Application Factor Values

Species	96 hr LC50 (µg/l)	Hardness (mg/l as $CaCO_3$)	MATC µg/l	A.F.	Reference
Brook trout, Salvelinus fontinalis	2,000	45	534-1,360	.43	Holcombe, et al. 1978
Fathead minnow, Pimephales promelas	600	46	78-145	.18	Benoit & Holcombe, 1978
Flagfish, Jordanella floridae	1,500	44	26-51	.02	Spehar, 1976

Geometric mean A.F. = 0.12 Geometric mean LC50 = 1,216 µg/l

Table 4. Freshwater invertebrate chronic values for zinc (Biesinger & Christensen, 1972)

Organism	Test*	Limits (ug/l)	Chronic Value (ug/l)	Hardness (mg/l as $CaCO_3$)
Cladoceran, *Daphnia magna*	LC	70-102	84.5	45

* LC = life cycle or partial life cycle

Chronic Value vs. hardness:

No hardness relationship could be derived for any invertebrate species.

Slope = 0.64 from invertebrate acute value.

Intercept for *Daphnia magna* = 2.00 (only species tested).

Final Invertebrate Chronic Value = $e^{(0.64 \cdot \ln(\text{hardness}) + 2.00)}$

Table 5. Freshwater plant effects for zinc

Organism	Effect	Concentration (ug/l)	Reference
Alga, Chlorella vulgaris	50% inhibition of cell division	5,100	Rosko & Rachlin, 1977
Alga, Chlorella vulgaris	Extended lag time to 7 days	7,500	Rosko & Rachlin, 1977
Alga, Chlorella vulgaris	Decrease chlorophyll a	7,500	Rosko & Rachlin, 1977
Alga, Chlorella vulgaris	50% reduction in growth rate 96 hrs	2,400	Rachlin & Farran, 1974
Alga, Scenedesmus quadricauda	Threshold toxicity	1,000-1,400	Bringmann & Kuhn, 1959
Alga, Selenastrum capricornutum	Algicidal	700	Bartlett, et al. 1974
Alga, Selenastrum capricornutum	Total growth inhibition	120	Bartlett, et al. 1974
Alga, Selenastrum capricornutum	Incipient growth inhibition	30	Bartlett, et al. 1974
Eurasian watermilfoil, Myriophyllum spicatum	50% root weight reduction	21,600	Stanley, 1974
Eurasian watermilfoil, Myriophyllum spicatum	50% root length reduction	21,600	Stanley, 1974
Eurasian watermilfoil, Myriophyllum spicatum	50% reduction in shoot length	20,900	Stanley, 1974
Diatom, Nitzschia linearis	LC50 120 hrs	4,300	Patrick, et al. 1968

Lowest plant value = 30 ug/l

Table 6. Freshwater residues for zinc

Organism	Bioconcentration Factor	Time (days)	Reference
Mayfly, *Ephemerella grandis*	1,130	14	Nehring, 1976
Stonefly, *Pteronarcys californica*	106	14	Nehring, 1976
Carp, *Cyprinus carpio*	8	60	Lebedeva & Kuznetsova, 1969
Stickleback, *Gasterosteus aculeatus*	12.2	0.66	Matthiessen & Brafield, 1977

Maximum Permissible Tissue Concentration

Organism	Action Level or Effect	Concentration mg/kg	Reference
White Rat	stillbirths and postnatal growth inhibition	2,000	Ketcheson, et al. 1969

Bioconcentration factor - 1,130

Lowest residue concentration = 2,000 mg/kg

$\frac{2,000}{1,130}$ = 1.77 mg/kg = 1,800 µg/l

Table (Continued)

Organism	Test Duration	Effect	Hardness (mg/l as $CaCO_3$)	Result (ug/l)	Reference
Bluegill, Lepomis macrochirus	20 days	LC50	370	10,500	Pickering, 1968
Bluegill, Lepomis macrochirus	20 days	LC50	370	12,000	Pickering, 1968
Bluegill, Lepomis macrochirus	20 days	LC50	370	10,700	Pickering, 1968
Pond snail, Physa heterostrapha	96 hrs	LC50 soft water	20	303	Wurtz, 1962
Pond snail, Physa heterostropha	96 hrs	LC50 hard water	100	434	Wurtz, 1962
Pond snail, Physa heterostropha	96 hrs	LC50 soft water	20	434	Wurtz, 1962
Pond snail, Physa heterostropha	96 hrs	LC50 hard water	100	1,700	Wurtz, 1962
Pond snail, Physa heterostropha	96 hrs	LC50 soft water	20	350	Wurtz, 1962
Pond snail, Physa heterostropha	96 hrs	LC50 hard water	100	1,100	Wurtz, 1962
Bluegill, Lepomis macrochirus	96 hrs	LC0	46	13,500 - 32,000 insoluble zinc	Cairns, et al. 1971
Bluegill, Lepomis macrochirus	96 hrs	LC100	46	18,000 soluble zinc	Cairns, et al. 1971

SALTWATER ORGANISMS

Acute Toxicity

The mummichog was the only non-anadromous saltwater teleost used for acute toxicity tests for zinc (Table 8). The unadjusted 96-hour LC50 value was 60,000 µg/l (Eisler and Hennekey, 1977). Longer exposure to zinc (Tables 12) did not significantly change the result; the 168-hour LC50 was 52,000 µg/l (Eisler and Hennekey, 1977) and the 192-hour LC50 was 66,000 µg/l (Eisler, 1967). Smolts of Atlantic salmon, Salmo salar, acclimatized to 70 percent salt water, were more sensitive to zinc than yearling rainbow trout, S. gairdnerii, at the same salinity under flow-through conditions, with unadjusted 48-hour LC50 values of 27,000 µg/l and 35,000 µg/l, respectively (Herbert and Wakeford, 1964). Both species were more resistant at 30 to 40 percent salt water; LC50 values were 39,000 µg/l for the salmon and 82,000 µg/l for the trout.

Application of the adjustment factors to the fish acute toxicity data gives a geometric mean of 33,450 µg/l which, when adjusted by the species sensitivity factor (3.7), results in a Final Fish Acute Value of 9,000 µg/l. No fish acute toxicity data from Table 8 is below 9,000 µg/l, indicating the procedure allows protection for at least 95 percent of the species.

Saltwater invertebrate species are more sensitive to acute zinc toxicity, as shown by data on various life stages of annelids, bivalve and gastropod molluscs, arthropod crustaceans, and echinoderms (Table 9). Among polychaete annelids, adults are more tolerant than young of the species. Adult Capitella capitata and Neanthes arenaceodentata had adjusted 96-hour LC50 values of 2,965 and 1,524 µg/l zinc, respectively (Reish, et al. 1976). While the level for

larvel C. capitata is 1.440 µg/l and that for juvenile N. arenaceodentata is 762 µg/l (Reish, et al. 1976). As with fish, salinity affected zinc sensitivity of adult polychaetes. Nereis diversicolor in 17.5 °/oo had an adjusted 96-hour LC50 value of 46,585 µg/l while a salinity of 3.5 °/oo, the LC50 was 9,317 (Bryan and Hummerstone, 1973).

Larval bivalve molluscs were the most susceptible invertebrate species to zinc. Forty-eight-hour LC50 values were 141 µg/l for Mercenaria mercenaria larvae (Calabrese, et al. 1977) to 287 µg/l for Crassostrea virginica (Calabrese, et al. 1973). Acute toxicity values for adult pelecypods ranged from 2,640 µg/l for Mytilus edulis planulatus (Ahsanullah, 1976) to 6,522 µg/l for Mya arenaria (Eisler and Hennekey, 1977). Among gastropod molluscs, the adjusted 96-hour LC50 value for Nassarius obsoletus was 42,350 µg/l (Eisler and Hennekey, 1977).

Among crustaceans, susceptibility to zinc varied between species and development stages. The adult crab, Carcinus maenas was the most resistant of those studied, with adjusted 96-hour LC50 values of 5,281 (Conner, 1972) and 4,370 µg/l (Portmann, 1968). Larvae of this species were more sensitive with an adjusted 96-hour concentrations of 847 µg/l (Conner, 1972). The copepod, Acartia tonsa was the most sensitive crustacean species tested, with a 96-hour LC50 value of 246 µg/l (Sosnowski, et al. 1979). Among echinoderms, Eisler and Hennekey (1977) showed that the adult starfish, Asterias forbesi, was rather insensitive to zinc, with an adjusted LC50 value of 33,033 µg/l.

Toxicity studies of longer duration with invertebrate species (Table 12) resulted in lower lethal zinc concentrations. Minimum

LC50 values were 195 µg/l (12 days) for larvae of the clam, Mercenaria mercenaria, (Calabrese, et al. 1977) and 200 µg/l (168 hours) for adult hermit crab, Pagurus longicarpus, (Eisler and Hennekey, 1977). The 168-hour LC50 value for adult polychaete, Nereis virens, was 2,645 µg/l (Eisler and Hennekey, 1977).

The Final Invertebrate Acute Value of 41 µg/l was calculated from the geometric mean of 2,026 µg/l and a species sensitivity factor of 49. This value does not exceed the adjusted LC50 value for any life stage of any invertebrate species (Table 9) thus affording 95 percent protection for invertebrate species. Since this level is lower than the Final Fish Acute Value (9,000 µg/l), 41 µg/l is the Final Acute Value.

Chronic Toxicity

No whole or partial life cycle chronic toxicity data are available for zinc and saltwater fish or invertebrate species.

Plant Effects

The minimum zinc concentration which inhibited growth among five species of microalgae (Table 10) was 50 µg/l; Skeletonema costatum was the most sensitive species tested (Bryan, 1964). At this concentration, zinc also interacted with copper to affect growth (Braek, et al. 1976). Maximum tolerance to growth inhibition among algae was 25,000 µg/l, as shown by Jensen, et al. (1974) with Phaeodactylum tricornutum. The most sensitive kelp species was Laminaria digitata, with growth inhibition occurring at 100 µg/l (Bryan, 1964).

The Final Plant Value is 50 µg/l.

Residues

Algal bioconcentration of zinc includes data for both microalgae and macroalgae (Table 11). The maximum BCF value for the

macroalgae, Fucus serratus, was 10,000 after 140 days exposure to 9.5 µg/l (Young, 1975). Among the microalgal species examined, Thallossiosira pseudonana, accumulated zinc 12,400 times over ambient water concentrations of 250 µg/l in 13 days (Jensen, et al. 1974).

Whole body concentration in adult Crassostrea Virginica was 2,708 mg zinc/kg wet weight after exposure to 0.1 mg/l for 140 days, resulting in a BCF of 27,080 (Shuster and Pringle, 1969). Shuster and Pringle (1968) reported a BCF of 15,240 for C. virginica exposed to 0.1 mg/l for 140 days. Among the soft-shell clams, adult Mya arenaria were poor concentrators of zinc, accumulating only 43 times over a water concentration of 500 µg/l after 112 days (Eisler, 1977b). Similarly, the hard shelled clam, Mercenaria mercenaria, had a bioconcentration factor of 85 (Shuster and Pringle, 1968) while mussel, Mytilus edulis accumulated zinc up to 500 times (Pentreath, 1973c).

Bioconcentration factors for crustaceans ranged from 266 in the mud crab (Duke, et al. 1969) to 9,000 for adult Carcinus maenas (Bryan, 1971).

Miscellaneous

Various saltwater phyla are well represented in studies of sublethal effects of zinc (Table 12). After a 14-day exposure to 10,000 µg/l, liver aminolevulinate dehydrase enzyme activity increased in the adult mummichog, Fundulus heteroclitus, (Jackim, 1973). Although no larvae of oysters, Crassostrea virginica, died during 48 hours in 75 µg/l (Calabrese, et al. 1973), C. gigas larvae did exhibit abnormal shell development in 70 µg/l after immersion for 48 hours (Nelson, 1972). Oyster larvae showed

reduced development in a slightly higher level of 125 µg/l (Brereton, et al. 1973). Adult bivalve molluscs were more resistant to zinc toxicity; Crassostrea virginica showed no significant mortality in 200 µg/l after 140 days (Shuster and Pringle, 1968; 1969). A small increase in temperature doubled toxicity to adult Mya arenaria. The 168-hour LC50 value at 20° C was 3,100 µg/l (Eisler and Hennekey, 1977) while at 22° C it was 1,550 µg/l (Eisler, 1977a). Larval stages of crustaceans were again the most sensitive to zinc, as shown by delayed development in crab, Rhithropanopeus harrisi, during a 16-day exposure to 50 µg/l (Benijts-Claus and Benijts, 1975). Polychaetes were generally tolerant of zinc; Reish and Car (1978) reported reduced survival after 21 days in 1,750 µg/l for Ophryotrocha diadema and in 10,000 for Ctenodrilus serratus. Growth of the protozoan, Cristigera sp., was reduced in 125 µg/l after 4 to 5 hours (Gray, 1974).

CRITERION FORMULATION

Saltwater-Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures. All concentrations herein are expressed in terms of zinc.

Final Fish Acute Value = 9,000 µg/l

Final Invertebrate Acute Value = 41 µg/l

Final Acute Value = 41 µg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = 50 µg/l

Final Chronic Value = 50 µg/l

0.44 x Final Acute Value = 18 µg/l

CRITERION: No saltwater criterion can be derived for zinc using the Guidelines because no Final Chronic Value for either fish or invertebrate species or a good substitute for either value is available, and there are insufficient data to estimate a criterion using other procedures.

Table 7. Other freshwater data for zinc

Organism	Test Duration	Effect	Hardness (mg/l as $CaCO_3$)	Result (ug/l)	Reference
Protozoa, Chilomonas sp.	10 mins	LC100	51-68	10,000	Ruthven & Cairns, 1973
Protozoa, Chilomonas sp.	3 hrs	LC0	51-68	3,200	Ruthven & Cairns, 1973
Protozoa, Tetrahymena sp.	10 mins	LC100	51-68	5,600	Ruthven & Cairns, 1973
Protozoa, Tetrahymena sp.	3 hrs	LC0	51-68	1,000	Ruthven & Cairns, 1973
Protozoa, Paramecium caudatum	10 mins	LC100	51-68	32,000	Ruthven & Cairns, 1973
Protozoa, Paramecium caudatum	3 hrs	LC0	51-68	15,500	Ruthven & Cairns, 1973
Protozoa, Paramecium multi-micronucleatum	10 mins	LC100	51-68	10,000	Ruthven & Cairns, 1973
Protozoa, Paramecium multi-micronucleatum	3 hrs	LC0	51-68	560	Ruthven & Cairns, 1973
Protozoa, Blepharisma sp.	10 mins	LC100	51-68	100,000	Ruthven & Cairns, 1973
Protozoa, Blepharisma sp.	3 hrs	LC0	-	10,000	Ruthven & Cairns, 1973
Cladoceran, Daphnia magna	24 hrs	LC50	-	14,000	Bringmann & Kuhn, 1977
Mayfly, Ephemerella grandis	14 days	LC50	30-70	>9,200	Nehring, 1976
Mayfly, Ephemerella subvaria	10 days	LC50	44	16,000	Warnick & Bell, 1969
Stonefly, Acroneuria lycorias	14 days	LC50	44	32,000	Warnick & Bell, 1969
Stonefly, Pteronarcys californica	14 days	LC50	30-70	>13,200	Nehring, 1976

Table 7. (Continued)

Organism	Test Duration	Effect	Hardness (mg/l as $CaCO_3$)	Result (ug/l)	Reference
Caddisfly, Hydropsyche betteni	11 days	LC50	44	32,000	Warnick & Bell, 1969
Coho salmon, Oncorhynchus kisutch	96 hrs	WBC-T counts depressed	3-10	500	McLeay, 1975
Sockeye salmon (embryo-smolt), Oncorhynchus nerka	18 mos	No effect on survival or growth	20-90	242	Chapman, 1978a
Cutthroat trout, Salmo clarkii	14 days	LC50	48	670	Nehring & Goettl, 1974
Rainbow trout, Salmo gairdneri	9 days	Gill tissue damage	44-55	40,000	Skidmore & Tovell, 1972
Rainbow trout, Salmo gairdneri	2 hrs	Increase in ventilation rate	66	40,000	Hughes & Adeney, 1977
Rainbow trout, Salmo gairdneri	48 hrs	Increased swimming velocity increased toxicity to Zn	320	1,680	Herbert & Shurben, 1963
Rainbow trout, Salmo gairdneri	7 days	Hyper-glycemia	374	214	Watson & McKeown, 1976
Rainbow trout, Salmo gairdneri	14 days	LC50	48	410	Nehring & Goettl, 1974
Rainbow trout, Salmo gairdneri	20 mins	Threshold avoidance level	13-15	5.6	Sprague, 1968
Rainbow trout, Salmo gairdneri	5 days	LC50	-	4,600	Ball, 1967
Rainbow trout, Salmo gairdneri	7 days	LC50	280	560	Lloyd, 1961
Rainbow trout, Salmo gairdneri	21 days	Median survival time	14	500-1,000	Grande, 1967
Brown trout, Salmo trutta	21 days	Median survival time	14	~1,000	Grande, 1967

Table 7. (Continued)

Organism	Test Duration	Effect	Hardness (mg/l as $CaCO_3$)	Result (ug/l)	Reference
Brown trout, *Salmo trutta*	14 days	LC50	48	640	Nehring & Goettl, 1974
Atlantic salmon *Salmo salar*	182 hrs	Incipient lethal level	14	150-1,000	Zitko & Carson, 1977
Atlantic salmon, *Salmo salar*	21 days	Median survival time	14	100-500	Grande, 1967
Brook trout, *Salvelinus fontinalis*	14 days	LC50	44	960	Nehring & Goettl, 1974
Golden shiner, *Notemigonus crysoleucas*	96 hrs	Avoidance	51	3,640	Waller & Cairns, 1972
Fathead minnow, *Pimephales promelas*	10 mos	Reproduction reduced	203	180	Brungs, 1969
Channel catfish, *Ictalurus punctatus*	12 hrs	Serum osmolarity decrease	206-236	12,000	Lewis & Lewis, 1971
Guppy, *Poecilia reticulatus*	30 days	Growth inhibition	80	1,150	Crandall & Goodnight, 1962
Stickleback, *Gasterosteus aculeatus*	3 days	Gill damage	282	500-1,000	Matthiessen & Brafield, 1973
Stickleback, *Gasterosteus aculeatus*	200 hrs	Increased oxygen uptake	282	1,000	Brafield & Mattheissen, 1976
Bluegill, *Lepomis macrochirus*	7 days	Increased breathing rate	51	8,700	Cairns & Sparks, 1971
Bluegill, *Lepomis macrochirus*	96 hrs	LC50 (swimming stress)	46	3,200	Burton, et al. 1972
Bluegill, *Lepomis macrochirus*	24 hrs	Increased cough response	-	40,000	Sparks, et al. 1972
Bluegill, *Lepomis macrochirus*	20 days	LC50	370	7,200	Pickering, 1968
Bluegill, *Lepomis macrochirus*	20 days	LC50	370	7,500	Pickering, 1968
Bluegill, *Lepomis macrochirus*	20 days	LC50	370	10,700	Pickering, 1968

Table 8. Marine fish acute values for zinc

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Mummichog (adult), Fundulus heteroclitus	S	U	96	60,000	32,802	Eisler & Hennekey, 1977
Rainbow trout (yearling), Salmo gairdnerii	FT	M	48	35,000	28,350	Herbert & Wakeford, 1964
Rainbow trout (yearling), Salmo gairdnerii	FT	M	48	82,000	66,420	Herbert & Wakeford, 1964
Atlantic salmon (smolt), Salmo salar	FT	M	48	27,000	21,870	Herbert & Wakeford, 1964
Atlantic salmon (smolt), Salmo salar	FT	M	48	39,000	31,590	Herbert & Wakeford, 1964

* S = static, FT = flow through
** U = unmeasured, M = measured
Geometric mean of adjusted values = 33,450 $\frac{33,450}{3.7}$ = 9,000 ug/l
Lowest value from flow-through test with measured concentrations = 21,870 ug/l

Table 9. Marine invertebrate acute values for zinc

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Polychaete (adult), Capitella capitata	S	U	96	3,500	2,965	Reish, et al. 1976
Polychaete (larvae), Capitella capitata	S	U	96	1,700	1,440	Reish, et al. 1976
Polycahete (adult), Neanthes arenaceodentata	S	U	96	1,800	1,524	Reish, et al. 1976
Polychaete (juvenile), Neanthes arenaceodentata	S	U	96	900	762	Reish, et al. 1976
Polychaete (adult), Nereis diversicolor	S	U	96	1,500	1,270	Bryan & Hummerstone, 1973
Polychaete (adult), Nereis diversicolor	S	U	96	55,000	46,585	Bryan & Hummerstone, 1973
Polychaete (adult), Nereis diversicolor	S	U	96	11,000	9,317	Bryan & Hummerstone, 1973
Sandworm (adult) Nereis virens	S	U	96	8,100	6,245	Eisler & Hennekey, 1977
Oyster (larva), Crassostrea virginica	S	U	48	310	262	Calabrese, et al. 1977
Oyster (larva), Crassostrea virginica	S	U	48	339	287	Calabrese, et al. 1973
Hard-shell clam (larva), Mercenaria mercenaria	S	U	48	166	141	Calabrese, et al. 1977
Hard-shell clam (larva), Mercenaria mercenaria	S	U	48	195	165	Calabrese & Nelson, 1974
Soft-shell clam (adult), Mya arenaria	S	U	96	5,200	4,404	Eisler, 1977a
Soft-shell clam (adult), Mya arenaria	S	U	96	7,700	6,522	Eisler & Hennekey, 1977

Table 9. (Continued)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Mussel, *Mytilus edulis planulatus*	S	M	96	2,500	2,640	Ahsanullah, 1976
Mud snail (adult), *Nassarius obsoletus*	S	U	96	50,000	42,350	Eisler & Hennekey, 1977
Copepod (adult), *Acartia tonsa*	S	U	96	290	246	Sosnowski, et al. 1979
Copepod (adult), *Acartia clausi*	S	U	96	950	805	Sosnowski, et al. 1979
Copepod (adult), *Pseudodiaptomus coronatus*	S	U	96	1,783	1,510	Sosnowski, et al. 1979
Copepod (adult), *Eurytemora affinis*	S	U	96	4,090	3,464	Sosnowski, et al. 1979
Copepod (adult), *Tigriopus japonicus*	S	U	96	2,160	1,830	Sosnowski, et al. 1979
Crab (larva), *Carcinus maenas*	S	U	48	1,000	847	Conner, 1972
Crab (adult), *Carcinus maenas*	S	U	48	14,500	5,281	Conner, 1972
Crab (adult), *Carcinus maenas*	S	U	48	12,000	4,370	Portmann, 1968
Hermit crab (adult), *Pagurus longicarpus*	S	U	96	400	339	Eisler & Hennekey, 1977
Starfish (adult), *Asterias forbesi*	S	U	96	39,000	33,033	Eisler & Hennekey, 1977

* S = static, FT = flow-through
** U = unmeasured, M = measured
Geometric mean of adjusted values = 2,026 µg/l $\frac{2,026}{49}$ = 41 µg/l

Table 10. Marine plant effects for zinc

Organism	Effect	Concentration (ug/l)	Reference
Alga, *Amphidinium carteri*	Growth inhibition	400	Braek, et al. 1976
Alga, *Amphidinium carteri*	Interaction with copper on growth	100	Braek, et al. 1976
Alga, *Dunaliella tertiolecta*	Reduction in potassium content	6,500	Overnell, 1975
Kelp, *Laminaria hyperiborea*	Growth inhibition	250	Hopkins & Kain, 1971
Kelp, *Laminaria digitata*	Growth inhibition	100	Bryan, 1964
Kelp, *Macrocystis pyrifera*	Photosynthesis inhibition	10,000	Clendenning & North, 1959
Alga, *Phaeodactylum tricornutum*	Growth inhibition	25,000	Jensen, et al. 1974
Alga, *Phaeodactylum tricornutum*	Interaction with copper on growth	1,000	Braek, et al. 1976
Alga, *Skeletonema costatum*	Growth inhibition	50	Bryan, 1964
Alga, *Skeletonema costatum*	Growth inhibition	200	Braek, et al. 1976
Alga, *Skeletonema costatum*	Interaction with copper on growth	50	Braek, et al. 1976
Alga, *Thalassiosira pseudonana*	Growth inhibition	500	Braek, et al. 1976
Alga, *Thalassiosira pseudonana*	Growth inhibition	400	Braek, et al. 1976

Table 10. (Continued)

Organism	Effect	Concentration (ug/l)	Reference
Alga, *Thalassiosira pseudonana*	Interaction with copper on growth	200	Braek, et al. 1976

Lowest marine plant value = 50 ug/l

Table 11. Marine residues for zinc

Organism	Bioconcentration Factor	Time (days)	Reference
Alga (live tip), *Ascophyllum nodosum*	55	4	Skipnes, et al. 1975
Alga (dead tip), *Ascophyllum nodosum*	950	7	Skipnes, et al. 1975
Alga, *Cladophora* sp.	1,785	12	Baudin, 1974
Alga, *Cladophora* sp.	4,680	34	Baudin, 1974
Alga, *Fucus serratus*	10,000	140	Young, 1975
Algae (mixed), Five genera	1,900	90	Cross, et al. 1971
Alga, *Laminaria digitata*	3,000	30	Bryan, 1964
Alga, *Phaeodactylum tricornutum*	8,100	14	Jensen, et al. 1974
Alga, *Skeletonema costatum*	1	13	Jensen, et al. 1974
Alga, *Thalassiosira pseudonana*	12,400	13	Jensen, et al. 1974
Polychaete (adult), *Nereis diversicolor*	55	9	Bryan & Hummerstone, 1973
Scallops (adult), *Aequipecten irradians*	321	15	Duke, et al. 1969
Oyster (adult), *Crassostrea virginica*	27,080	140	Shuster & Pringle, 1969
Oyster (adult), *Crassostrea virginica*	146	15	Duke, et al. 1969
Gastropod (adult), *Littorina obtusata*	670	50	Young, 1975

Table 11. (Continued)

Organism	Bioconcentration Factor	Time (days)	Reference
Hard-shell clams (adult), Mercenaria mercenaria	22	15	Duke, et al. 1969
Hard-shell clams (adult), Mercenaria mercenaria	85	70	Shuster & Pringle, 1968
Soft-shell clam (adult), Mya arenaria	85	50	Pringle, et al. 1968
Soft-shell clam (adult), Mya arenaria	43	112	Eisler, 1977b
Mussel (adult), Mytilus edulis	460	13	Phillips, 1977
Mussel (adult), Mytilus edulis	500	21	Pentreath, 1973
Mussel (adult), Mytilus edulis	105	20	Van Weers, 1973
Mussel (adult), Mytilus edulis	330	35	Phillips, 1976
Amphipod, Gammarus locusta	400	27	Fowler, et al. 1975
Crab (adult), Carcinus maenas	9,000	32	Bryan, 1971
Crab (adult), Carcinus maenas	5,400	42	Bryan, 1966
Mud crab (adult), Panopeus herbstii	266	15	Duke, et al. 1969

Table 12. Other marine data for zinc

Organism	Test Duration	Effect	Result (ug/l)	Reference
Mummichog (adult), Fundulus heteroclitus	96 hrs	LC28	60,000	Eisler & Gardner, 1973
Mummichog (adult), Fundulus heteroclitus	24 hrs	No histological damage	36,000	Eisler & Gardner, 1973
Mummichog (adult), Fundulus heteroclitus	24 hrs	Histological damage	60,000	Eisler & Gardner, 1973
Mummichog (adult), Fundulus heteroclitus	168 hrs	LC0	10,000	Eisler & Hennekey, 1977
Mummichog (adult), Fundulus heteroclitus	168 hrs	LC50	52,000	Eisler & Hennekey, 1977
Mummichog (adult), Fundulus heteroclitus	168 hrs	LC100	120,000	Eisler & Hennekey, 1977
Mummichog (adult), Fundulus heteroclitus	14 days	Increase in liver ALA-D enzyme activity	10,000	Jackim, 1973
Mummichog (adult), Fundulus heteroclitus	48 hrs	LC0	10,000	Thomas, 1915
Mummichog (adult), Fundulus heteroclitus	48 hrs	LC100	157,000	Eisler, 1967
Mummichog (adult), Fundulus heteroclitus	192 hrs	LC0	43,000	Eisler, 1967
Mummichog (adult), Fundulus heteroclitus	192 hrs	LC50	66,000	Eisler, 1967
Protozoan, Cristigera sp.	4-5 hrs	Reduced growth	125	Gray, 1974
Protozoan, Cristigera sp.	—	Growth reduction	125	Gray & Ventilla, 1973
Protozoan, Euplotes vannus	48 hrs	EC10 (reproduction)	10,000	Persoone & Uyttersprot, 1975

Table 12. (Continued)

Organism	Test Duration	Effect	Result (ug/l)	Reference
Polychaete, Ctenodrilus serratus	21 days	Reduced survival	10,000	Reish & Carr, 1978
Sandworm (adult), Nereis virens	168 hrs	LC50	2,600	Eisler & Hennekey, 1977
Polychaete, Ophryotrocha diadema	21 days	Reduced survival	1,750	Reish & Carr, 1978
Polychaete, Ophryotrocha labronica	13 hrs	LC50	1,000	Brown & Ahsanullah, 1971
Oyster (larva), Crassostrea gigas	5 days	Substrate attachment inhibition	125	Boyden, et al. 1975
Oyster (larva), Crassostrea gigas	48 hrs	Reduced development	125	Brereton, et al. 1973
Oyster (larva), Crassostrea gigas	6 days	Growth inhibition	125	Brereton, et al. 1973
Oyster (larva), Crassostrea gigas	48 hrs	Abnormal shell development	70	Nelson, 1972
Oyster (larva), Crassostrea virginica	48 hrs	LC0	75	Calabrese, et al. 1973
Oyster (larva), Crassostrea virginica	48 hrs	LC100	500	Calabrese, et al. 1973
Oyster (adult), Crassostrea virginica	140 days	No significant mortality	200	Shuster & Pringle, 1968, 1969
Hard-shell clam (embryo), Mercenaria mercenaria	42-48 hrs	LC100	279	Calabrese & Nelson, 1974
Hard-shell clam (larva), Mercenaria mercenaria	12 days	LC5	50	Calabrese, et al. 1977

Table 12. (Continued)

Organism	Test Duration	Effect	Result (ug/l)	Reference
Hard-shell clam (larva), Mercenaria mercenaria	12 days	LC50	195	Calabrese, et al. 1977
Hard-shell clam (larva), Mercenaria mercenaria	12 days	LC95	341	Calabrese, et al. 1977
Soft-shell clam (adult), Mya arenaria	168 hrs	LC50 @ 20°C	3,100	Eisler & Hennekey, 1977
Soft-shell clam (adult), Mya arenaria	168 hrs	LC50 @ 22°C	1,550	Eisler, 1977a
Mussel (adult), Mytilus edulis	14 days	Decrease in cadmium uptake	500	Jackim, et al. 1977
Coot clam (adult), Mulinia lateralis	14 days	Decrease in cadmium uptake	500	Jackim, et al. 1977
Mud snail (adult), Nassarius obsoletus	72 hrs	No effect on behavior	100	MacInnes & Thurberg, 1973
Mud snail (adult), Nassarius obsoletus	72 hrs	Decreased oxygen consumption	200	MacInnes & Thurberg, 1973
Mud snail (adult), Nassarius obsoletus	168 hrs	LC50	7,400	Eisler & Hennekey, 1977
Isopod (adult), Idoten baltica	120 hrs	LC40 @ 34°/oo S	10,000	Jones, 1975
Barnacle (adult), Balanus balanoides	5 days	LC90	8,000	Clarke, 1947
Crab (larva), Carcinus maenas	0.22 hrs	LC50	33,000-100,000	Conner, 1972
Hermit crab (adult), Pagurus longicarpus	168 hrs	LC50	200	Eisler & Hennekey, 1977
Crab (larva), Rhithropanopeus harrisi	16 days	Delayed development	50	Benijts-Claus & Benijts, 1975

Table 12. (Continued)

Organism	Test Duration	Effect	Result (ug/l)	Reference
Sea urchin (spermatozoa), Arbacia puctulata	4 mins	Decreased motility	163-817	Young & Nelson, 1974
Sea urchin (spermatozoa), Arbacia puctulata	4 mins	Decreased motility	81	Young & Nelson, 1974
Sea urchin (spermatozoa), Arbacia puctulata	4 mins	Decreased motility	1,635	Young & Nelson, 1974
Sea urchin (egg), Arbacia puctulata	15 hrs	Abnormal development	1,250	Waterman, 1937
Starfish (adult), Asterias forbesi	168 hrs	LC50	2,300	Eisler & Hennekey, 1977
Starfish (adult), Asterias forbesi	24 hrs	Equilibrium loss	2,700	Galtsoff & Loosanoff, 1939

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Mammalian Toxicology and Human Health Effects

Introduction

More than 100 years ago it was shown that zinc was essential for the growth of Aspergillus niger. It was then shown that it was an essential metal for plant life. In the 1930's, the essentiality of zinc for the growth of rats was shown. Zinc has for a long time been regarded as an essential element for human beings but not until the 1960's was it shown that zinc deficiency could cause a certain syndrome and that therapy with zinc salts could alleviate or even cure the symptoms of zinc deficiency. During the recent past some other disease states including congenital diseases have been related to zinc. Zinc therapy has attracted the interest of clinicians. The evergrowing interest in the metabolism of zinc and the relationship between zinc and certain diseases has, during the last decades, been reflected in a large number of reviews and books (Brewer and Prasad, 1977; Halsted et al., 1974; National Research Council, 1978; Pories et al., 1974; Prasad, 1966; Prasad, 1976; Prasad, 1978; Sandstead, 1975; Sandstead 1973; Vallee, 1959; Underwood, 1977). The National Research Council (NRC) report contains 1,855 references and gives information not only on metabolism and essentiality of zinc for human beings but also much information on occurrence of zinc, analytical methods, and human health hazards form excessive exposure to zinc. Since this chapter to a large extent relies on the NRC report, reference will be given to chapters or page numbers in that report whenever it is quoted in this or following sections.

The information given will mainly rely on the above mentioned references and specific references will only be given when there is information which might add to the understanding of the metabolism and effects of zinc, esp-cially in human beings.

EXPOSURE

Ingestion from Water

The National Research Council (NRC) (1978) (Chapter 2 pp. 25-28 and Chapter 11 pp. 269-271) summarized available data on zinc in drinking water and concluded that generally the concentrations were well below 5 mg/l. In a study by the Department of Health, Education and Welfare (HEW) (1970) 2595 water samples were tested and of them 8 had zinc concentrations above the 5 mg/l level. The highest concentration found was 13 mg/l. The average zinc concentration was 0.19 mg/l. In water leaving treatment plants, Craun and McCabe (1975) found that all samples contained less than 5 mg/l of zinc, but that in cities with soft acidic water the concentration increased in the distribution system. Tapwater could thus have concentrations around 5 mg/l. In a study by EPA (1975) it was found that in 591 water samples all had zinc concentrations below 4 mg/l.

Uncontaminated fresh water generally contains less than 0.01 mg of zinc/l (NRC, 1978). Analysis of filtered surface waters in the U.S. revealed that of 714 samples only 7 had concentrations exceeding 1 mg/l and that 607 (85 percent) had concentrations below 0.1 mg/l (Durum et al., 1971).

The concentration of zinc in both natural waters and in drinking water are generally low, but may increase due to pollution of water systems or release of zinc from distribution systems and household plumbing respectively.

Ingestion from Food

In the NRC document the content of zinc in different foodstuffs is listed in detail (Appendix A-I pp. 313-326). It was noted that meat products contain relatively high concentrations of zinc, whereas fruits and vegetables have relatively low concentrations and contribute little to the daily intake. Zinc

concentrations in milk are generally low, but at a high intake, milk can make an important contribution to daily intake of zinc.

Additional data are provided by Mahaffey et al. (1975) who calculated that meats, fish, and poultry on an average contained 24.5 mg/kg of zinc, whereas grains (and cereal products) and potatoes only provided 8 and 6 mg/kg, respectively. These data were obtained from Food and Drug Administration market basket studies which are based on the diets of teenage males, 15 to 20 years old. In the years 1973 and 1974 it was calculated that the daily intake in this age group was 18 and 18.6 mg/day of zinc, respectively. Greger (1977) calculated the daily intake of zinc in subjects living in an institution for the aged, with an average age of 75 years, and found that on an average the intake was 18.7 mg/day. In girls 12 to 14 years old, Greger et al. (1978) found that the average intake of zinc was 10 mg/day.

In the "recommended dietary allowances" the National Research Council (National Academy of Sciences, 1974) recommended that adults should have a zinc intake of 15 mg/day, but pregnant women should have an intake of 20 mg/day and lactating women an intake of 25 mg/day. As a requirement of pre-adolescent children, 10 mg/day was recommended. In infants up to 6 months old, 3 mg/day was recommended and for children aged 0.5-1 year 5 mg/day was suggested. Based on body weight the requirement for zinc would be about 0.5 mg/kg for the infant and about 0.2 mg/kg in the adult.

A bioconcentration factor (BCF) relates the concentration of a chemical in water to the concentration in aquatic organisms. A recent survey on fish and shellfish consumption in the United States (Cordle et al., 1978) found that the per capita consumption is 18.7 g/day. From the data on the nineteen major species identified in the survey, the relative consumption of the four major groups can be calculated.

At least one BCF from an exposure of 28 days or more is available for each of the four major groups:

Species	BCF	Reference
o Freshwater fish		
Carp, *Cyprinus carpio*	8	Lebedeva & Kuznetsova, 1969
o Saltwater fish		
Plaice (adult) *Pleuronectes platessa*	373	Pentreath, 1973
o Saltwater molluscs		
Hard-shell clams (adult) *Mercenaria mercenaria*	85	Shuster & Pringle, 1968
Soft-shell clam (adult), *Mya arenaria*	85	Pringle et al. 1968
Soft-shell clam (adult), *Mya arenaria*	43	Eisler, 1977
Soft-shell clam (adult), *Mya arenaria*	52-78	Eisler, 1977
Clam (adult), *Tapes japonica*	500	Kameda et al. 1970
Scallops (adult), *Aequipecten irradians*	282-321	Duke et al. 1969
Oyster (adult), *Crassostrea virginica*	15,290-27,080	Shuster & Pringle, 1969
Oyster (adult), *Crassostrea virginica*	15,240	Shuster & Pringle, 1968
Oyster (adult), *Ostrea edulis*	450	Romeril, 1971
Mussel (adult), *Mytilus edulis*	130-310	Phillips, 1976
o Saltwater decapods		
Crab (adult), *Carcinus maenas*	8,000-9,000	Bryan, 1971
Crab (adult), *Carcinus maenas*	5,400	Bryan, 1966
Lobster (adult), *Homarus vulgaris*	142	Bryan, 1964

From these data the geometric mean bioconcentration factor for each group can be calculated.

Group	Consumption (Percent)	Bioconcentration factor
Freshwater fishes	12	8
Saltwater fishes	61	373
Saltwater molluscs	9	306
Saltwater decapods	18	980

Using the data for consumption and BCF for each of these groups, the weighted average BCF for zinc is 432 for consumed fish and shellfish.

Inhalation Via Ambient Air

Air quality data compiled in the NRC document (1978) show that zinc concentrations throughout the U.S.A. generally are less than 1 $\mu g/m^3$ (Chapter 3 p. 42-43). In 1975 and 1976, EPA (1979) observed zinc concentrations at approximately 50 National Air Surveillance Network sites throughout the U.S. Zinc concentrations in most areas were below 1 $\mu g/m^3$, quarterly average.

The air levels of zinc are, in most areas, fairly constant. As an example, Lioy et al. (1978) presented data on zinc concentrations in New York City during the years 1972 to 1975 where the annual averages varied from 0.29 to 0.38 $\mu g/m^3$. Much higher concentrations have been reported near smelters. About 1.5 miles from a smelter in Kellogg, Idaho, Ragaini et al. (1977) found in ambient air a yearly mean zinc concentration of 5 $\mu g/m^3$. The 24-hour values ranged from 0.27 to 15.7 $\mu g/m^3$. It should be mentioned that the average

lead and cadmium concentrations were 11 and 0.8 $\mu g/m^3$, respectively, indicating very severe environmental pollution. The U.S. data may be compared to data from 15 cities in a heavily industrialized European country, Belgium (Kretzschmar et al., 1977). During the period May 1972 to April 1975 the average concentrations in 15 locations were from 0.22 to 3.05 $\mu g/m^3$. The highest value recorded during 24 hours was 57 $\mu g/m^3$.

These data from industrialized countries may be compared to background levels of zinc which have been measured at the South Pole and over the Atlantic Ocean. At the South Pole an average concentration of 0.03 ng/m^3 was found. In the air over the Atlantic Ocean concentrations were from 0.3 to 27 ng/m^3 (Duce, 1975; Maenhaut, 1977; Zoller, 1974).

Exposure Via Smoking

In cigarettes and other tobacco products zinc concentrations have been reported to vary from 12.5 - 70 µg/g. (Menden et al., 1972; Dermelj et al., 1978; Franzke et al., 1977). In the studies by Menden et al. and Franzke et al. the amount of zinc in the mainstream smoke was determined by simulated smoking in a smoking machine. Menden et al. found in two brands of cigarettes that 0.06 and 0.36 µg, respectively, was in the mainstream leaving the cigarette, whereas Franzke et al. found in 16 brands that from 0.12 to 0.92 µg was in the same fraction. These data indicate that by smoking 20 cigarettes up to 20 µg of zinc might be inhaled. There might have been some differences in experimental techniques, since Menden et al. found that about 85 percent of the zinc remained in the ash, whereas Franzke et al. found that in some cigarettes only about 10 percent remained in the ash.

Quantification of Total Intake; Relative Contribution From All Routes of Exposure

The major source of zinc for the general population in the U.S. is food. The average intake is generally above 10 mg in adults. An individual inhaling air with an average concentration of 5 $\mu g/m^3$, would have an additional daily intake of 100 µg, assuming that he inhales 20 m^3 of air per day. Smoking would contribute even less than that. Compared to the intake via food, airborne exposure is insignificant.

The intake via drinking water might be of more significance. Levels around 1 mg/l are not uncommon and levels around 5 mg/l have been reported. Assuming a daily intake of 2 liters of water this might result in daily intakes of 2 and 10 mg, respectively. The latter amount might double the intake for people on a low dietary intake, but the total intake will still be within recommended limits. In people with recommended daily intakes of zinc, i.e., 15-20 mg, the additional intake via water will result in total daily intakes of 25-30 mg. As discussed later, the homeostatic regulation of zinc ensures that such amounts and even larger amounts can generally be well tolerated.

PHARMACOKINETICS

Metabolism and Homeostatic Regulation

Inhalation

The fate of inhaled particles containing zinc will depend on particle size and solubility as well as functional state of the lungs. The quantitative features of the deposition patterns of particles have been reviewed by the Task Group on Lung Dynamics (1966) and the Task Group on Metal Accumulation (1973). There are no quantitative data on the deposition and absorption of zinc compounds, but experiments on human beings by Sturgis et al. (1927) and Drinker et al. (1927) indicated that both zinc oxide fumes and zinc oxide powder with very small particle size were deposited in the alveoli. That inhaled zinc is absorbed is shown by the finding of increased serum and plasma levels of zinc in exposed workers. It should be pointed out, however, that part of the inhaled material will be transported to the gastrointestinal tract via ciliary activity and some zinc may also be absorbed that way.

Gastrointestinal Absorption

The absorption of ingested zinc will depend mainly on the zinc status of the organism. The presence or absence of other nutritional constituents may also influence absorption.

Spencer et al. (1965) showed in human beings that ^{65}Zn as the chloride was rapidly taken up, with plasma peak values within 4 hours. It was calculated that about 50 percent was absorbed, but with a wide range (20 to 80 percent). In that study it was not possible to show that the amount of calcium in the diet influences the uptake of zinc from the gut. There are difficulties

in assessing the absorption of zinc, since there is also considerable excretion of absorbed zinc via the gastrointestinal tract . There are also several other earlier studies which show that there are wide variations in the absorption rates of ingested zinc (NRC Chapter 6 pp. 145-154).

The protein content of the diet has been shown to influence the uptake of zinc. In studies done on people with zinc deficiency it has been noted that the effect of zinc therapy is enhanced by a simultaneous administration of protein. It has also been shown that the absorption of zinc will be reduced if the diet contains large amounts of phytate especially in the presence of large amounts of calcium (NRC Chapter 7 pp. 183-187). Since phytates are found in cereals, zinc in vegetable diets including large amounts of unleavened bread may be less available for absorption. Arvidsson et al. (1978) found that the average absorption of ^{65}Zn added to bread during baking was 25 percent ranging from 12.2 to 39.1 percent in 11 subjects. The study was repeated after one month and the same average absorption was found. In this study, the influence of phytate seems to have been small. The fiber content of the diet may influence the uptake of zinc (Sandstead et al., 1978). Zinc in animal proteins seems to be easily available and thus meat is a good source of zinc.

The influence of oral contraceptive agents on the absorption of zinc was studied in 14 women and compared to 8 who did not take contraceptive pills (King et al., 1978). All were of similar age. Zinc was administered as a stable isotope, ^{70}Zn, and the absorption was determined from the difference between intake and fecal output of the stable isotope which was measured by neutron activation analysis. Among the women taking the contraceptive agents, the average absorption was 33 percent and in the control group it was 46

percent. The difference, however, was not statistically significant, and the authors concluded that there was no difference in absorption.

The mechanisms for absorption of zinc are homeostatically controlled, and data from animal experiments suggest that several proteins and low molecular weight compounds may be involved in the absorption process. There is evidence that metallothionein, a low molecular weight, metal-binding protein, in the intestinal mucosa may bind zinc (Richards and Cousins, 1977). Zinc binding ligands with molecular weights lower than metallothionein have been found in animals. Evans et al. (1975) proposed that such a compound was produced in the pancreas and through the pancreatic secretions could bind zinc in the gastrointestinal tract and enhance absorption.

Of special interest is a zinc binding ligand which occurs in human milk, but has not been found in bovine milk. In 1976, Eckhert et al. (1976) reported that gel chromatography of cow's milk and human milk showed that in cow's milk zinc was associated with high molecular weight fractions, whereas in human milk it was mainly associated with low molecular weight fractions. This species difference was taken by these authors as an explanation for the congenital disease acrodermatitis enteropathica which usually occurred when infants were weaned from human breast milk. Similar results were reported by Evans and Johnson (1976) who thought that the low molecular weight zinc binding ligand in milk was similar to the ligand found in pancreatic secretions from the rat. During the last years several studies have been performed to isolate and identify this ligand (Song and Adham, 1977; Evans and Johnson, 1977; Shricker and Forbes, 1978; Lönnerdal et al., 1979; Evans and Johnson, 1979). The data are controversial and at present no certain conclusions can be drawn regarding the nature of the ligand or ligands. It has also been shown by

Cousins, et al. (1978) that degradation products of intestinal proteins including metallothionein may occur as low molecular weight zinc binding complexes in rat intestine. The role of ligands in zinc absorption has recently been discussed by Cousins (1979).

Other Absorption Routes

Zinc salts will be absorbed through intact skin of the rat as shown by Keen and Hurley (1977). According to these authors, the amount of zinc absorbed was higher in zinc-deficient animals and was of a magnitude which might be clinically significant.

Hallmans (1978a, 1978b) showed that in rats with excisional wounds there was a high absorption of zinc from gauzes containing zinc sulfate. At a concentration of 20 percent there were even systemic effects; Hallmans concluded that the absorption from zinc sulfate was higher than from zinc oxide. Hallmans (1977) also showed that in humans treated for burns with gauzes containing zinc oxide, there was absorption of zinc.

Anteby et al. (1978) reported that in women using an intrauterine device containing copper and zinc a slight rise in serum zinc could be shown, but no abnormal values were found.

Transport and Deposition

Zinc is found in erythrocytes mainly due to the presence of the zinc metallo enzyme carbonic anhydrase and in leucocytes where several zinc metallo enzymes are present. In plasma, zinc is mainly bound to albumin and it is thought that the binding is to one of the histidine moieties of the albumin molecule. About one third of the serum zinc is bound to an α_2-macroglobulin and a few percent to amino acids. In the albumin and the amino acids there is

an exchange of zinc, whereas there is no exchange with zinc in the α_2-macroglobulin. The zinc bound to amino acids constitutes the diffusible serum zinc (Giroux, 1975; Giroux 1976; NRC, 1978).

Of special interest is the relationship between zinc and histidine. It has been shown in human beings that oral administration of histidine will cause decreases in serum zinc and an increase in urinary zinc excretion (Henkin et al., 1975). This observation has also been made in experiments on rats (Freeman and Taylor, 1977) and dogs (Yunice et al., 1978). The latter authors also showed that cysteine caused a considerable increase in excretion of zinc. This is thought to be one explanation for the losses of zinc seen in patients given parenterally hyperalimentation, since the fluids given usually contained large amounts of essential amino acids, without sufficient amounts of essential metals (Agarwal and Henkin, 1978; Kumar, 1976).

In the tissues, the highest concentrations of zinc are found in the male reproductive system where the prostate has the highest content. Other organs with high concentrations of zinc are the muscle, bone, liver, kidney, pancreas, and some endocrine glands, especially the thyroid. The largest amounts of zinc are found in the muscles and the bone. Within tissues there may be variation; in the human prostate gland the highest zinc concentrations are found in the lateral prostate and the lowest in the interior and inner prostate. Also significant is the finding that semen has a high zinc content. In most organs there are relatively small variations in zinc levels during a lifetime except that in the newborn, zinc concentrations generally are higher than later in life. It should also be pointed out that the zinc content of the kidney and liver will, to a large degree, depend on the cadmium concentrations and renal zinc concentrations will vary with age (Elinder et al., 1978; Piscator

and Lind, 1972; Schroeder et al., 1967). Regarding the form in which zinc is stored in different organs, zinc is generally an essential component of many enzymes (see section on essentiality). Zinc is also found in metallothionein (see special section on metallothionein).

Excretion

Zinc is mainly excreted via the gastrointestinal tract but part of that zinc is reabsorbed. Urinary excretion of zinc is relatively small and during certain conditions, i.e., extreme heat or exercise, much larger quantities may be excreted in sweat (Cohn and Emmett, 1978; Hohnadel et al., 1973). Zinc is also excreted via hair and milk, and in the female there is a placental transfer to the fetus.

Losses of zinc may also occur via menstrual blood losses and skin. Molin and Wester (1976) determined by neutron activation the zinc content of epidermis. They calculated that the daily losses by desquamation would be about 20 to 40 µg, only about one tenth (1/10) of the urinary excretion.

Biological Half-time

The long-term biological half-time of zinc will depend on the zinc status; it has been shown that after oral intake or injection of ^{65}Zn to human beings, the half-time may vary from about 200 to about 400 days, depending on the zinc status (NRC Chapter 6 pp. 151-154). Arvidsson et al. (1978) gave eight subjects single injections of ^{65}Zn. After the injection, measurements were taken for 84 to 190 days. The slow component for the half-time of the injected zinc for this group was on an average 247 days. Kennedy et al. (1978) found that the average half-time was 412 days in 19 female patients undergoing treatment for rheumatoid and osteoarthritis who were given an oral dose of ^{65}Zn . In certain

body compartments, e.g., bone, the half-time may be considerably longer (NRC Chapter 6 pp. 149-154).

Metallothionein

Metallothionein was briefly discussed in previous reports and books concerning zinc, but during the last several years there has been an enormous increase in the number of papers on this protein. Recently a very comprehensive report on metallothionein has been prepared (Nordberg and Kojima, 1979). Mammalian metallothionein is a protein with a molecular weight of 6,000 to 7,000 which is characterized by a very special amino acid composition, a high cysteine content, but lack of aromatic amino acids and histidine. Metallothionein was first discovered in equine renal cortex by Margoshes and Vallee (1957) and has now been shown to occur in most mammalian tissues, and also in lower organisms. Total metal content of metallothionein can reach 6 to 7 g atoms per mole. The metals generally found in metallothionein are zinc, copper, and cadmium. The relative occurrence of these metals will depend on a number of factors. In fetal liver metallothionein, zinc and copper are the major constituents, whereas in animals exposed to cadmium, cadmium will be the dominating metal especially in the renal protein. A number of factors can induce the synthesis of metallothionein. In addition to administration of the above-mentioned metals, metallothionein synthesis seems also to be indirectly induced by factors that might influence zinc metabolism. Thus, environmental stresses of different kinds may induce the synthesis.

With regard to zinc metabolism, it has been shown that parenteral or dietary administration of zinc will cause an increase of the synthesis of metallothionein (Bremner and Davies, 1975; Richards and Cousins, 1975a; Richards and Cousins, 1975b; Richards and Cousins, 1977). Recently, it was shown that

hepatic zinc was increased and metallothionein synthesis stimulated in response to several environmental stresses, such as cool and hot environments, burns, and exercise (Oh et al., 1978). Food restriction and bacterial infections have been shown to cause such changes (Bremner and Davies, 1975; Richards and Cousins, 1976; Sobocinski et al., 1978). Failla and Cousins (1978) demonstrated that glucocorticoids in vitro stimulated the uptake of zinc in liver parenchymal cells, a process that required synthesis of metallothionein. Such findings indicate that metallothionein may serve as a regulator of plasma zinc levels and constitute an easily available pool for acute replacements of zinc in certain situations. Also of interest is the finding of large amounts of metallothionein containing zinc and copper in fetal livers reported by several investigators (Bremner et al., 1977; Hartmann and Weser, 1977; Rydén and Deutsch, 1978), which gives similar indications. Much is still unknown about the biological function of metallothionein, but there is no doubt that this protein must play a very important role in the regulation of zinc in the mammalian body (Nordberg and Kojima, 1979).

Normal Levels in Tissues and Fluids

In the National Research Council (NRC) report (1978), extensive information is given on concentrations of zinc in blood, urine and tissues (Chapter 6 pp. 123-145). The NRC report concluded that the mean serum-zinc concentration in humans is approximately 1 mg/liter, the same in healthy men and women. The zinc content of whole blood will be about 5 times higher than the serum level, since the concentration in the red cells is about 10 times the amount found in serum. A lowering of the serum concentrations of zinc may be seen in women who take contraceptive pills, during pregnancy, and as a result of certain stresses such as infections. In the same individual the zinc

concentration in serum will be higher than in plasma mainly due to the release of zinc from platelets (Foley et al., 1968). In 14 subjects the mean serum level was 1.15 mg/l and the mean plasma level 0.98 mg/l, the average difference being 16 percent.

The influence of age and sex on plasma zinc levels was studied by Chooi et al. (1976). They found that in both males and females there was a decrease in plasma zinc from age 20 to age 90. Between men and women below the age of 50 no difference in plasma zinc levels could be noted between the sexes. However, females using contraceptive agents had lower zinc levels than women who did not take contraceptive agents. Average plasma levels in the groups studied were around 0.7 mg/l.

In a recent report, Hartoma (1977) stated that men had higher serum zinc levels than women. The average concentration in 154 male blood donors was 1.24 mg/liter (range 0.74 to 2.2 mg/l), and in 95 women it was 1.11 mg/liter (range 0.64 to 1.82 mg/l). The difference was highly significant according to the author. It was not stated to what extent the women took contraceptive pills. Hartoma also found that there was a slight tendency to a lowering of the serum concentration of zinc in men with increasing age, and that there was a significant correlation between serum zinc and serum testosterone in males aged 36 to 60 years. In men 28 to 35 years of age, there was a negative correlation, which was not significant. In these two studies plasma and serum levels, respectively, were lower and higher than earlier reported data which indicates that methodological problems in sampling and analysis may still exist. In both studies samples were taken in the morning after overnight fasting.

In the NRC report (Chapter 6 p. 129) it was stated that approximately 0.5 mg of zinc is excreted in the urine every 24 hours by healthy persons. Additional data have been provided by Elinder et al. (1978) who studied the urinary excretion of zinc in different age groups. They found that there was a tendency towards a higher zinc excretion in smokers than in non-smokers. Among non-smokers there was a tendency to decreased zinc excretion from about age 20 to higher ages (See Table C-1). The tissue concentrations of zinc are generally higher in the newborn. After the first year of life there are fairly small changes in the zinc levels in most organs except the kidney where the zinc concentrations are dependent on the accumulation of cadmium (Elinder et al., 1977; Piscator and Lind, 1972; Prasad, 1976). In the liver the zinc level is constant during a lifetime. In the pancreas there is a decrease in zinc levels with increasing age on a wet weight basis, whereas if the pancreas values are calculated on an ash weight basis that decrease is not seen (Elinder et al., 1977). This is in agreement with Schroeder et al. (1967). In the study by Elinder et al. (1977), the average concentrations of zinc in liver and pancreas were 45 and 27 mg/kg wet weight, respectively. The highest concentrations of zinc are found in the prostate, where the concentration is about 100 mg/kg wet weight. In human semen concentrations of 100 to 350 mg/l have been reported. The zinc concentrations in hair will vary depending on age and geographical location (NRC Chapter 6 pp. 140-141). Sorenson et al. (1973) found that in 13 communities in the U.S. the average zinc concentration in hair from adults varied from 148 to 210 mg/kg. The newborn has zinc levels in hair similar to levels in the adult, but at age 1-4 the levels are lower than in adults (Hambidge et al., 1972; Petering et al., 1971). Zinc concentrations in hair will decrease during pregnancy (Baumslag

TABLE C-1. ZINC CONCENTRATIONS IN THE URINE OF SWEDISH PEOPLE

Group	Number of persons	Zinc, average (a)[a] (mg/g of creatinine)	Standard Deviation (a)[a]	Zinc, calculated average (mg/24 hr)
Men, non-smokers (age in years)				
2 to 9	4	0.86	0.23	0.33
17 to 19	10	0.38	0.19	0.71
20 to 29	10	0.32	0.13	0.59
30 to 39	10	0.29	0.10	0.49
40 to 49	16	0.25	0.16	0.39
50 to 59	15	0.32	0.09	0.45
60 to 69	9	0.27	0.17	0.35
70 to 79	11	0.40	0.18	0.46
80 to 89	9	0.35	0.12	0.35
Men, smokers (age in years)				
40 to 49	5	0.35	0.19	0.55
50 to 59	5	0.39	0.09	0.55
66	1	0.32	--	0.41
75	1	0.27	--	0.31
Women, non-smokers (age in years)				
3	4	1.23	0.21	0.37
40 to 49	10	0.23	0.17	0.20
50 to 59	10	0.47	0.38	0.34

[a] a, arithmetic averages.

et al., 1974; Hambidge and Droegemueller, 1974). The determination of zinc in hair has been used as a screening tool for zinc deficiency (Hambidge et al., 1972). The total body store of zinc in adult humans has been estimated to be 2.3 mg for a 70 kg man (NRC Chapter 6 p. 123).

The Homeostatic Regulation of Zinc

The homeostatic regulation of zinc absorption in the rat was studied by Evans et al. (1973). Rats fed an optimal intake of zinc were compared to rats which had been on a diet for 7 and 13 days, respectively, containing less than 1 mg/kg of zinc. Whereas, in the controls the absorption was about 15 percent measured by examining the radioactivity in the carcass 1 hour after a gastric dose of ^{65}Zn, it was about 35 and 50 percent, respectively, in the two experimental groups.

Weigand and Kirchgessner (1978) studied the homeostatic mechanisms for zinc absorption in 36 weanling rats, where in groups of six they were given a diet with the following zinc contents: 5.6, 10.6, 18.2, 38, 70, and 141 mg/kg. After 6 days the animals had adjusted to the respective intakes and the absorption of zinc was from 100 to 34 percent in inverse relation to the intake of zinc. The true zinc absorption and the fecal excretion of endogenous zinc could be determined by measuring the turnover of radioactive zinc which had been injected at the start of the experiment. The figure of 100 percent seems surprisingly high, but these were weanling rats which were growing rapidly. This may also explain the relatively high absorption figure for the group receiving 141 mg/kg feed of zinc. The daily zinc retention was the same in the groups receiving 38, 70, and 141 mg/kg, whereas it was lower in the groups receiving 5.6, 10.6, and 18.2, indicating that in this study this supply was not sufficient. In the three highest exposure groups both total

absorption and total fecal excretion of endogenous zinc increased in proportion to the daily intake.

The homeostatic regulation of ingested zinc was also studied by Ansari et al. (1975). Male rats were given a diet containing 53 ppm zinc, and at different times groups were given a diet with 600 mg/kg of added zinc beginning 7, 14, 21, or 42 days before sacrifice. One week before sacrifice each rat was given, by gavage, an oral dose of ^{65}Zn as the chloride. Feces were collected for 7 days. The elimination of fecal zinc was similar in all groups except the control group irrespective of length of exposure, whereas the fecal elimination of ^{65}Zn increased with length of exposure. Also, analysis of tissues revealed that the longer the exposure to the high zinc level in the diet the more rapidly ^{65}Zn was eliminated. Tissue levels of stable zinc were only slightly influenced by the high zinc content of the diet. Only in the liver could a significant increase in the zinc level be noted. Levels in kidney, muscle and heart did not differ from controls. These results also show the extreme capacity of the organism to handle excess zinc in the diet. They also show how rapid the exchange will be between absorbed zinc and tissue stores of zinc.

Ansari et al. (1976) gave male rats dietary zinc at levels of from 1200 to 8400 ppm zinc for 3 weeks. One week before sacrifice each rat was given ^{65}Zn as the chloride by gavage and after that feces were collected for one week. The high zinc content of the diet did not affect weight gains or feed consumption or produce any obvious signs of toxicity. In controls 65 percent of the ^{65}Zn was eliminated in one week in contrast to 86 percent in the rats given 1200 ppm zinc in the diet. At still higher levels of dietary zinc there was no further increase of fecal ^{65}Zn. Rats given 1200 ppm zinc in the diet

had significantly higher levels of stable zinc in liver, kidney, and tibia than controls, whereas there was no change in concentrations in heart and muscle. No further increase was seen at levels of 2400 to 7200 ppm in the diet, but at 8400 ppm level a new increase was seen, also in heart but not in muscle. The amount of radioactive zinc was, at all exposure levels, only a few percent of the amount found in the controls. There were no obvious changes with increasing dietary zinc, except in tibia where, at the highest levels, there occurred an increase compared to the previous levels. In heart and muscle there was a slight but continuous decrease. In liver and kidneys there was no change. The authors concluded that the data indicated that there was a good homeostatic control in the range 2400 to 7200 ppm. The authors also concluded that the homeostatic regulation of zinc was much more effective in the rat than in calves. Stake et al. (1975) found that calves given a diet containing 600 mg/kg of zinc after one week had considerably higher zinc levels in liver, kidney, and pancreas than calves fed a diet containing 34 mg/kg. There was, however, no change in heart or muscle zinc levels.

Essentiality of Zinc, Zinc Metalloenzymes and Zinc Deficiency

The topics of zinc essentiality and zinc deficiency have been extensively treated in the National Research Council (NRC) report (1978) and also in a recent review by Prasad (1978). In 1934, it was shown by Todd et al. (1934) that zinc was necessary for the growth of rats and since then many studies have been made on the essentiality of zinc, including studies of human beings.

In human beings zinc is necessary for normal growth and for normal development of the gonads. Prasad et al. (1963) found that in certain villages

in Egypt many subjects exhibited a syndrome characterized by dwarfism and anemia, hypogonadism, hepatosplenomegaly, rough and dry skin, and mental lethargy. These young persons had a very low intake of animal proteins with bread as their main food. Zinc deficiency was demonstrated by the finding that zinc concentrations in plasma, red cells, and hair were decreased; that subjects had a higher turnover of radioactive zinc than normal, and that the excretion of zinc in feces and urine was less than in controls. Improvements were seen after oral administration of zinc with a still greater effect observed upon additional protein supplementation.

Similar syndromes have been reported in other parts of the world. There are, however, studies that show that zinc deficiency with less pronounced symptoms may be more common than thought earlier. In the U.S., evidence of symptomatic zinc deficiency has been found in Colorado by Hambidge et al. (1972). Zinc concentrations in hair were used as an index of the zinc status. Hambidge et al. found that in 132 children ages 4 to 16, 10 children had hair zinc concentrations below 70 mg/kg, whereas most children had concentrations above 125 mg/kg. Eight out of 10 of these children were found to have heights at the lower range for their age group. Poor appetite and a low intake of meat was thought to be one reason for the zinc deficiency. In these children hypogeusia (impaired taste acuity) was also found. After zinc supplementation, this condition was normalized. An increase in hair zinc could be shown parallelling the supplementation with zinc. In five children with hair zinc levels of 10 to 63 mg/kg before therapy, the levels were 67-170 mg/kg after 4 months of therapy. There are studies in other parts of the U.S. showing that low zinc levels in children's hair is not an uncommon finding (Prasad, 1978).

The reason for the signs and symptoms caused by the zinc deficiency is not clear, but it is known from a number of studies in a variety of organisms including human beings (NRC Chapter 8) that zinc is an essential constituent of many metalloenzymes. Typical examples of such metalloenzymes are alcohol dehydrogenase, carboxypeptidase, leucine aminopeptidase, alkaline phosphatase, carbonic anhydrase, RNA polymerase and DNA polymerase. Also, thymidinekinase is thought to be a zinc dependent enzyme. Zinc may be involved in the synthesis and catabolism of RNA and DNA.

In addition to nutritional zinc deficiency, which is caused solely by a low dietary zinc intake, there are instances of zinc deficiency which are thought to have other causes. These are:

(1) zinc deficiency in dialysis patients, which has been attributed to depletion of body zinc stores (Atkin-Thor et al., 1978);

(2) zinc deficiency after intravenous hyperalimentation, which might lead to increased excretion of zinc because of the large amounts of amino acids in the infusion fluids (Bernstein and Leyder, 1978; Freeman et al., 1975);

(3) zinc deficiency after excessive alcohol ingestion (Ecker and Schroeter, 1978; Weismann et al., 1978); and

(4) zinc deficiency after operations such as intestinal bypass surgery (Atkinson et al., 1978; Weismann et al., 1978). The signs noted are generally changes in the skin and hypogeusia.

There is also a rare congenital disease called acrodermatitis enteropathica which generally occurs in children after weaning. As has been discussed earlier, human milk seems to contain a factor or factors necessary for the absorption of zinc. Signs in this disease may come from many organs, among

them the skin, central nervous system, and the gastrointestinal tract. As in other zinc deficiencies in children, there will be retarded growth and hypogonadism. Large oral doses of zinc will correct the condition.

Prasad et al. (1978) have recently reported on experimental zinc deficiency in humans. They studied four male volunteers who were hospital patients with various diseases. They were given a diet containing about 3 mg Zn/day for several weeks. In order to decrease the zinc intake it was necessary to give subjects cereal protein instead of animal protein during the study. In all subjects considerable weight losses occurred during the zinc depletion period. The plasma zinc level decreased significantly in all subjects and in three of four subjects there was a decrease in zinc excretion. Connective tissue was analyzed in two patients; during the period of low zinc intake thymidinekinase activity could not be detected, whereas after zinc supplementation it became close to the normal values. Also, plasma alkaline phosphatase activity decreased along with a decrease in plasma lactic dehydrogenase activity during the zinc depletion. In the connective tissue the RNA and DNA ratio showed changes during the restriction period.

EFFECTS

Zinc deficiency will not be covered in this section since it has been discussed in a previous section; the emphasis will be on the effects caused by excessive exposure to zinc via inhalation or via ingestion. The literature on such adverse health effects is limited. One probable reason for the limited information is that zinc has generally been accepted as a beneficial substance and adverse effects have neither been expected nor looked for.

Inhalation of Excessive Amounts of Zinc

Effects on the lungs and systemic effects after inhalation of zinc compounds have only been reported from occupational settings. A special case is the lung damage seen after inhalation of zinc chloride from smoke bombs. As will be discussed later, not only zinc chloride but also the hydrochloric acid formed are of importance for the development of such effects. Health effects observed in workers exposed to zinc and the results of some studies on animals will be discussed. Information on the health hazards of zinc will also be found in most textbooks on occupational hygiene and in the recent National Institute on Occupational Safety and Health (NIOSH) criteria document on zinc oxide (NIOSH, 1975).

Acute Effects

Most of our knowledge about metal fume fever and its relationship to exposure to zinc oxide fumes comes from the beginning of the century when there was extensive research on this acute type of poisoning (Drinker et al., 1927; Drinker et al., 1928; Sturgis, et al., 1927). Reviews on metal fume fever, often also containing case reports, have been published in large numbers (Anseline, 1972; Hegsted et al., 1945; Kehoe, 1948; Rohrs, 1957). Metal fume

fever is described in all textbooks on occupational hygiene. It should also be mentioned that metal fume fever has not only been associated with inhalation of zinc oxide fumes, but with many other metal fumes which may produce similar symptoms.

Metal fume fever only appears after exposure to freshly produced metal fumes (McCord, 1960; Rohrs, 1957) which can penetrate deep into the alveoli. Zinc oxide dust or other metal dusts are not capable of producing the disease. Typical for metal fume fever is symptom occurrence within a few hours after exposure. The symptoms may persist for 1 to 2 days and are characterized by influenza-like symptoms such as headache, fever, hyperpnea, sweating, and muscle pains. Among the laboratory findings leukocytosis is the most prominent. There have never been any fatalities from metal fume fever. Metal fume fever generally occurs at the beginning of the working week when the worker has not been exposed for a couple of days and further exposure will not cause new symptoms, indicating a type of immunity. This disease has also been given the name "Monday fever." It has been suggested by McCord (1960) that there is an allergic basis for the mechanism of metal fume fever. Several theories have been put forward, but there is no definite evidence for any of the proposed different mechanisms for this reaction. One reasonable theory is that the metal fume penetrates deep into the alveoli, and combines with proteins which might act as sensitizing agents. There is a lack of data on the levels of zinc oxide fumes in air that might cause the disease. The only available information is from experiments on human beings in 1927 by Sturgis et al. (1927), who exposed 2 subjects to zinc oxide fumes at a level of 600 mg zinc/m^3. It was calculated that the subjects inhaled 48 and 74 mg zinc, respectively.

There was a report on acute emphysema in cattle reported to have been exposed to zinc oxide fumes (Hilderman and Taylor, 1974). This episode occurred in a barn where oxy-acetylene cutting and arc welding of galvanized pipe were done during remodelling of the barn. Three heifers were severely affected. Within a short time all three died. Autopsy showed severe changes in the lungs with edema, emphysema, and hemorrhages. Zinc concentrations in liver, kidney, and lungs were not above normal values in two animals examined. In this case, a galvanized material was suspected but the extremely severe condition caused by the fumes showed either that cattle are extremely sensitive to zinc oxide fumes or that other metals (such as cadmium) might have been responsible.

Acute pulmonary damage and even death may occur after the inhalation of zinc chloride which is the major component in smoke coming from so-called "smoke bombs" which are often used in military exercises. Accidental inhalation of such smoke in confined spaces may rapidly lead to severe disease, but it should be pointed out that the toxic action may not only be due to the zinc. The hydrochloric acid component in the smoke may contribute. Further details on exposure to zinc chloride are provided by Milliken et al. (1963).

The effects of inhalation of zinc chloride in smoke from smoke bombs have also been described by Schmal (1974) who reported on 11 cases, of which two had very severe reactions including edema of the lungs. However, no severe sequelae were seen. In one case, however, it was almost 2 years before the lung function was normalized.

Chronic Effects

Batchelor et al. (1926) made an extensive investigation of workers exposed to zinc in a smelter in New Jersey. The authors pointed out that this smelter

was well suited for studies on chronic effects of zinc since the amounts of lead, cadmium, and arsenic in the ore were very low compared with other types of zinc ores processed in other parts of the U.S. Of a total work force of 1,620 men, a number of workers were selected from different work areas for the special studies. Twelve men were selected from bag rooms where zinc oxide was handled. From a zinc oxide packing house five men were selected; four of them never wore respirators. From another zinc oxide plant two men were selected and two men were selected from a plant handling metallic zinc. Finally, three workers from a lithopone packing house were selected. A number of determinations of zinc concentrations in air were made. In the bag house an average concentration of 14 mg/m^3 was observed. In other workplaces mean concentrations were generally below 35 mg/m^3. In the zinc dust plant a maximum concentration of 130 mg/m^3 was measured. The 24 subjects underwent a number of examinations which included x-rays, physical examinations, interviews, blood pressure measurements, and measurements of zinc in blood, urine and feces. Regarding the laboratory findings, it may be noted that 14 of the 24 men showed a slight leukocytosis; hemoglobin was reported to range between 72 and 97 percent with an average of 81 percent (100 percent is assumed to be 150 g/l). Twenty-four hour zinc elimination via feces in controls was reported to vary from about 4 to 20 mg, with an average of 9.32 mg, which is in good agreement with present daily values. In the exposed subjects, 24-hour excretion of zinc via feces averaged 46.8 mg which indicates an exposure via the gastrointestinal tract or massive excretion into the intestine. The conclusion of the authors was that the workmen could be exposed to zinc compounds in a smelter for decades without any symptoms or chronic disease.

Chmielewski et al. (1974a, 1974b) reported on the examination of 60 shipyard workers who were exposed to zinc oxide in different operations. As a control group, 10 healthy subjects who did not work in the shipyard and 10 shipyard workers not exposed to zinc oxide were used. Interviews showed that most of the workmen had experienced metal fume fever several times. Exposure levels varied between 1.7 and 18 mg/m^3 of zinc oxide, but a maximum value of 58 mg/m^3 was found during welding on one occasion. Laboratory investigations showed a tendency to leukocytosis, but other laboratory investigations gave no conclusive results. Some enzyme activities were determined before work and after work. Also in control groups changes were noted during the workday. It is obvious that in this study many of the workers must have been exposed to substances other than zinc oxide. For example, levels of nitrogen oxides were high in some workshops, the highest being 120 mg/m^3, with mean concentrations varying from 2-20 mg/m^3. Also, the total dust was high in some workplaces with levels around 100 mg/m^3 in several places.

Pistorius (1976) studied the effect of zinc oxide on rat lungs in an 84-day study. The rats were divided into groups so that they were exposed for 1, 4, or 8 hours a day to a concentration of 15 mg/m^3 of zinc oxide, at particle size less than 1 micron. A number of lung function tests were performed after 2, 4, and 7 weeks and at the end of the experiment. For most parameters there was no difference between controls and exposed animals, but in specific conductance and difference volume there was a significant decrease after two weeks. Further exposure resulted in all three exposure groups getting closer to the control values. Paradoxically the animals with the 1-hour exposure per day had the lowest values and the 8-hour exposure animals the highest values. The results were interpreted as a bronchial constriction. The author also

explained the improvement in lung function with extension of exposure as a result of an increased elimination from the lung due to an increase in macrophages.

Pistorius et al. (1976) exposed male and female rats for 1, 14, 28, and 56 days to zinc oxide dust at a concentration of 15 mg/m^3 4 hours a day, 5 days a week. Animals were killed 24 hours after the last exposure and the zinc content of lungs, liver, kidney, tibia, and femur was measured. After a single exposure the total zinc content of the lung in males and females was about 46 and 49 µg, respectively. In the male rats similar amounts were found after the longest exposure, whereas in female rats the zinc content after repeated exposure was lower in all groups than at the first exposure. Zinc concentrations were highest in the lung after 1 and 14 days of exposure. In liver and kidney there were no major changes during the experiment, but it should be pointed out that a non-exposed control group was not followed. No differences could be noted in bone. Histological examination of the lungs showed infiltration of leukocytes and inflammatory changes; after 28 and 56 days of exposure, an increase in macrophages could be shown. These studies indicate that there is a rapid elimination of inhaled zinc from the lungs, and that the absorbed zinc is rapidly eliminated from the body through the homeostatic mechanism.

Zinc stearate is a compound other than zinc oxide which is often encountered in the plastic industry and is suspected of causing lung disease. °Votila and Noro (1957) reported on a fatal case involving a worker employed for 29 years in a rubber plant. The autopsy showed the cause of death was a diffuse fibrosis of the lungs with histochemical examination of the lungs showing increased deposits of zinc. However, no quantitative determinations of the zinc content

of the lung were made. The role of zinc stearate as a cause of chronic lung disease has since then been discussed by Harding (1958) and by Weber et al. (1976). Harding gave rats intratracheal instillations of 50 mg of zinc stearate which caused about half of the animals' deaths. In the survivors (living up to 259 days after instillation of the compound) fibrosis could not be detected. Harding also found that the zinc stearate had disappeared from the lungs within 14 days. Weber et al. described autopsy findings in a man who was employed for the last 8 years of his life in a plastics industry and who was exposed to zinc stearate. Fibrosis was found in the lungs with the zinc content of 62 mg/kg of lungs on a dry weight basis (Weber et al., 1976). The same authors found that thirty persons from the same area had concentrations between 3.3 to 69.3 mg/kg of zinc in lungs. The man had also had other occupations, but his exposure to silica quartz in another occupation could not explain the fibrosis. The authors concluded that zinc stearate could not have caused the fibrosis, one reason being that the zinc content of lungs was within the normal limits. However, as pointed out by Harding (1958), zinc stearate is relatively rapidly cleared from the lungs, so a normal content of zinc in the lungs does not exclude the possibility that zinc stearate might have contributed to this disease.

Tarasenko et al. (1976) exposed rats to a single intratracheal administration of zinc stearate in a dose of 50 mg, and found, like Harding, that 50 percent of the animals died after that dose. In animals that survived, pathological changes were seen in the lungs 2 months later. Still later a picture of chronic alveolar emphysema and bronchitis was seen. According to the report, doses of 10 mg and 5 mg were also given but the results were not presented.

Ingestion of Excessive Amounts of Zinc

The hazards of keeping food or liquids in galvanized containers are illustrated by a report by Brown et al. (1964) on two outbreaks of food poisoning assumed to be caused by zinc in California in 1961. In one instance the food poisoning was caused by keeping chicken with tomato sauce and spinach in galvanized tubs. In the other instance a punch drink had been kept in galvanized containers. Zinc content of the food was estimated by repeating the preparation of the meal. After 24 hours of storage the mixture of chicken and tomato sauce contained close to 1000 ppm of zinc. The other poisoning was caused by punch containing 2200 mg/l of zinc. It was calculated that the doses of zinc would be 325-650 mg. In the first instance symptoms occurred 3 to 10 hours after ingestion. Severe diarrhea with abdominal cramping was the main symptom. Vomiting was not common, whereas after drinking the punch the first symptoms were nausea and vomiting which occurred within 20 minutes after ingestion. Diarrhea was also noted in the latter instance. No after effects were observed. It may be noted that in the first instance zinc was ingested with food and the delay in symptoms may have been caused by a simultaneous occurrence of vegetables and meat, whereas in the second instance a more acute effect occurred, since only drinks were served. Cadmium was not determined in either of these studies. Galvanized materials often contain relatively large amounts of cadmium.

Murphy (1970) reported on a 16-year-old boy who tried to promote wound healing by ingesting a large amount of zinc, 12 g of elemental zinc mixed with peanut butter. The zinc was ingested over a two-day period in doses of 4 and 8 g per day. He became lethargic, had difficulties in staying awake, experienced a slight staggering of gait, and noted problems in writing legibly.

Nine days after the ingestion of the first dose of zinc, he was admitted to a hospital. Neurological and laboratory examinations did not reveal anything abnormal, except a slight rise in serum-amylase and lipase. Zinc in whole blood was slightly elevated whereas serum zinc was within the normal range. There was no increase in the zinc level of cerebrospinal fluid. He was treated with dimercaprol and there was a rapid decrease of whole blood levels of zinc to subnormal values. This treatment removed his lethargy. The author's conclusion was that this case showed symptoms indicating an influence of zinc on the pancreas and the cerebellum, but that these effects were easily reversible and no sequelae were seen.

Chunn (1973) studied a group of hospitalized children with anemia. There were 3 children who had levels of zinc in urine above 1 mg/l, but it was not stated by which method the zinc concentrations were determined. The author attributed the common factor for anemia and high zinc excretion in these children to the fact that all 3 children played with metal cars made from an alloy containing zinc. The author also suggested that the zinc could have been ingested by the children imbibing water when they were in the bath tub playing with toys. In a test it was found that placing a toy car in warm water resulted in zinc levels of 1.8 mg/l in water. However, it does not seem likely that significant amounts of zinc could have been taken up by exposure via that route.

Greaves and Skillen (1970) reported on 18 patients who were given daily doses of zinc sulfate corresponding to 150 mg zinc per day for between 16 and 26 weeks as treatment for venous leg ulcerations. Before treatment the plasma zinc levels varied between 0.68 and 1.2 mg/l, and after completion of treatment the levels were between 0.84 and 1.92 mg/l. During the study a number of laboratory investigations were undertaken on several occasions, but copper

levels were not determined. No ill effects could be noted from the treatment with zinc and there were no changes in hemoglobin or serum enzymes.

In animal experiments it has been shown that zinc may interfere with copper metabolism and that when the intake of copper is low, excessive zinc may induce a copper deficiency and anemia (NRC Chapter 9 pp. 256-257; Underwood, 1977; Hamilton et al., 1979; Murthy and Petering, 1976). The animal data indicate that prolonged excessive intakes of zinc may constitute a hazard in patients treated with oral zinc supplements.

During the last years there have been some reports on copper deficiency in human beings after treatment with zinc. Prasad et al. (1978) and Porter et al. (1977) have reported hypocupremia after a long-term treatment with zinc sulfate in doses of 660 mg/day, i.e., 150 mg zinc per day. In both cases it was easy to correct the hypocupremia. No chronic effects of the treatment were seen, but Porter et al. pointed out that the daily doses of 660 mg zinc sulfate may be too high for long treatment. It should be noted that in both studies patients with severe diseases were treated (sickle-cell anemia and coeliac disease).

Zinc poisoning has occurred in cattle. In the outbreak described by Allen (1968), the zinc poisoning of cattle was caused by dairy nuts which had been contaminated by error with zinc so that the zinc concentration was 20 g/kg. It was stated that the cows had an intake of about 7 kg/day of these dairy nuts, which would correspond to an intake of 140 g of zinc per cow per day. Exposure was only for a couple of days but it resulted in severe enteritis. On one farm 7 out of 40 cows were so severely affected that they died or had to be slaughtered. The post-mortem findings showed severe pulmonary emphysema with changes in both myocardium, kidneys, and liver. There were also some

indications that copper levels were lower than normal. Zinc concentrations in liver were extremely high, measured on a dry matter basis, 1,430 and 2,040 mg/kg in two analyzed livers.

Lead poisoning has occurred in horses living near lead-zinc smelters. In foals, some symptoms, lameness and joint afflictions especially, have been described and related to exposure to zinc in areas near smelters. Willoughby et al. (1972) gave foals a diet containing 5,400 mg/kg of zinc and another group received, in addition, lead in the amount of 800 mg/kg. The groups were compared with a control group and a group given only the excessive amount of lead. It should be mentioned that the groups consisted of only two or three animals each. In three animals given excessive amounts of zinc, bone changes, especially in the epiphyseal areas of the long bones, were noted as a first sign; later the animals had difficulties in standing and walking. In animals given lead and zinc the symptoms associated with exposure to zinc dominated. There were less effects from the exposure to lead and zinc than in animals given only lead. It should be noted that in this experiment exposure to zinc was extremely high but taken together with the above-mentioned reports on actual findings in animals living near smelters it is obvious that exposure to zinc in high amounts may constitute a hazard to horses.

Aughey et al. (1977) gave zinc (as the sulfate) to mice for up to 14 months in drinking water at a concentration of 500 mg/l. The concentrations of zinc in feed for controls and exposed animals were not stated. That zinc is readily absorbed was seen by a rapid rise in plasma concentrations of zinc during the first days of exposure. During 6 months no difference between controls and exposed animals could be shown regarding zinc concentrations in liver, spleen, and skin nor was there any difference between the sexes.

Histological examination showed that several endocrine glands were affected by the administration of zinc. Hypertrophy was found in the adrenal cortex; in the pancreatic islets and in the pituitary gland changes consistent with hyperactivity were noted.

Kang et al. (1977) gave rats, by pair-feeding, diets containing 1.3, 55, and 550 mg zinc/kg of feed for 4 weeks. The animals were killed after that time and tissue concentrations of zinc and a number of other metals were determined. The low zinc diet gave typical signs of zinc deficiency, whereas there was no difference in weight gains and food efficiency ratios in the two groups given higher amounts of zinc; this fact, according to the authors, suggested that the highest level (550 mg/kg) was not toxic. Liver and kidney concentrations of zinc were slightly higher in the group given the largest amount of zinc, but no difference was noted in the heart. Iron concentrations in liver were inversely related to the intake of zinc, whereas no difference in copper concentrations or magnesium concentrations in the liver could be seen between the two highest zinc levels. In the kidney there was also a tendency for decreasing iron concentrations with increasing zinc intakes as well as for copper, but there was practically no difference between the two highest dose levels, nor was there a difference in magnesium.

In pigs given zinc in the diet in concentrations ranging from 500 to 8000 mg/kg, Brink et al. (1959) found that signs of toxicity in the form of weight gain and feed intake were seen at levels above 1000 ppm. In pigs, given from 2000 ppm and higher, deaths occurred as soon as 2 weeks after exposure and severe gastrointestinal changes were seen with hemorrhages. There were also signs of brain damage due to hemorrhages. Changes in the joints were also seen, mainly in the form of swollen joints. In liver samples from these pigs levels of zinc above 1000 mg/kg wet weight were found.

Effects Caused by Exposure Via Other Routes

In a woman given total parenteral nutrition after an operation, acute zinc poisoning occurred due to an error in prescription. During a period of 60 hours she received 7.4 g of zinc sulfate. She became acutely ill with pulmonary edema, jaundice, and oliguria, among other symptoms. The serum zinc concentration was 42 mg/l. In spite of treatment she remained oliguric and hemodialysis did not improve renal function. She died after 47 days of illness (Brocks et al., 1977).

It has been reported that zinc and copper could be introduced in excessive amounts into the blood during hemodialysis (Blomfield et al., 1969). Petrie and Row (1977) described nine cases of anemia in dialysis patients due to the release of zinc from a galvanized iron tubing in the dialysis system. Copper levels were not measured in these cases but there was a rise in hemoglobin concentrations after removal of the source of the zinc.

Acute effects of hemodialysis have been described by Gallery et al. (1972). A woman on home dialysis used water stored in a galvanized tank and two hours after the first dialysis at home she had symptoms including nausea, vomiting and fever. Similar severe symptoms were experienced by her at two subsequent dialyses, but subsided between dialyses. Dialyses at the hospital were then done without any symptoms, but she had symptoms again when she started dialysis at home. At new admission to the hospital she was found to be severely anemic. It was then found that the zinc concentration in the tank water was 6.25 mg/l. The patient's zinc concentration in red cells was 35 mg/l and after 6 weeks dialysis in the hospital it was reduced to 12 mg/l. During the same period plasma levels decreased from 7 mg to 1.58 mg/l. Blood copper was not decreased.

Carcinogenesis, Mutagenesis, and Teratogenesis

The relationship between zinc and cancer has been reviewed earlier by the NRC (1978) (Chapter 7 pp. 208-209, Chapter 9 pp. 231-234 and Chapter 10 pp. 258-261) and by Sunderman (1971). It was concluded that during certain experimental conditions, injections of zinc salt into the testes could induce testicular tumors. There was no evidence that zinc given via the oral route or parenterally could cause tumors. However, zinc is of interest with regard to cancer since zinc seems to be indirectly involved by being of importance for the growth of tumors. As discussed earlier zinc is necessary for DNA and RNA synthesis. It has been shown that in zinc-deficient rats tumor growth was reduced (Petering et al., 1967; DeWys et al., 1970). These earlier findings have recently been confirmed in other studies.

The effect of different levels of dietary zinc on the development of chemically-induced oral cancer in rats has recently been studied by Wallenius et al. (1978) and Mathur et al. (1978). In the study by Wallenius et al. (1978), three groups of female rats were fed diets for 3 weeks which contained 15 mg/kg, 50 mg/kg, and 200 mg/kg of zinc, respectively. The palatal mucosa was then painted with the carcinogen 4-nitro-quinoline-n-oxide three times a week. The animals were killed after cancer could be observed macroscopically in the oral cavity. It was found that in animals given the diet with the highest level of zinc, the macroscopical signs of cancer appeared earlier, as compared with animals given lower amounts of zinc. In the study by Mathur et al. (1978),a similar design was used but the levels of zinc in that experiment were 5.9, 50, and 260 mg zinc/kg diet. Three, 9, 13, and 23 weeks after the beginning of exposure the groups of animals were sacrificed and blood, liver, and palatal mucosa were sampled. Control animals were killed at the same

time. The carcinogen had been applied 3 times a week. It was found that after 3 weeks the animals with the lowest zinc intake, which was regarded as producing zinc deficiency, showed more advanced histological changes than animals given 50 or 260 mg/kg diet of zinc. After 20 weeks' application of the carcinogen, there was no difference in the development of tumor between zinc deficient and zinc supplemented groups. It may be noted that both in the low and high level zinc groups, carcinoma in situ and fully developed carcinomas were found, whereas in the group given 50 mg zinc/kg diet, regarded as an adequate level, even after 20 weeks only moderate dysplasia was seen. The groups studied were quite small and thus did not allow any detailed statistical analysis. The results were interpreted to mean that zinc deficiency made the animals more susceptible to the induction of cancer but at the same time caused a slower growth rate of tumors and that a high zinc intake initially gave some protection against the development of tumors but that later excessive zinc intake promoted tumor growth.

Another example of the importance of zinc deficiency for the development of cancer is the study by Fong et al. (1978). One group of rats was fed a diet containing 60 mg/kg of zinc and one group of rats was fed a diet containing 7 mg/kg of zinc. After 12 weeks on these diets the carcinogen methylbenzylnitrosamine was administered by intragastric intubations twice weekly in doses of 2 mg/kg body weight for 12 weeks. In another experiment the design was similar but the carcinogen was administered after 4 weeks with the length of exposure of 9 weeks. Some animals were killed at the end of exposure and some animals were killed 5 weeks later. In a third experiment the carcinogen was given for 4 weeks and animals were sacrificed 63 days after the start of exposure. Finally, there was one experiment where the exposure was only for 2

weeks for a total of four doses of the carcinogen. As expected, zinc levels in the esophagus were lower in zinc deficient animals than in controls, but they were also lower in animals on an adequate intake of zinc, but which were given the carcinogen. A general finding was also that in zinc-deficient animals more carcinomas of the esophagus were found than in animals fed an adequate intake of zinc. It was also noted that in the groups given the lowest doses of the carcinogen, the difference between groups was most significant; a total of eight doses gave figures of 79 and 29 percent, respectively, for tumor incidence and at a total of four doses the corresponding figures were 21 percent and zero (0) percent.

Regarding human beings, there is no definite evidence that zinc deficiency in itself has any etiological role in human cancer. However, many studies have been performed on the levels of zinc in both malignant and non-malignant tissues in human beings. The zinc concentrations have been found to be both low and high and no definite pattern has occurred (NRC (1978) Chapter 9 pp. 231-234 and Chapter 10 pp. 259-261). As an example it has been shown that in cancer of the esophagus in human beings zinc concentrations were lower than normal which is in accordance with the above mentioned experiments on rats (Lin et al., 1977). However, there is one organ in the human being where there seems to be a more consistent pattern, the prostate gland. It has been discussed earlier that zinc concentrations in the prostate normally are very high; there has been a consistent finding that in cancer of the prostate there is a decrease in zinc in the carcinomatus tissue of the prostate.

In the study by Habib et al. (1976), zinc concentrations in the neoplastic tissue were less than half of the concentrations in normal tissue or in hypertrophic prostates. These authors also reported that the cadmium levels were

higher in the carcinomatous tissues than in the normal or hypertrophic tissue. High industrial exposure to cadmium has been implicated as a possible cause of prostatic cancer and since there are interactions between cadmium and zinc, this might have some bearing on the problem of the relationship between zinc and cancer of the prostate. Habib (1978) has reviewed the role of zinc in the normal and pathological prostate.

Regarding hyperplastic prostatic tissue, it may be noted that most reports have stated that there are the same concentrations of zinc in the hyperplastic tissues as in normal tissue. There is one exception; the study by Györkey et al. (1967) found considerable increases in zinc levels in hyperplastic tissue--more than three times the normal.

The mutagenic effects of zinc have been discussed by the National Research Council (Chapter 10 p. 261) which could not find literature that suggested that zinc is mutagenic in animals and human beings nor have any new data appeared on this subject. The same conclusions are made with regard to teratogenesis. The greatest risk is related to zinc deficiency which might cause malformations. However, it is reasonable to assume that indirectly zinc might have an effect since long-term supplements with large amounts of zinc will cause disturbances in copper metabolism.

In a study by Cox et al. (1969), it was shown that if rats were fed a diet containing 4,000 ppm of zinc during gestation, copper levels were reduced in the fetal body and liver whereas zinc concentrations increased. Ketcheson et al. (1969) fed rats diets containing up to 5,000 mg of zinc/kg during gestation. Even at that level malformations were not observed, but there was a reduction in the copper concentrations of the fetal liver.

A brief statement in a report by Kumar (1976) states that in a small group of women supplements of zinc administered during the third trimester of pregnancy in a dose of 100 mg of zinc sulfate per day (23 mg zinc per day) caused premature births and one still-birth in four consecutive subjects. Kumar then made studies in rats and gave them a daily supplement of 100 ppm zinc orally (it is not quite clear how the dose was calculated, but it is stated in the report "received additionally 150 ppm zinc as a 2% zinc sulphate solution"). The concentration of copper and other nutrients in the diet was not stated. In the zinc-supplemented animals there was a significant increase in the number of resorptions of the inplantations. Supplementation for pregnant women has been recommended, but due to the known interaction between zinc and copper, excessive zinc intakes during prolonged times could have an adverse effect on the fetus. It is well documented in animal experiments that zinc deficiency during pregnancy might have an adverse effect on the fetus (NRC Chapter 7 pp. 179-180).

INTERACTIONS OF ZINC WITH OTHER METALS

As has already been discussed in the section concerning effects of excessive intakes of zinc, interactions between zinc and other metals may occur. It was demonstrated that excessive intakes of zinc could influence the metabolism of iron and copper, but it is also possible that excessive intakes of other metals may also have an influence on the metabolism of zinc. Such metal-metal interactions have recently been discussed at an international meeting and reported (Nordberg, 1978). Interactions between zinc and other metals have also been reviewed by Underwood (1977) and NRC (Chapter 7 pp. 186-187).

Cadmium

Interactions between cadmium and zinc were extensively discussed in the NRC report (Chapter 10 pp. 261-268) and the literature up to 1974 was reviewed and discussed. It was concluded that exposure to cadmium would cause changes in the distribution of zinc with increases in liver and kidney where cadmium also accumulates. In animals on marginal zinc intakes there could be a zinc deficiency in certain organs parallel with the increase in liver and kidney. It has also been shown that in both human beings and horses the increase in renal concentrations of zinc is parallel to the increases in cadmium and that this increase is nearly equimolar up to cadmium concentrations of about 60 mg/kg wet weight. These earlier findings have recently been confirmed in new studies both in human beings and in horses (Elinder and Piscator, 1977; Elinder and Piscator, 1978). The increase in renal zinc is also related to the occurrence of cadmium in metallothionein. It has recently been shown that whereas at low levels of cadmium in the kidney there are about equimolar amounts of zinc and cadmium in metallothionein, with increasing cadmium concentrations the ratio

of cadmium to zinc will increase. It was also shown that at a level of about 200 mg/kg wet weight of cadmium the amount of zinc in metallothionein would be close to zero (Nordberg et al., In Press 1979) and that corresponds to the critical level which has been estimated for renal cadmium related to the occurrence of renal tubular dysfunction (Friberg et al., 1974).

Although a large number of animal studies have been performed, there might be some difficulties in drawing conclusions with regard to the human situation. A review of the literature by Elinder and Piscator (1978) showed that there are clear differences between some large mammals (e.g., man, horse) compared to small laboratory animals. In the rat especially (the most commonly used laboratory animal), exposure to cadmium will result mainly in an increase in hepatic zinc, whereas the increase in renal zinc is rather small. On the other hand, exposure to cadmium causes increases in renal copper concentrations. Such differences make it reasonable to conclude that one must be cautious when drawing conclusions from experiments done with rats. The differences between species are illustrated in Figure C-1. Zinc deficiency alone is known to cause effects on the fetus. If animals are exposed to cadmium during the gestation period, this may also influence the mineral distribution in the fetus. Pond and Walker (1975) showed that both low zinc concentrations and copper concentrations and decreases in birth weight were found in rat pups that had been given cadmium orally. Since cadmium does not pass the placental barrier to any significant extent, this is thought to be due to retention of zinc in the dam parallelling the accumulation of cadmium as mentioned above. Data by Choudhury et al. (1978) indicate that in the rat fetus a decrease of copper and iron occurs before the zinc levels are affected.

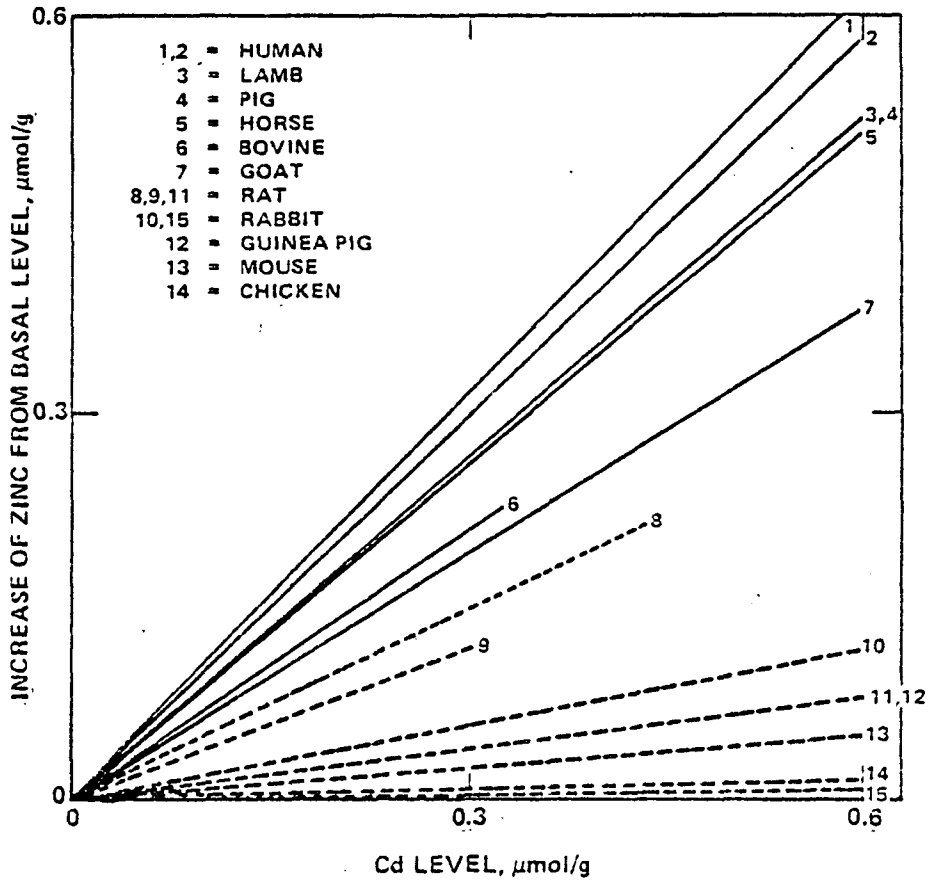

Figure C-1. Increase of zinc as a function of increasing cadmium concentration in kidney of 11 different species. (Courtesy Elinder and Piscator, 1978.)

Lal (1976) found that oral exposure to cadmium could cause testicular and pulmonary lesions in rats on a marginal intake of zinc, 5 mg/kg feed, whereas such lesions were not seen when the diet contained 40 mg zinc/kg. The exposure to cadmium in that experiment was 17.2 mg/l of drinking water. Zinc concentrations in the testes of zinc-deficient animals were 104 mg/kg, compared to 143 mg/kg in the animals at the higher level of exposure.

Copper

It has been mentioned earlier that excessive intakes of zinc may cause copper deficiencies in human beings and result in anemia, which can be easily corrected by decreasing the intake of zinc and giving copper supplementation. It has also been suggested by Klevay (1975) and Klevay and Forbush (1976) that the ratio between copper and zinc in the American diet contributes to coronary heart disease. The main reason for this may be that the copper content of the typical American diet is less than the requirement. These theories have not been substantiated, even though Klevay (1973) found that in rats hypercholesterolemia occurred with an increasing zinc-copper ratio in the diet. It has since been shown that it is the copper status that is the main factor with regard to cholesterol levels (Petering et al., 1977; Murthy and Petering, 1976; Allen and Klevay, 1978)

Evans et al. (1974) found that in zinc deficient rats excessive amounts of copper did not influence the uptake of ^{65}Zn from the gut, but in zinc-supplemented rats excess copper had an influence on the uptake of ^{65}Zn. The authors tried to explain the findings by suggesting that in the zinc deficient rats a larger number of zinc binding sites on plasma albumin would be available and that at such sites there would be no competition with copper.

Kinamon and Bunce (1965) fed groups of rats a basic diet containing 18 mg/kg of copper, 70 mg/kg of zinc and less than 1 mg/kg of molybdenum. To these diets zinc, copper, or molybdenum and combinations of these metals were added in amounts of 100 mg/kg of copper, 1,800 mg/kg of molybdenum, and 5,000 mg per kg of zinc. The length of the experiment was 7 weeks. At the end of the experiment all animals were given an injection of radioactive zinc. After 4 days the animals were killed. As in other studies, it was found that an increase in dietary zinc resulted in a decreased retention of the isotope, but that even the very high level of copper or molybdenum did not influence the retention of the isotope. These data indicate that the influence of zinc on copper metabolism is probably of greater importance than the opposite, i.e., influence of copper on zinc metabolism.

Calcium

The influence of calcium on absorption of zinc from the gut was discussed by NRC (1978) (Chapter 7 pp. 184-185). It was concluded that calcium levels in the diet do not influence zinc absorption except for some indications that calcium could have an influence when zinc intake is marginal. Also Underwood (1977) has reviewed the relationships between zinc and calcium. The study by Hurley and Tao (1972) shows an interesting example of interaction between zinc and calcium. Beginning on the first day of gestation, female rats were given either a zinc-deficient diet containing 0.4 mg zinc per kg or a zinc-deficient and calcium-deficient diet which contained the same amount of zinc but 15 mg/kg feed of calcium. The animals were killed on the 21st day of gestation, and the fetuses were removed and examined. The results showed that in females deficient in both calcium and zinc the resorption rate in the uterus was lower

and there was a larger number of live births per litter than among the rats given only the zinc-deficient diet. Eighty-three percent of the fetuses from females on the zinc-deficient diet showed malformations whereas the corresponding figure for zinc-deficient and calcium-deficient group was 57 percent. Analysis of maternal bone showed that there was a reduction in both ash weight and total calcium content of the femur in the females given the zinc-deficient and calcium-deficient diet. This was interpreted as calcium being withdrawn from the bone during pregnancy to provide calcium to the fetus. There was also lower zinc content in the bones of rats on the calcium-deficient diet. This suggested that zinc was released from bone during the release of calcium. This zinc could then be available and transported to the fetus, whereas in animals on a zinc-deficient diet and high calcium intake there would be no release of zinc from bone and thus the large amount of zinc stored in bone would not be available to the fetus. This study shows how two essential metals can interact with each other.

Iron

As mentioned earlier, high intake of zinc may affect iron metabolism, but much less is known about the effects of iron on zinc. Sherman et al. (1977) gave pregnant rats diets containing 5, 29, and 307 mg/kg of iron. Eighteen days after parturition both the dams and pups were killed and examined. It was found that the zinc to copper ratio in spleen increased in dams but tended to decrease in the pups as a result of iron restriction. In the pups the zinc to copper ratio was considerably lower in the liver of iron-deficient animals but in the dams no differences were seen between groups with high and low iron intake. In the iron-deficient pups increased levels of serum lipids were associated with decreased ratio of zinc to copper in the tissues.

Hamilton et al. (1978) studied the intestinal absorption of zinc in iron-deficient mice and found that zinc uptake from the gut was inhibited by adding iron to the duodenal loop system used. It was concluded that there were some common mucosal binding sites for both iron and zinc.

Lead

It was mentioned earlier that in horses there can be simultaneous exposure to lead and zinc and there seem to be some interactions; there was a lower uptake of lead in animals with high intake of zinc. Cerklewski and Forbes (1976) studied the influence of three dietary levels of zinc (8, 35, and 200 mg/kg) on rats given 50 and 200 mg lead per kg feed. They found that with higher dietary zinc concentrations the symptoms of lead toxicity decreased. The lead concentrations in tissues were lower in animals with high zinc intake, but also the hematological changes were less. It was concluded that the main interaction was in the gut.

Lead will also have an influence on the zinc concentrations in tissues as was shown by El-Gazzar et al. (1977) in rats given drinking water containing 5 and 50 mg/l of zinc and 100 mg/l of lead. Lead exposure decreased the plasma zinc in the low level zinc group but increased erythrocyte zinc. Further exposure caused reduced plasma zinc levels also in the high zinc level group. There were also reductions in the zinc levels in liver and tibia of both groups. There was no change in the brain concentration of zinc.

An effect which has attracted great interest the last years is the effect of zinc on the activity of ALA dehydratase, a zinc dependent enzyme, in blood. In a number of studies both *in vivo* and *in vitro* it has been shown that zinc is antagonistic to lead regarding the ALA dehydratase activity, and that zinc decreases the excretion of ALA seen in lead-intoxicated rats (Abdulla et al.,

1976; Border et al., 976; Finelli et al., 1975; Thawley et al., 1978; Thomasino et al., 1977).

Thawley et al. (1977) gave rats a basic diet containing 30 mg/kg of zinc and 7 mg/kg of lead and then groups were given additions of 5,000 mg/kg of lead or 6,300 mg/kg of zinc and combinations thereof. These diets were also combined with two levels of calcium in the diet, 0.9 and 0.1 percent respectively. The findings indicate that the increase in ALA excretion caused by lead was reduced by the additional exposure to the high level of zinc. The exposure to zinc caused larger reductions in serum iron than lead exposure. The most severe anemia was seen in animals on a high lead and a high zinc intake together.

Interactions Between Zinc and Drugs

In the previous chapters it has been mentioned several times that contraceptive pills have an influence on zinc metabolism. The influence of oral contraceptives on the excretion of zinc in women on a low intake of zinc, copper, and iron was studied by Hess et al. (1977). Urinary zinc excretion decreased in women both on contraceptives and not on contraceptives. The greatest decrease was in the contraceptive group with a decrease of 83 percent and a 62 percent decrease for those not on contraceptives.

The usual intake of zinc in these women before the study started was estimated to be about 10 mg/day. During the study the intake averaged only 0.17 mg/day. At the beginning of the study, before the zinc intake was lowered, the average excretion of zinc in urine was 0.36 and 0.4 mg, respectively, for the group on contraceptives and for the control group. These data indicate that whereas contraceptives will have relatively little influence on zinc metabolism during normal zinc intake, they may have a more profound influence when the zinc intake is low. In this study the zinc intake was extremely low.

Many other drugs, especially drugs with chelating properties, may influence zinc metabolism. Thiazids and penicillamine can increase the excretion of zinc. Substances in food such as phytate can influence the absorption. Also, alcohol will have an influence on zinc metabolism especially if a state of chronic alcoholism has been reached with cirrhotic changes in the liver. Such cases often have low serum levels of zinc and an increased excretion.

CRITERION FORMULATION

Existing Guidelines and Standards

The National Institute of Occupational Safety and Health (NIOSH, 1975) has recently reviewed the occupational hazards of exposure to zinc oxide and no changes were suggested regarding the existing standard for zinc oxide of 5 mg/m^3. The American Conference of Government Industrial Hygienists (ACGIH, 1976) has an adopted threshold limit value (TLV) for zinc oxide of 5 mg/m^3 and the Occupational Safety and Health Administration (OSHA, 1978) has a workplace standard for zinc oxide of 5 mg/m^3, eight-hour time-weighted average. The TLV value has also been adopted in other countries. For zinc chloride a limit of 1 mg/m^3 has been adopted by ACGIH and OSHA also adopted a standard of 1 mg/m^3 for zinc chloride.

The present standard for drinking water, 5 mg/l, is based on organoleptic effects, i.e., some people will recognize the bitter taste caused by zinc present at such levels. The World Health Organization (WHO) has also proposed that the level should be 5 mg/l; however, the USSR has established a limit for zinc at 1 mg/l for other than health reasons (National Academy of Sciences (NAS), 1977).

There is no acceptable daily intake for zinc in food. As mentioned earlier zinc is an essential nutrient and there has been no reason to restrict the zinc levels in food.

In 1974, the National Academy of Sciences recommended that adults should have an intake of 15 mg of zinc per day, that pregnant women should have an intake of 20 mg/day and

that pre-adolescent children should have 10 mg/day of zinc (National Academy of Sciences, 1974).

Current Levels of Exposure

It has been well established in several studies that the present intake of zinc via food for the adult U.S. population is from 10 to 20 mg. For the majority of the population the intake of zinc via drinking water will be only a few percent of the intake via food, but for some individuals the zinc concentration in tap water may cause an additional daily intake of 2 to 10 mg of zinc. The average exposure to zinc via ambient air will, even in the vicinity of zinc emitting industries, be in the order of only a few tenths of a milligram. Smoking will contribute even less.

Special Groups at Risk

Since zinc may interfere with copper and other minerals, excessive intakes of zinc by people with a tendency to copper deficiency might cause reversible health effects. Patients treated for months or years with large oral doses of zinc salts, about ten times the intake via food, for curing of various diseases caused by zinc deficiency or to promote wound healing may constitute a group at special risk. Infants with copper deficiency or low intakes of copper may constitute another risk group. Occupational exposure to zinc oxide fumes may cause acute reversible reactions which may put persons subjected to such exposure at special risk.

Basis and Derivation of Criterion

Zinc is an essential element and is not a carcinogenic agent. Studies on experimental animals and on human beings

given zinc for therapeutic purposes together with observations of occupationally exposed persons show that large doses of zinc can be tolerated for long periods, provided that the copper status is normal.

Daily ingestion of about 150 mg of zinc as the sulphate has not resulted in adverse effects in most patients even after several months of treatment. A reduction of copper levels has been reported in patients with diseases such as sickle cell anemia and coeliac disease. A reduction of the dose of zinc and copper supplementation corrected the copper deficiency.

Laboratory animals have been shown to tolerate zinc concentration in the range of 100 to 300 mg/kg food and even higher for long periods when the intake of copper has been adequate. Copper deficient animals have been shown to be more susceptible. In many animal experiments zinc concentration in the diet of 1000 to 2000 mg/kg have been reported to be without effect. These concentrations should be compared to the average zinc content of human food, which is about 10 mg/kg.

The water quality criterion for zinc in water based on available data on effects of ingested zinc would be about 10 mg/l for the adult U.S. population. Assuming a water intake of 2 liters per day, this exposure would not cause more than an additional intake of 20 mg which can be well tolerated. This concentration is above the present standard for drinking water which is 5 mg/l based on organoleptic effects.

There are some indications that infants and small children may have a high intake of water and an additional intake of 10 to 20 mg might have an influence on copper metabolism in children with low copper intakes or with copper deficiency due to, e.g. intestinal diseases. However, due to insufficient amount of information available for this special groups at risk, derivation of criterion lower than the current standard would be difficult to justify. Therefore, it is recommended that the current level be maintained for water quality criteria purposes (5 mg/l). As additional information becomes available reconsiderations of appropriateness of the current standard should be performed.

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