ATTACHMENT VI

ASSESSMENT OF ESTIMATED RISK

RESULTING FROM

AFLATOXINS IN CONSUMER PEANUT PRODUCTS

AND OTHER FOOD COMMODITIES

BUREAU OF FOODS

FOOD AND DRUG ADMINISTRATION

January 19, 1978

SUMMARY

Although direct proof that aflatoxins (B_1, B_2, G_1, G_2) induce cancer in humans does not exist, laboratory tests have demonstrated that they are animal carcinogens. Further, epidemiology studies in Thailand and parts of Africa show a significant relationship between liver cancer incidence and estimated levels of aflatoxin intake.

Aflatoxins cannot be completely eliminated from food products without eliminating the products themselves. FDA has been enforcing a limit of 20 parts per billion (ppb) for aflatoxins in certain foods and is considering reducing that limit to 15 ppb for peanuts and peanut products (39 FR 42748).

Unfortunately, the direct risks, if any, to humans from ingestion of aflatoxins cannot be measured. Therefore, risk assessments must rely on mathematical treatment of animal toxicology and epidemiology studies. Such risk assessments have been made by FDA and are described herein.

Aflatoxins can occur in a variety of grains and nuts and can also occur in the meat, milk, and eggs of food animals that have consumed aflatoxin-containing feeds. Corn products and peanut products only have been considered in the risk calculations since inclusion of other products, because of contamination levels and/or frequency of contamination or consumption does not significantly affect the numerical results. Emphasis has been placed on corn products in the Southeastern United States because both consumption and aflatoxin contamination levels are relatively high in that region.

Utilizing FDA and USDA aflatoxin survey and food consumption data, it is estimated that aflatoxin intake ranges from an average of 2.7 to a maximum of 9.0 nanograms/kilogram of body weight/day (0.1 to 0.3 parts per billion in the diet) in the Southeast.

An extensive body of data exists on aflatoxin toxicology in laboratory animals. Because it would be impractical to make risk calculations for each such study, five studies, involving long-term feeding of aflatoxins to three species of rats, were selected. (Rats in general, and male rats of the Fisher strain in particular, are considered the most aflatoxin-susceptible mammals.) Using the mathematical procedure of Mantel and Bryan, estimates of lifetime liver cancer incidence rates were derived for each study, and for the five studies combined. These estimates range from 30 to 1400 per 100,000 for the individual rat studies and from 240 to 1100 per 100,000 for their combination. By way of comparison, risk estimates derived from studies on rats and other species combined by Cornfield and co-workers yield a range from 17 to 126 per 100,000.

The actual lifetime liver cancer incidence rate from all causes in the U.S. is approximately 161 per 100,000. Actual incidence rates in Georgia and Alabama are approximately 103 and 100 per 100,000 respectively. (Rates for other Southeastern states are not readily available.)

The fact that the risk estimates for rats in general exceed the human incidence rate for liver cancer from all causes can be attributed, in part, to the conservative mathematical procedures employed. In

addition, available *in vitro* data would indicate that humans are biologically closer to relatively resistant animals such as mice and monkeys than to aflatoxin-susceptible rats.

Epidemiology studies conducted in Thailand and several parts of Africa show a positive correlation between actual liver cancer incidence and estimated intake of aflatoxins. Utilizing the relationship derived by Peers and Linsell, risk estimates were calculated to range from 20.2 to 67.0 per 100,000 for estimated average and maximum aflatoxin intakes. How applicable such epidemiological studies are to the U.S. is not known, particularly since the liver cancer incidence rates in these areas outside the U.S. may be greatly influenced by the presence of pyrrolizidine alkaloids in herbal medicines and the existence of hepatitis-B virus.

Risk estimates calculated from the epidemiology data for peanut products only yield a range of 1.1 to 2.7 per 100,000. Assuming that a proportional reduction in aflatoxin levels would result from the proposed regulatory enforcement limit of 15 ppb yields a projected range of 0.3 to 2.1 per 100,000. For the lowest enforcement limit currently possible, 5 ppb, the theoretical range would be 0.3 to 0.7 per 100,000. Although the ranges are broader, the animal data yield a similar comparison between a limit of 15 ppb and that of 5 ppb.

Neither the estimated incidence rates calculated from the animal data nor those from the epidemiology studies can be construed as representing the actual human risk from aflatoxins. It is reassuring,

however, that the two approaches yield similar results, at least when inter-species differences are taken into account. Assuming that these approaches at least provide conservative indications of potential human risk, there appears to be little, if any, gain in public health protection associated with a tolerance for aflatoxins in peanut products at 10 ppb or 5 ppb as opposed to the 15 ppb level being considered. Again assuming that these approaches have some validity, it appears prudent to continue efforts to control the largely intra-state problem with aflatoxins in corn in the Southeast--notwithstanding the apparently lower actual incidence of liver cancer in the Southeast.

The several other reasons why a 15 ppb tolerance for aflatoxins in consumer peanut products is deemed appropriate were described in the preamble to the proposal to establish the tolerance.

INTRODUCTION

The Food and Drug Administration (FDA) is considering a regulation that establishes a tolerance for aflatoxins in shelled peanuts and peanut products used as human food. The regulation would set a 15 parts per billion (ppb) tolerance for total aflatoxins ($B_1 + B_2 + G_1 + G_2$) in these products.

Aflatoxins are mold-produced toxins which are unavoidable contaminants in peanuts and a number of other food commodities (1). Although the human health effects of chronic exposure to aflatoxins are not known with certainty there is evidence which associates chronic dietary exposure to aflatoxins with the induction of primary liver cancer. In particular, several studies have indicted aflatoxins as animal carcinogens (2).

At present, it is not possible to determine a level of dietary exposure to carcinogenic substances that would not lead to a finite risk of human cancer. Therefore, assurance of absolute safety for the consumer (i.e., no risk of cancer) is achievable only through complete elimination of carcinogenic substances from the diet and from other sources. However, unlike chemicals intentionally added to food, unavoidable food contaminants cannot be prohibited from the diet, unless the food susceptible to contamination is itself prohibited.

This approach to the assurance of absolute safety for food unavoidably contaminated with aflatoxin would mean the complete elimination of those food commodities that have been shown to be susceptible to such contamination. These food commodities include corn, peanuts, sorghum, rice, wheat, soybeans, walnuts, almonds, pecans, pistachio nuts, Brazil nuts, figs, and the edible

tissue (meat, eggs, and milk) from food-producing animals that consume animal feed containing these compounds (3,4).

Because not all lots of these foods are expected to contain measurable aflatoxins, an alternative approach to indiscriminately eliminating from the diet both contaminated and non-contaminated food is to prevent from entering consumer channels only those lots demonstrated to contain aflatoxin.

In the case of consumer peanut products, aflatoxins at or above a level of 5 parts per billion (ppb) can be measured with the degree of certainty required of FDA to initiate regulatory action (e.g., seizure) to prevent the marketing of aflatoxin-contaminated peanuts. In short, the goal of attaining a "zero" tolerance for aflatoxin would translate to an enforcement level of 5 ppb, i.e., the lowest level at which it can be determined with certainty whether aflatoxin is or is not present in peanuts. (It should be noted that aflatoxins at levels less than 5 ppb can be detected in peanuts, but the validity of measurements at such levels is questionable.)

While a level of 5 ppb may represent the lowest enforceable tolerance consistent with FDA's consumer protection objectives of minimizing dietary exposures to aflatoxins, such a tolerance would be beyond the capability of manufacturers to meet consistently. This is the case because of the high variability of aflatoxin levels within and among peanut lots. Such variability requires that quality control limits in manufacturing be set much lower than the regulatory tolerance (5). For example, consistent production of lots conforming to the proposed tolerance of 15 ppb would require quality control limits on the order of 3-7 ppb. Lower tolerances would require proportionately lower quality control limits. A tolerance of 5 ppb would thus

require a quality control limit below the level of reliable detection and would result in the inadvertent release of illegal lots into commercial channels, there to be seized by FDA.

In brief, if peanut products are not to be entirely prohibited, consumer exposure to aflatoxins from these products can only be kept below detectable levels (i.e., 5 ppb) by seizure (and a significant loss of product). For a higher tolerance (e.g., 15 or 10 ppb), the emphasis would be on manufacturing quality control (and there would be less loss of product).

Because of the foregoing characteristics of the control situation, information is needed to assess the human risks associated with low levels of aflatoxin exposure. Unfortunately, such information is not readily available. However, evaluation of that information which is available from toxicology and epidemiology studies does help to put the risk question in perspective. In the following, risk estimates are derived from animal tests and from epidemiology studies. Such estimates cannot be construed as representing actual human risk but they do provide an indication of the relative potential toxicity of aflatoxins.

INFORMATION NEEDED FOR RISK ASSESSMENT

Existing data indicate that the most likely potential effect from chronic aflatoxin exposure is primary liver cancer (1,2). In all risk estimates to follow, it is this disease that is being considered.

An estimate of the risk of primary liver cancer in humans due to exposure to dietary aflatoxins requires two types of information. First, some measure of the toxicity of aflatoxin to humans must be available. For purposes of

this assessment, the most relevant toxicity data would be those relating long-term, low-level aflatoxin exposure to primary liver cancer in the expose group. Ideally, what is sought is a dose-response curve expressing the relationship between the level of aflatoxin exposure (the dose) and the incidence of liver cancer (the response) in the exposed group.

The most relevant and least suspect of such information would be that obtained by direct experimentation in human beings. Clearly no such data are available nor, for ethical reasons, could they ever be developed. Therefore, reliance must be placed on data resulting from: 1) epidemiological studies in groups of humans known to have been inadvertently exposed to aflatoxins; or 2) direct experimentation in laboratory animals. Epidemiological studies, which should provide the most relevant information obtainable, nonetheless have several disadvantages, perhaps the most important of which are their inherent limitations in establishing clear causal relationships and their relative insensitivity in detecting such relationships. Studies in experimental animals are usually more sensitive than epidemiological studies and, when properly conducted, are capable of establishing direct causation and dose-response relationships of relatively high certainty. But they have been criticized on the grounds of being irrelevant to humans. It must also be kept in mind that epidemiological and animal data obtained from relatively small, homogenous population groups requires, for estimation of risks in an entire population, extrapolation to very large, heterogeneous groups of humans. It is not known how to estimate the uncertainty associated with extrapolations of these types.

In addition to toxicity information, risk assessment depends on data concerning the level and duration of human exposure to the toxic material. For purposes of this assessment, the relevant data are the food commodities in which aflatoxins occur, the levels of aflatoxins in those foods, the frequency and amounts of human consumption of those foods, and the length of time of exposure. As with the toxicity information, the human exposure facts in the risk assessment equation is also subject to much uncertainty.

DIETARY EXPOSURE TO AFLATOXINS

a. Occurrence of Aflatoxins in Food: The food classes that contribute most significantly to dietary exposure to aflatoxins in the United States are dry milled corn products (e.g., corn meal and grits) and peanuts and peanut products (3). Exposure to aflatoxins through contaminated corn occurs mainly in the southeastern states (i.e., North Carolina, South Carolina, Georgia, Alabama, Florida, Mississippi, and Louisiana), where the contamination of corn is most severe. In this area corn is a dietary staple and the corn consumed is primarily of local origin. On the basis of FDA and USDA survey data, it is estimated that the average level of total aflatoxins in dry milled corn products has been in the range of 5-10 ppb (3,6,7). Corn produced and consumed in other regions of the nation has a substantially lower aflatoxin content. Therefore, the United States population groups that appear to be at highest risk, those of the southeastern states, have been selected for emphasis in this risk assessment. To be conservative, the upper level of 10 ppb is used in the risk calculations.

Peanuts, while grown in the Southern states, are processed and consumed throughout the country. Data from surveys conducted by FDA indicate an estimated average level of 2 ppb total aflatoxins in consumer peanut products (3,6,7). This estimated level is equally applicable to population groups on a national or regional basis.

As previously mentioned, aflatoxins may also occur in other food commodities consumed in the United States. However, survey and experimental data indicate that either the levels and/or incidence of aflatoxin in these foods and/or their consumption patterns are not comparable to those found in peanuts and corn (3,6,7). Calculations used in the estimates of total risk would not be significantly affected by ignoring these other food items.

The relevant data on the aflatoxin occurrence in food is presented in Table I.

TABLE I: Major Food Classes With Aflatoxins (B_1 - B_2 - G_1 - G_2)

Food Class	Estimated Average Level (total aflatoxins, ppb)
Peanuts and Peanut Products	2
Corn Products	5-10 *

* Average is for Southeastern States; average in all other areas is lower (see text).

b. Consumption of Aflatoxin - Containing Food Products: A survey conducted by the U.S. Department of Agriculture (USDA) in 1965 provides the best available data for estimating human consumption of the significant food sources of aflatoxins (3). The USDA survey data were collected through personal interviews which required the respondent to recall all foods and the amounts actually consumed during the 24-hour period prior to the interview. The data collected, which covered the entire United States, are available for four major regions--Northeast, North Central, West, and South.

For purposes of this risk assessment, the data collected for the Southern region were used. This survey region included the states of Alabama, Florida, Georgia, Louisiana, Mississippi, North Carolina, South Carolina, Arkansas, Kentucky, Delaware, District of Columbia, Maryland, Oklahoma, Texas, Virginia, and West Virginia. Although it would have been more appropriate to base estimates of intake on the southeastern states alone (i.e., the first seven states listed), since dry milled corn products which may contain aflatoxins are mainly produced and consumed in these states, the food intake estimates used in the risk calculations assume that dietary patterns of the South and Southeast are identical.

Food intake estimates were used for the consumer peanut products and dry milled corn products listed in Table II.

TABLE II: Food Items From USDA Survey Used To Estimate Intake Of Aflatoxin-Susceptible Food (3).

Consumer Peanut Products

peanuts, shelled and in-shell	peanut butter & jelly sandwich
peanut butter	peanut butter & banana sandwich
peanut butter sandwich	peanut butter & jelly

Dry Milled Corn Products

corn bread & muffins	cornmeal pancakes
corn pone	corn grits, hominy grits
spoonbread	cornmeal, cornmeal mush
johnnycake	grits with fat
hush puppies	fried cornmeal mush

The estimated average levels of aflatoxins in consumer peanut products and dry milled corn products (Table I) are derived from surveys of these food items as marketed as opposed to food items prepared for consumption (i.e., as eaten). Therefore, conversion factors were applied, where appropriate, to the amount of intake of food items listed in Table II to obtain the amount of intake expressed in terms of the food items listed in Table I.

Calculation of the average and maximum daily intakes of foods susceptible to aflatoxin contamination also requires knowledge of the frequency at which these foods are consumed. Direct knowledge of the frequency of consumption of these foods is not available. To estimate daily consumption, it was necessary to make use of the information that the total population in the South surveyed by USDA consisted of 6,268 persons, 560 of whom had eaten peanut products and 1,580 of whom had eaten corn products during the 24-hour period preceding the questioning. Since it would be expected that these individuals would not consume these foods every day, the ratio of "eaters" for one day versus "non-eaters" for one day was used to establish the estimated frequency at which these foods were eaten. This ratio, or frequency factor, was applied to both the average amount and to the amount consumed by the 90th percentile of the "eaters" surveyed to derive an estimate of average and maximum daily intakes. These estimates are presented in Table III.

TABLE III: Estimated Consumption Rates For The Southeastern United States Of Food Products Which May Contain Aflatoxins.

	Peanut Products	Corn Products
One day average intake (grams)	45	53
One day maximum (90th percentile) intake (grams)	116	186
Factor for frequency of consumption	.090	.252
Estimated average daily intake (grams)	4	14
Estimated maximum daily intake (grams)	10	47

c. Human Exposure to Aflatoxins: The estimates of consumption contained in Table III can be combined with the levels of aflatoxin contamination (Table I) to estimate average and maximum human exposure to aflatoxins in the southeastern part of the country (the exposure in all other regions being lower). The results of these calculations are presented in Table IV. Also shown are the estimated average and maximum human intakes of dietary aflatoxin expressed in ng/kg body weight/day and in parts per billion (ppb) in the diet.

TABLE IV: Estimated Average and Maximum Daily Aflatoxin Intake In The Southeastern U.S.

DAILY AFLATOXIN INTAKE

	Average			Maximum		
FOOD CLASS	ng[1/]	ng/kg[2/]	ppb[3/]	ng[1/]	ng/kg[2/]	ppb[3/]
Peanuts and Peanut Products	8	0.15	0.005	20	0.37	0.013
Corn Products	140	2.58	0.093	470	8.66	0.313
TOTAL	148	2.73	0.098	490	9.03	0.326

1/ ng = nanograms (1×10^{-9} grams)

2/ ng/kg body weight; average body weight of 54.3 kg

3/ ppb in diet; average daily food intake of 1500 g

RISK ASSESSMENT

a. Animal Toxicity Data: The toxic effects of aflatoxin have been examined in several studies in a variety of species and strains of experimental animals. These include several strains of rats as well as mice, marmosets, tree shrews, trout, ducks, rhesus monkeys, and hamsters (2). The literature is much too extensive to cover exhaustively in this report. Therefore, selected studies are employed in the following to illustrate the range of results obtained in animal studies. Generally, the rat, and in particular the male Fisher strain rat, is considered the mammalian species that is most sensitive to aflatoxin carcinogenesis (2). For this assessment, five studies involving three strains of rats were examined and the statistical procedure developed by Mantel and Bryan (9) as modified (10) was applied to the experimental results. This statistical procedure is one of several available which allow the estimation of carcinogenic risks associated with dose levels of the carcinogen below those necessary to yield a positive carcinogenic response in the animal experimentation. In the present example, the levels of interest are the average and maximum intakes, 0.1 and 0.3 ppb aflatoxins, respectively (see Table IV). No experiments have been conducted in rats at these low dose levels, so no direct measure of risk can be made; but, as noted, the Mantel-Bryan procedure can be applied to the available animal data to estimate the risks associated with the 0.1 and 0.3 ppb dose levels. It must be kept in mind that the Mantel-Bryan procedure estimates animal, not human, risks. The relative sensitivities of humans and, in the present case, rats, remains to be considered. The results of the risk assessment in rats are presented in Table V.

As can be seen from Table V, the estimated lifetime liver cancer incidence rates vary widely among the rat studies, ranging from a low of 50 to a high of 1400 per 100,000. Another indication of the inherent variability in these experiments is provided by the upper 99% confidence limits or risk shown in parentheses in Table V.

TABLE V: Estimated Lifetime Cancer Risks In Laboratory Animals (Rats)-- Incidence Rate Per 100,000[1/]

DATA SOURCE (Reference No.)	AFLATOXIN INTAKE (0.1 ppb)	(0.3 ppb)
(11)	2/(60)[3/]	2/(320)[3/]
(12)	30(220)	160(990)
(13)	70(500)	360(2300)
(14)	140(520)	650(2400)
(15)	320(1400)	1400(4600)
COMBINED RAT STUDIES	240(470)	1100(1900)
COMBINED ANIMAL STUDIES[4/]	17(—)	126(—)

1/ Incidence rates are based on the procedure of Mantel and Bryan (9), as modified by Mantel, et al. (10).

2/ Cannot be estimated.

3/ Numbers in parentheses are upper 99% confidence limits.

4/ Includes rats, rainbow trout, ducks, and tree shrews. See text. Risks are graphically estimated.

The upper 99% confidence limits on the lifetime risks derived from the studies in Table V are not only conservative risk estimates (i.e., they represent a "worst case" estimate), but also are useful for comparing the several studies since the confidence limits take into account differences in sample size and other variables in experimental design.

Although the results of these five rat studies are too variable to justify statistically their pooling, they have been combined in Table V to indicate an overall level of response in rat studies involving different strains.

Another approach to aflatoxin risk assessment based on animal studies is that taken by Cornfield, et al. (16). Combining data from experiments on the rainbow trout, duck, tree shrew, and six different studies on five different strains of rats, these authors fitted various mathematical models. A probit model with a slope of 1.2 probits per $\log_{10}$ dose appeared to give the best fit. Estimates from graphs in this paper yield lifetime incidence rates of approximately 17 and 126 per 100,000 for doses of 0.1 and 0.3 ppb, respectively.

As shown in Table IV, the average and maximum dietary intakes of aflatoxin contributed by peanuts are approximately 0.005 and 0.01 ppb, respectively. For the combined rat studies, the risk estimates for these aflatoxin levels are 2 and 7 per 100,000, respectively. Utilizing the Cornfield approach yields risk estimates on the order of less than 0.1 per 100,000 (graphically estimated) for the 0.005 and 0.01 ppb levels.

To assess the reasonableness of these animal derived risk estimates, it is of interest to compare them to the overall human liver cancer incidence rates in the United States. The total crude incidence per year of primary liver cancer in the total United States population, estimated in 1969, was $2.2/10^5$ (17). For purposes of comparison with the lifetime animal risk data, it is necessary to break down the above crude yearly incidence rate in terms of age-specific rates, to multiply each age-specific rate by a factor which reflects the proportion of the total liver cancer rate contributed by members of that age group, and then to multiply each such age-specific rate by the expected human lifespan of 70 years. Recombining the age-specific rates yields a calculated lifetime risk for liver cancer occurrence of 161 for every 100,000 in the total U.S. population. Primary liver cancer lifetime incidence rates in Alabama and Georgia, estimated in the same way, are $100/10^5$ and $103/10^5$, respectively (18). The rates for these two states, which are the only ones readily available for the southeastern states, are most appropriate for comparison with the risks estimated from the animal data since they represent the region with the highest anticipated exposure to aflatoxins.

The risks calculated from the rat data in Table V not only differ greatly among themselves, demonstrating an intraspecies difference in susceptibility, but, at the 0.3 ppb dose level, individually exceed the lifetime risks of primary liver cancer in the human population of the United States from all causes. Possible explanations for these differences are: 1) the level of human exposure to aflatoxin has been over-estimated; 2) the Mantel-Bryan extrapolation procedure is overly conservative in this case; and/or 3) rats may not be an appropriate model for predicting aflatoxin-induced

primary liver cancer in humans. While data to test the validity of the first or second explanation are not available, the third receives some corroboration from studies showing differences in aflatoxin metabolism among various animal species, most relevant of which are the differences between rats and humans observed *in vitro*. Available *in vitro* data indicate that the ability of an animal species to metabolize aflatoxin B_1 to a metabolite called aflatoxicol (AFL) is related to the sensitivity of the species to acute aflatoxicosis, and that the ratio of reductive and oxidative activities, measured as the ratio of AFL concentration to that of an oxidized metabolite known as Q_1, is an index of species susceptibility to the carcinogenic effects of B_1. Although *in vitro* data for humans are extremely limited, the data available indicate that, with respect to these modes of metabolic behavior, humans are closer to relatively resistant species such as mice and monkeys than they are to the highly susceptible rat strains (19).

b. Epidemiology Data: Data reflecting actual consumption of aflatoxin over defined periods of time by particular individuals who develop liver cancer are not available. The data most closely representing that situation are those derived from studies in Thailand (20), Kenya (21), Mozambique (22), and Swaziland (23). For two or more districts in each of these countries, average aflatoxin content in samples of meals actually consumed were determined. These estimates of average aflatoxin content were then correlated with official annual liver cancer mortality statistics. As previously stated, there are limitations to these epidemiology data, not the least of which is their inherent inability to establish direct cause-effect relationships. For example, any comparison based on these epidemiological data

rests on the assumption that sample meals are representative, that current contamination levels are indicative of past experience (i.e., 10-20 years ago), and that there is no significant exposure to other possible causes of liver cancer.

With respect to other possible causes, there is evidence that pyrrolizidine alkaloids consumed in herbal medicines and hepatitis-B virus may play a role in the etiology of primary liver cancer in some of the areas studies (24,25). Thus, the appropriateness of applying the human epidemiology data derived from these studies to low-incidence western countries is questionable. Several other interfering factors, well-described by van Rensburg (24), further cloud the epidemiological data. The calculations made below should be considered against this background of uncertainty.

The results of the various epidemiology studies have been standardized by van Rensburg (24) and these data are presented in Table VI. There is a highly significant positive correlation between cancer rate and estimated level of aflatoxin B_1 intake in the geographical areas studied, and a linear relationship between log aflatoxin B_1 level and cancer incidence, expressed as follows:

$y = 6.449 \log_{10} x - 2.4115$

where y = total cancer rate/10^5/year and x = aflatoxin concentration in ng/kg/body weight/day.

TABLE VI: Summarized Results of Epidemiology Studies Measuring Primary Liver Cancer Rate and Aflatoxin Intake (ng/kg body weight/day). (From Reference 24.)

Locality	Liver Cancer Rate (10^5/year)	Estimated Aflatoxin Intake (ng/kg body weight/day
Kenya - High Altitude	0.7	3.5
Thailand - Songkhla	2.0	5.0
Swaziland - Highveld	2.2	5.1
Kenya - Middle Altitude	2.9	5.8
Swaziland - Middleveld	4.0	8.9
Kenya - Low Altitude	4.2	10.0
Thailand - Ratburi	6.0	45.0
Swaziland - Lowveld	9.7	43.1
Mozambique - Inhambane	13.0	222.4

Using the estimated average and maximum chronic exposures for dietary levels of aflatoxins in the southeastern states (2.7 and 9.0 ng/kg body weight/day, respectively, Table IV) and the log relation between dietary aflatoxin and cancer incidence derived from the epidemiological studies, the calculated range in the expected crude cancer incidence/year is 0.37 to 3.74 per 100,000. The actual crude rates/10^5/year in Alabama and Georgia are 0.97 and 1.18, respectively (18).

It should be noted that the above calculations involve a significant assumption that quite possibly is not the case. They assume that the background liver cancer rate (i.e., that rate due to unknown factor(s) other than aflatoxin present in the areas of the epidemiological studies) is equal to that of the United States. Of course, there is also the implicit assumption that aflatoxin contributes to the rate of liver cancer in this country; there is no evidence that this is true. And certainly there are other substances in the environment, including the workplace, that are known to be hepatotoxic and could contribute to this disease rate.

In an attempt to reduce the effects of this possible error, a different type of risk estimate has been made. Specifically, a linear, non-logarithmic relationship, derived from the human epidemiological data tabulated by Peers and Linsell (26), allows estimation of the human cancer rate related to dietary aflatoxins (or to other interfering factors, since these epidemiologic studies cannot conclusively show that the increased rate of liver cancer above background is due only to dietary aflatoxin). The relationship is:

$y = .106\ x + 2.2$,

where y and x have the same meaning as above and 2.2 is the background cancer incidence/10^5/year when $x = 0$.

ESTIMATES OF RISKS AT ALTERNATIVE TOLERANCES

Using the last derived relationship, theoretical risk estimates have made for various aflatoxin levels that might result from alternative tolerances. These are shown in Table VII and are based on the assumption that the legal maximum level of aflatoxins in peanut products is directly proportional to the average level of aflatoxins actually found in these product For example, the current FDA action level of 20 ppb leads to survey estimate of average levels of 2 ppb in peanuts and peanuts products and 10 ppb in dry milled corn products. This information is based on data collected while the 20 ppb action level was in effect for all food commodities. If one assumes a direct proportional relationship, a reduction of the 20 ppb level to 15 pp for peanuts and peanut products could produce an average level of 1.5 ppb aflatoxins in this type of food. Similarly, a reduction of the tolerance to 10 ppb and 5 ppb could produce average levels of 1.0 ppb and 0.5 ppb, respectively. Since, for purposes of this assessment, the legal limit for corn is not under consideration, the estimated average level of aflatoxins in this food is held constant.

TABLE VII: Estimated Lifetime Cancer Rates Based on Epidemiology Studies - Incidence Rates Per 100,000 1/

	PEANUTS 2/			CORN 3/			TOTAL	
Aflatoxin Level	Risks Resulting From Daily Intake 4/		Aflatoxin Level	Risks Resulting From Daily Intake 4/		Risks Resulting From Daily Intak		
(ppb)	Average	Maximum	(ppb)	Average	Maximum		Average	Maximum
2	1.1	2.7	10	19.1	64.3		20.2	67.0
1.5	0.8	2.1	10	19.1	64.3		19.9	66.4
1.0	0.5	1.3	10	19.1	64.3		19.6	65.6
0.5	0.3	0.7	10	19.1	64.3		19.4	65.0

/ Based on Peers and Linnell (26). See text.

/ Aflatoxin levels are those which might be expected in peanuts and peanut products if the tolerance were reduced from the current 20 ppb to 15, 10, and 5 ppb, respectively.

/ Aflatoxin levels in corn products assumed to be an average of 10 ppb.

/ Incidence rate per 100,000 population.

As shown in Table VII, the theoretical cancer rates over a lifetime of exposure (70 years) are estimated for the Southeast to range from 20.2 to $67.0/10^5$ at the current 20 ppb action level; 19.9 to $66.4/10^5$ at a 15 ppb tolerance, 19.6 to $65.5/10^5$ at a 10 ppb tolerance and 19.4 to $65.0/10^5$ at a 5 ppb tolerance.

Thus, based on the epidemiological data (26), assessment of the estimat risk of human exposure to varying levels of aflatoxins in peanuts and peanut products shows relatively no significant gain in the protection of the publi health (i.e., reduction in liver cancer) by adopting a tolerance of 5 ppb (currently the lowest enforceable tolerance) as opposed to FDA's proposed tolerance of 15 ppb. This analysis applies to the population at highest risk, namely that of the southeastern United States.

In other areas of the country, where aflatoxin contamination of corn is not a significant problem, the health risks from aflatoxins are due, for the most part, to exposure to contaminated peanuts. The estimated lifetime risk to humans from this source of exposure only, based on the same type of calculations used to derive Table VII, ranges from 0.8 to $2.0/10^5$, if it is assumed that all peanut products contain 1.5 ppb aflatoxins (under the proposed 15 ppb tolerance). This theoretical lifetime risk of cancer would be reduced to $0.3-1.3/10^5$ at a 10 ppb tolerance and $0.3-0.7/10^5$ at a 5 ppb tolerance.

For the convenience of the reader, the lifetime liver cancer incidence rates listed in the foregoing tables are summarized in Table VIII.

TABLE VIII: Summary of Maximum Expected Lifetime Liver Cancer Incidence Rates Due to Aflatoxin Exposures Under Current FDA Guideline of 20 PPB

Actual Incidence Rates 1/

Total U. S. - 161 per 100,000
Alabama - 100 per 100,000
Georgia - 103 per 100,000

Estimated Incidence Rates Due to Aflatoxins

From Combined Rat Studies 2/

Total Consumption:	240 to 1100 per 100,000
Peanut Products Only:	2 to 7 per 100,000

From Combined Animal Studies 2/

Total Consumption:	17 to 126 per 100,000
Peanut Products Only:	Less than .1 per 100,000

From Epidemiology Studies 3/

Total Consumption:	20.2 to 67.0 per 100,000
Peanut Products Only:	1.1 to 2.7 per 100,000

1/ See Text, pages 15, 16.
2/ See Text, Table V.
3/ See Text, Table VII.

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CHEMICAL MANUFACTURERS ASSOCIATION EXHIBIT C

Consultants Comments

on

Individual Criteria Documents

AN EVALUATION OF THE PROPOSED AQUATIC LIFE CRITERION ON ARSENIC

Conclusion

It is suggested that the fish data be utilized to generate the freshwater criteria. There should be no criteria established for saltwater organisms.

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Summary Sheet

ARESENIC

EPA Criteria

Freshwater - 57 ug/l as a 24 hour average and 130 ug/l as the maximum concentration.

Saltwater - 29 ug/l as a 24 hour average and 67 ug/l as the maximum concentration.

Residues - No Residue Limifed Toxicant Concentration could be determined for fresh or saltwater since no maximum permissible tissue concentration for arsenic is available.

Conclusions

It is suggested that the fish data rather than the invertebrate data be used for deriving a freshwater criterion for the following reasons: 1) There is larger data base for the fish and 2) A portion of the invertebrate data may or may not be LC50 data. Therefore, the following criteria is proposed to protect freshwater organism. 1331 ug/l as a 24-hour average and the concentration should not exceed 3025 ug/l at any time.

There should be no criterion established for saltwater organisms since the data are meager and lack credibility.

General Comments

There is a fair data base for freshwater fish and a meager amount for freshwater invertebrates and saltwater organisms. The acute value for the freshwater invertebrate are used to establish the criterion for freshwater organisms rather than the chronic data.

Specific Comments

Page A-1. In surface freshwater in the U.S. the mean As concentration is 64 ug/l. 57 ug/l of As is the 24 hour average. Those discharges using average surface water will obviously exceed the 57 ug/l as a 24 hour average. Those discharges that utilize surface waters with As concentrations greater than 130 ug/l would never be able to discharge.

Page A-5. The top line of this page states that As has been shown to bioconcentrate in fresh and saltwater organisms, however, on page B-6 the documents states that As is not bioconcentrated. Also, on C-4 there is a table that shows no bioconcentration. The statement on page A-5 is incorrect and should be deleted.

Page B-3. The report by Hughes and Davis (1967) should be considered suspect since the As levels were not measured in the tests. With the large differences between their results and others it may be that they simply calculated incorrectly their final concentrations.

Page B-3. Line 5 from the top states that "All results are expressed as arsenic." In the original articles the toxicant were expressed usually as arsenate organic arsenic, etc.

Page B-4. Line 11 from the bottom begins a discussion of the geometric mean for Table 1. The EPA calculated a geometric mean of 17,239 ug/l for freshwater fish. With the same adjusted values, I arrived at a geometric mean of 11,860 ug/l. It is not clear as to how EPA arrived at their geometric mean.

Page B-4. Line 4 from the bottom begins a discussion of the data in Table 2 of the document. There are two points that need to

be made about the table. 1) Sanders and Cope (1966) did not generate LC50 values for D. pulex or S. serrulatus rather they estimated 48-hour EC50 immobilization values for these organisms. 2) The geometric mean for their adjusted values should read 3,166 ug/l and not 2,784 ug/l.

Page B-5. The chronic toxicity tests gave values higher than the adjusted acute values, therefore, the acute values were used to establish the criterion. This again appears to be a case of attemptin, to place the criterion at unnecessarily low levels.

Page B-6. The bioconcentration factors were all derived from unpublished data, therefore, little value can be placed on them.

Page B-8. The Final Fish Acute Value should read 3025 ug/l, The Final Invertebrate Acute Value should read 150 ug/l, The Final Acute Value should read 150 ut/l and 0.44 times Final Acute Value should read 66 ug/l.

Page B-12. The saltwater data are meager and lack credibility (no measurements were made), therefore, no criterion should be formulated

Criterion Formulation

It is suggested that the fish data rather than the invertebrate data be used for deriving a freshwater criterion for the following reasons: 1) There is larger data base for the fish and 2) A portion of the invertebrate data may or may not be LC50 data. Therefore, the following criteria is proposed to protect freshwater organism. 1331 ug/l as a 24-hour average and the concentration should not exceed 3025 ug/l at any time.

There should be no criterion established for saltwater organisms since the data are meager and lack credibility.

AN EVALUATION OF THE EPA AMBIENT WATER QUALITY CRITERIA DOCUMENT ON

ARSENIC

CONCLUSION: The criteria is appropriate for inorganic arsenic but the data does not support such a criteria for the organic arsenicals. The document should be revised in order to treat these two classes of arsenicals separately.

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GENERAL COMMENTS

The document, in the largest sense, represents a rather complete review of the literature on arsenic. Unfortunately, there appears to be an operating sense that everything ever written about the toxicity of arsenic must be reviewed. This makes the document cumbersome, causing substantial difficulties in interpretation. It is really ynnecessary to constantly repeat acute toxic effects and subchronic effects of As by individual reference to all of the studies reporting this information.

The major problem with the document is a reflection of the attempts to be encyclopedic. That is, there is no clear distinction made between inorganic and organic As. Whereas evidence for carcinogenicity is alleged for inorganic As, no such information is available on the organic arsenicals such as disodium methyl arsenic and monosodium methyl arsenic. A major problem in this regard is the problem of speciation of arsenicals in soil, water, etc. This should be addressed in the document so that the problem of criteria applying to inorganic As and those to organic As are dealt with separately. It might even be a good idea to deal with the two general forms in separate sections, bringing the sections together when establishing criteria. This is a critical point and the clarification must be made if the document is to be useful.

The means of derivation of the criterion per se seems to be O.K. considering the difficulty in dealing with an apparent human carcinogen in the absence of confirming animal data.

SPECIFIC COMMENTS

C-13 The citation of Holland (1904) is a good example of overkill.

C-7 Under Absorption, the statement that particles smaller than 0.1 um do not come out of suspension in the inhaled air stream is wrong. There is much newer data than that of Falk and Kotin which shows that smaller particles will impact on the alveolar surface.

C-8 The estimate by Stockinger and Woodward that 80% of ingested inorganic arsenic is absorbed, vs. 20% of inhaled As, is not an estimate -- it is a guess. And one made with no evidence to suggest that it is a good one.

AN EVALUATION OF THE

PROPOSED AQUATIC LIFE CRITERION ON

BENZENE

The criterion for freshwater is of dubious value and a criterion should not be set until better data are available. The criterion for saltwater should be based on empirical data rather than on extrapolation of freshwater data. This draft document is not as valuable as the previous document. Major criticisms include: 1) use of data not available for peer review; 2) high error in estimating final criterion values; 3) poor review of the pertinent literature; 4) bias in data selection, expecially for plants; and 5) mathematical errors in calculating geometric means.

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Aquatic Criterion

For benzene the criterion to protect freshwater aquatic life as derived using the Guidelines is 3,100 µg/ℓ as a 24-hour average and the concentration should not exceed 7,000 µg/ℓ at any time.

The data base for saltwater aquatic life is insufficient to allow use of the Guidelines. The following recommendation is inferred from toxicity data for freshwater organisms.

For benzene the criterion to protect saltwater aquatic life as derived using procedures other than the Guidelines is 920 µg/ℓ as a 24-hour average and the concentration should not exceed 2,100 µg/ℓ at any time.

General Comments

EPA is requested to read three documents previously submitted by the American Petroleum Institute (API) in response to the Water Quality Criteria "adjustment factors" published in the Federal Register (43[97]:21506; 1978). These comments from API are on the public record and they address the problems in trying to correct an inadequate toxicity data base.

It is unfortunate that EPA has chosen not to consider fate and effects which were included in the earlier draft document. Ambient levels of benzene that will impact on aquatic life will rarely occur because of its high volatility and the rapidity of microbial degradation (e.g., Howard and Kurkin, 1974). The natural degradation of benzene in water was estimated at 200 to 330 x 10^3 µg/ℓ/day (Lee, 1977, Prevention and Control of Oil Spills 1977: 611). The half life of benzene in a cubic meter of water was estimated to be 37.3 minutes if mixing was complete (McKay and Wolkoff, 1973, Environ. Sci. Tech. 7:611). To ignore these data while establishing water quality criteria based on "adjustment factors" is incredulous.

Some of the toxicity data are from EPA documents which have not been

subjected to peer review. These data also lack credibility because they were not collected following published EPA methodologies.

Specific Comments

Freshwater Organisms

p B-1

In reviewing the acute fish toxicity data the following references were ignored: Liebmann, 1960, Handbuch der Frischwasser und Abwasser Biologie. II. Oldenburg, Munich.

Hubault, 1936, C. R. Seanc. Acad. d'Agric. France 22:130.

Reichenbach-Klinke, 1967, Arch. Fish. Wiss. 17:122

Shelford, 1917, Bull, Ill. State Lab. Nat. Hist. 11:381.

Turnbull et al., 1954, Indust. Engineer. Chemistry 46:324.

Even if the above data were included in the final document the questionable test methods used by the cited authors may invalidate their use.

Table 1

Because the 24-hr LC50 values reported by Pickering and Henderson are not significantly different from the 96-hr LC50 values, why weren't the data corrected accordingly? If adjustments of data are to be used, they should be used accordingly.

p B-1 and Table 1

The geometric mean for fish acute toxicity data is wrong. It should be 22,348 µg/ℓ. Consequently the final fish acute value should be 5,730 µg/ℓ. The final fish acute value calculated to be 7,000 µg/ℓ has an approximate error in prediction of 128%.

p B-1

The *Daphnia magna* data should be available for public comment because this EPA funded study did not follow published EPA test methodologies.

In our opinion this is academically unsound. D. magna were not the only invertebrate tested. The mosquito Aedes aegypti (Berry and Brammer, 1977, Environ. Pollut. 13:229) has also been exposed to benzene.

p B-1 and Table 2

How do you derive a mean for one value? After adjustment the error in prediction may be as high as 295%.

p B-2 and Table 3

Again the study is not readily available for public comment. Presumably the test methodology is also questionable (e.g., benzene concentrations may have been nominal).

What good is the chronic value if no inhibiting levels were obtained?

The possible error in predicting a final invertebrate chronic value is 95%.

The explanation proposed to account for a chronic value higher than an adjusted acute toxic value is unbelievable. One of the two studies must be in error or this illustrates the problems in applying "adjustment factors".

Another geometric mean of one number.

p B-2 and Table 4

While the validity of the Chlorella data was questioned (Atkinson et al., 1977, Water, Air and Soil Pollut. 8:235), because of poor test methodology it is our opinion that algal tests conducted with cotton stoppered bottles (which allows exchange with the air) more closely approximate what may happen in nature. Lastly, the lowest level of benzene reported to exert an effect on Chlorella was 500,000 and not 525,000 ug/l.

There are three other studies on the effects of benzene to plants which should be examined for applicability in setting water quality criteria. These include studies on yeast (Levan, 1947, Hereditas 33:457), Elodea and Potamogeton (Frank et al., 1961, Weeds 9:515; Currier and Peoples, 1954, Hilgardia 23:155).

p B-2

Residues - The n-octanol/water partition coefficient is 134.9 and not 132 as reported (Chiou et al., 1977, Environ. Sci. Tech. 11:475; Friend, et.al., 1977, Environ. Health Perspect. 20:55).

Bioconcentration (BCF) data for benzene do exist for marine fishes (see below). To discuss BCF data for benzene may be unwarranted because benzene and/or its metabolites are rapidly depurated (see below).

p B-3 and Table 5

Why is the datum for Salmo trutta placed under miscellaneous when the 24-hr value could be corrected and placed in Table 1?

p B-4

The final chronic value derived by multiplying 7,000 µg/ℓ by another adjustment factor of 0.44 has an estimated error in prediction of 68%.

The final 24-hr average concentration criterion has an accumulated error in estimation of up to 175%. As such the calculated value should be raised accordingly if EPA persists in using these correction factors.

Because the maximum concentration is estimated to be 7,000 µg/ℓ and because the probable error of estimating this value is up to 128%, the final value should also be raised accordingly.

Saltwater Organisms

p B-10

We agree with the statement that unique effects may occur at benzene concentrations as low as 700 µg/ℓ; however, more research is needed. Struhsaker (1977) did admit that adult fish were collected from San Francisco Bay which is known to be polluted.

p B-10 and Table 6

In reviewing the acute fish toxicity, two references were omitted:

Brocksen and Bailey, 1973, Proc. Joint Conf. Prev. Control Oil Spills: 783.
Morrow et al., 1975, Copeia 1975:326.

There is an error in the geometric mean and it should be 8,147 µg/ℓ. Consequently, after dividing by 3.7 the value should be 2,201 µg/ℓ. The approximate error in predicting the Final Acute Fish Value is up to 175%.

p B-10 and Table 7

Under invertebrate acute toxicity the following references were ignored:

Barnett and Kontogiannis, 1975, Environ. Pollut. 8:45.
Benville and Korn, 1977, Calif. Fish and Game 63:204.
Donohue et al., 1977, Environ. Pollut. 13:187.
Eldridge et al., 1977, Calif. Nevada Wildlife Trans. 1977:90.
Hubault, 1936, C. R. Seanc. Acad. d'Agric. France 22:130.
LeGore, 1974, Diss. Abst. B 35(7):3168.
Potera, 1975, Diss. Abst. B 36(5):2010.
Price et al., 1974, JWPCF 46:63.
Neff et al., 1976, In Sources, Effects and Sinks of Hydrocarbons in the Aquatic Environment, p. 66-83.
Tatem et al., 1978, Est. Coast. Mar. Sci. 6:365.

The estimated error in predicting the Final Invertebrate Acute Value is up to 757%.

The datum in Table 7 for Tigriopus is wrong. The correct reference is Barnett and Kontogiannis (1975) and not Korn et al. (1976) who never studied

this copepod. The calculated 96-hr LC50 may be in error. Given the poor experimental design of this assay we feel that a 24-hr LC50 would be more accurate.

p B-11 and Table 8

The research reported for marine algae will not realistically apply to the real world because this research was conducted with sealed flasks. Volatile compounds, especially benzene, are rapidly lost to the atmosphere, etc.

Why were the data for Dunaliella left out of the document? At low concentrations benzene was stimulatory and at concentrations up to 100 mg/ℓ benzene had no effect on Dunaliella. The fact that these data were left out implies that there was bias in the selection of data.

It is also possible that Amphidinium growth was inhibited at concentrations of benzene as low as 0.001 µg/ℓ.

The authors of the document selected the data by Atkinson et al. (1977) for Skeletonema for the lowest effect on plants (20,000 µg/ℓ). This is interesting because the authors are the same as those in the other paper referenced (Dunstan et al., 1975). Because a) the research in both studies was conducted in the same laboratory by the same workers, and b) Atkinson et al.'s research was conducted at the same time as Dunstan et al.'s, why do these differences exist? This problem should be reconciled before placing confidence in the 20,000 figure.

p B-11

While no steady state BCF is available for benzene there are limited data to suggest that the estimated BCF of 24 may be too high. For example, after seven days marine eels concentrated benzene 15 times above ambient (Ogata and Miyake, 1975, Water Res. 9:1075). Other data are available for benzene and/or

its metabolites and these were included in the first draft but ignored in this draft. Why? Lastly, depuration of benzene is quite rapid so the discussion of a BCF of 24 probably is not warranted (Korn et al., 1976; Roubal et al., 1977, Arch. Environ. Cont. Toxicol. 5:513; Struhsaker, 1977).

The partition coefficient for benzene is higher than reported in this document (see above).

p L-11 and Table 9

There is a myriad of other literature on benzene which has been ignored by the authors of this document and they may be of value in setting water quality criteria. More data could be extracted from Struhsaker et al. (1974) and Struhsaker (1977).

The paper by Korn et al. (1976) was misquoted. The concentration of benzene was 6 µℓ/ℓ. When converted to µg/ℓ the value should be 5,300 and not 6,000.

p B12-13

We agree that no saltwater criterion can be derived for benzene "because no Final Chronic Value for either fish and invertebrate species or a good substitute for either value is available." Why then do the authors propose to apply Daphnia data which are both questionable and unavailable for peer review?

To multiply the Final Invertebrate Acute Value by 0.44 is to increase the potential error in predicting the final value by up to 804%.

The final 24-hr average concentration criterion has an accumulated error in estimation of up to 804%. We suggest that the final average concentration be increased accordingly.

The final maximum concentration has an accumulated error up to 125% so

the final maximum value should also be increased accordingly.

Summary

In spite of earlier problems, this document is not as valuable or as scientifically valid as was the earlier draft. The major criticisms include:

a) reliance on data for Daphnia which were poorly generated and not available for peer review,

b) high additive errors in estimating final criterion values because of the inadequate data base used to generate "adjustment factors",

c) poor review of the pertinent literature,

Conclusion

EPA should not persist in using "adjustment factors" to correct an inadequate data base. The errors in their calculations and data base are scientifically incredulous and indefensible.

If EPA persists in using "adjustment factors" to correct an inadequate data base, they should increase the final criterion values by the compounded error terms. Further, EPA should support research comparing predictions of final criterion values and empirically derived data to determine if their "adjustment factors" are valid.

Fate and effects of benzene should be considered before setting water quality criterion.

AN EVALUATION OF THE EPA AMBIENT WATER QUALITY CRITERIA DOCUMENT ON

BENZENE

CONCLUSION: Though this is a well-written document, there is no scientific information presently available which can justify setting the criteria at this proposed level.

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GENREAL COMMENTS

This report presents a comprehensive and critical evaluation of the data on benzene. However, it is inappropriate to set the criteria limit on the basis of ambient water level alone, since oral exposure represents only a minor route. Inhalation of benzene is a more significant problem. Oral intake may be important to toxicologically since adverse health effects of benzene are cumulative. Therefore ingested benzene, together with inhaled benzene, may pose a health problem. The authors indicate it would be appropriate to set the criteria level at zero. However, the authors suggest criteria based on the data available.

SPECIFIC COMMENTS

C-7 The data demonstrate that only trace levels of benzene have been found in water, and then in only a small percentage of the sources analyzed.

C-2 The reports on dietary intake of benzene conclude that this route of exposure is not considered to be a problem. However, fairly high levels are found in certain foods. This suggests a potential problem.

C-7 Benzene is extensively metabolized mostly via the MFO in the liver. It is these metabolites that are responsible for its toxicity. Since this system is inducible by benzene itself, as well as other compounds, a potential problem that warrants important consideration is the interaction of benzene with other compounds.

Benzene is metabolized to a highly reactive arene oxide intermediate. Since this compound covalently binds with cellular macromolecules, there is a

reasonably large potential for mutagenesis and carcinogenesis. This aspect needs further elucidation.

C-11 What types and at what concentration were the effects observed on the G-I tract?

C-11 -12 At what exposure levels and doses were these effects observed?

C-12 In Aksoy's study, the workers were exposed to benzene and to other compounds.

C-13 In Lange's study on the chronic effects of benzene on the immune system, the range of concentrations used was not presented.

C-15 The study on the effects of benzene on cell renewal rate is questionable, without more details. Evaporation of benzene may have occurred during the incubation thus changing the concentration to which the cells were exposed. Also, it is important to know whether the cells were constantly fed and new drug added or just counted daily.

C-15 As the authors point out, most human studies on health effects involve workers exposed to high concentrations of benzene as well as other compounds. The potential interaction of benzene acting either synergistically or antagonistically with other compounds is very important and warrants further investigation. This could be a significant factor in setting the criterion level.

C-15 No indication is given in Gofmekler's study on the route of exposure.

C-16 It is not clear how subcutaneous injections of benzene is relevant in the evaluation of its health hazard. The primary route of exposure is inhalation, and the criterion is for ambient water levels.

C-16 The fact that benzene was not mutagenic in the Salmonella/microsome <u>in vitro</u> assay is not a definitive evaluation of its <u>mutagenic potential</u>, since other known carcinogens are also false negatives in this system (i.e. metals).

The relevance of subcutaneous injections of benzene as a test for mutagenicity in Kissling and Speck's study is unclear.

The fact that the effects of benzene and toluene are additive is very

important and should be considered in setting the final criterion levels.

C-16 Ip. and subcutaneous injections do not seem relevant to benzene health hazards, except as potential *in vivo* assays.

C-17 Under what conditions (i.e. dose, time, duration, etc.) were the experiments on cultured human leukocytes conducted?

C-17 -18 How are the workers exposed to benzene and toluene separated, if they worked in the same plant?

C-18 -19 Lignac's study should not be included in evaluation of benzene since the routes of administration were inappropriate for the comparison to incidence of leukemia in humans. The fact that no controls were run severely limits the validity of data.

C-20 The data on leukemia induced by injection of benzene into the animals is not appropriate for comparison to human incidence of leukemia induced by inhalation of benzene.

The animal studies on leukemia, induced by inhalation of benzene, have proven negative. On the other hand, the human epidemiological evidence is strongly suggestive of a causal relationship. This may be due to the fact that most human cases involved occupational exposure to benzene mixed with a variety of other agents. As reported earlier, the effects of benzene are additive with toluene in toxicity studies. It may be a combination of benzene with some as yet unknown agent that is responsible for the induction of leukemia.

C-21 Although the authors suggest a convincing association between benzene exposure and leukemia, they indicate there are problems with the data. A significant problem is the role of related compounds and/or metabolites in the exposed patients.

C-21 -22 The case histories are only suggestive since the subjects were exposed to benzene and other compounds.

C-24 That benzene can produce Hodgkins disease at lower concentrations (150-210 ppm) suggests a potential synergism with other agents.

C-26 The retrospective studies of Girard and Revol, looking at history of benzene exposure and leukemia, may be limited.

C-28 The report by Thorpes is questionable since "potential exposure to benzene does not necessarily effect true exposures.

C-31 These patients might also have been exposed to other compounds that were synergistic with benzene.

AN EVALUATION OF THE PROPOSED AQUATIC LIFE CRITERION ON BERYLLIUM

The proposed criterion using logarithmic extrapolations as a measure of relative species sensitivity with water hardness is unacceptable for beryllium. This recommendation was based upon acute toxicity using the least squares regression of the natural logarithm for three fish species combined with the chronic value of one invertebrate (Daphnia magna). Data used from the two Daphnia studies could not be evaluated since both studies were not published in the open literature or available for review. These assumptions or judgments using slopes obtained from the relationship of hardness and toxicity require more testing before use in the establishment of water quality criteria.

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GENERAL COMMENTS

The criteria to protect freshwater aquatic life, which include the 24-hour average concentration, $e^{(1.24\ \ln\ [\text{hardness}]\ -\ 6.65)}$, and the maximum concentration at any time, $e^{(1.21\ \ln\ [\text{hardness}]\ -\ 1.46)}$, are unacceptable for beryllium. These data were based upon acute studies of three fish combined with chronic studies of one invertebrate (Daphnia magna). The experimental design and methodology for the Daphnia studies are not available for review and have not been published in the open literature. Until such data are reviewed by the scientific community and more organisms including fish are tested, the criterion document as proposed lacks credibility.

The criterion to protect freshwater aquatic life is based on only one invertebrate or cladoceran species and should be so stated.

It is agreed that no criterion for beryllium can be derived from the insufficient data available for saltwater aquatic life.

Specific Comments

p A-2. 1) The reference Sutt et al. 1950, which is missing in all reference sections, has not been located in the literature. Is the spelling and/or date of the reference correct?

p B-2. 1) The Slonim and Slonim 1973 study, as cited in the second paragraph, is not listed in any reference section of this document.

p B-3. 1) In paragraph 2, lines 7-9, the calculation leading to the assumption that there is "a range of species sensitivity to beryllium of only two-fold when corrected for hardness effects", is misleading. These corrected values were based on only three fish species. The slopes for the derived equations exhibit some degree of variability and are presented in the preceding paragraph. Therefore, when a geometric mean of these variable results is calculated and then used to calculate the intercepts for each species, the variability in intercept values is reduced.

2) In lines 6-8 of paragraph 3, the statement that "a similar relationship exists between acute beryllium toxicity and hardness for invertebrate species as was demonstrated for fish" may be true. However, the application of the fish acute mean slope (1.24) to invertebrate acute and chronic data on p. B-4 is questionable. This distinction is important because the final freshwater criterion is based on invertebrate chronic values that are modified by fish acute toxicity data.

3) The adjusted 48-hour LC50 value of 1,175 is 1,775 µg/ℓ in Table 2.

4) Acute toxicity data and chronic toxicity information (on p B-4) were taken from one species (*Daphnia magna*) in two studies (U.S. EPA 1978, and Kimball-Manuscript). Neither paper was a primary reference, being either an internal EPA document or one of unknown origin which was unavailable for review. Establish-

ing a standard from the response of only one species is considered inadequate, even if the studies in question were available for scrutiny.

p. B-4. 1) The word "realtionship" in the second and third lines of the last paragraph should be "relationship".

There are many errors in the citing of references in the text relative to their omission in the reference sections. It is assumed that for the sake of repetition, a reference was listed once in either reference section A, B, or C, instead of listing all references each time they appeared in their respective section of the text. If so, references cited in the text would supposedly be found just once in any of the three sections of reference. However, citations were referenced in more than one section (e.g., Wagner et al. 1969, Wagoner et al. 1978, Van Ordstand et al. 1945, U.S. EPA 1978, Van Cleave and Kaylor 1955, Gardner and Heslington 1946, Grier 1949, Berg and Burbank 1972, Barnes 1948, Branion et al. 1931, Loeb and Sirover 1977, Luke et al. 1975, Tepper 1972b, Toda 1968, Thornton 1950). These illustrations were taken by randomly selecting the first letter, "W", "V", "G", "B", "L", and "T", of authors' last names listed in both reference sections A and C.

Since references were listed more than once, it was assumed that each section had all references listed that were cited in that section. Unfortunately, reference section A failed to have

citations for: National Academy Science 1958, Tepper 1972a, Raven and Spronk 1953, Slonim 1973, Reeves 1965, Wagner et al. 1969, Sutt et al. 1950, and Mullen et al. 1972. In reference section B, the following were not listed: Tarzwell and Henderson 1960, Slonim and Slonim 1973, U.S. EPA 1978, Slonim and Ray 1975, Slonim 1973, and Jackim et al. 1970 (cited as Jackin).

There were also several important studies from which data were used in the establishment of guidelines which were not referenced in any section of the document. These included: Slonim 1973 (nine bioassays in Table 1), Slonim and Slonim 1973 (four bioassays in Table 1), Slonim and Ray 1975 (eight bioassays in Table 6), all of which were discussed and cited in the text. The basic premise for protection of freshwater aquatic life was based upon the mean slope (1.24) through the geometric mean toxicity value and hardness for each fish species. Much of this information was based upon Slonim's studies. Other missing references included Jackim et al. 1970 (reduced alkaline phosphatase activity in the mummichog) which is presumably Jackin et al. 1970.

The Kimball (Manuscript) reference in Table 2, concerning Daphnia magna mortality included no address of the authority in the literature reference. However, chronic effects of beryllium at 36 µg/ℓ and reproductive data for D. magna were utilized, adjusted, and manipulated to obtain slopes for chronic toxicity. This reference and the EPA 1978 study are unacceptable until made available for assessment of the experimental design. The reference

to Sutt et al. 1950 concerning human health effects was missing in all reference sections. It is assumed that Knejci and Schell 1966 (ionic behavior of beryllium to pH) is Krejci and Schell 1966, and that Nas 1958 (concerning human health) is Nash 1958. The document is difficult to evaluate and interpret from these discrepancies listed above.

A general review paper by Reeves 1977 ("Beryllium in the environment") should be included into the document. Another uncited paper by Eisler 1974 ("Radiocadmium exchange with seawater by Fundulus heteroclitus [L.] [Pisces:Cyprinodontidae]") related the exchange of beryllium from water into whole body residues relative to the concentration factor (0.66-0.85 from 5 to 50 mg/ℓ in water) of fish. Hildebrand and Cushman 1976 ("Toxicity of gallium and beryllium to developing carp eggs [Cyprinus carpio] utilizing copper as a reference") reported that hatching success of carp eggs was not inhibited by beryllium concentrations up to 0.08-0.09 ppm while no hatch was reported at 0.20 ppm. This study should also be incorporated into the document.

CRITERION FORMULATION

The guidelines used for establishing a final acute and chronic toxicity criterion from the Daphnia magna data represent only two values which are the minimal number which contribute to a mean (Tables 2-5). The adjusted LC50 value of 6,691 µg/ℓ (U.S. EPA 1978) from the LC50 of 7,900 µg/ℓ may be erroneous depending upon how it was calculated. The adjusted LC50 of 1,775 µg/ℓ from Kimball (Manuscript) differs from the value quoted in the text (1,175 µg/ℓ). It does not seem logical to assume that the Final Invertebrate Chronic Value derived from Daphnia data should become the Final Chronic Value since no chronic test data were available for fish. It is possible that Daphnia represent the most sensitive species.

Evaluation of the guidelines for establishing a final toxicity criterion cannot be completed at this time since important key data were taken from two improperly documented (manuscript form) or unreferenced studies which represented approximately 50% of the bioassays listed in Tables 1-6. Until these studies are properly referenced and/or published in the open literature with peer review, the criterion proposed lacks credibility.

MISSING AND ADDITIONAL REFERENCES

1. Eisler, R. 1974. Radiocadmium exchange with seawater by Fundulus heteroclitus (L.) (Pisces:Cyprinidontidae). J. Fish Biol. 6:601-612.

2. Hildebrand, S. G. and R. M. Cushman. 1978. Toxicity of gallium and beryllium to developing carp eggs (Cyprinus carpio) utilizing copper as a reference. Toxicology Letters 2:91-95.

3. Reeves, A. L. 1977. Beryllium in the environment. Clinical Toxicology 10:37-48.

4. Slonim, A. R. 1973. Acute toxicity of beryllium sulfate to the common guppy. J. Water Poll. Contl. Fed. 45:2110-2122.

5. Slonim, C. B. and A. R. Slonim. 1973. Effect of water hardness on the tolerance of the guppy to beryllium sulfate. Bull. Environ. Contamin. Toxicol. 10:295-301.

6. Slonim, A. R. and E. E. Ray. 1975. Acute toxicity of beryllium sulfate to salamander larvae (Ambystoma spp.). Bull. Environ. Contamin. Toxicol. 13:307-312.

AN EVALUATION OF THE EPA AMBIENT WATER QUALITY CRITERIA DOCUMENT ON

BERYLLIUM

CONCLUSION: The proposed Water Quality Criteria based on beryllium as a carcinogen is inappropriate. Experimental evidence does not show beryllium to be carcinogen when ingested. The document should be thoroughly revised.

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23 April 1979

GENERAL COMMENTS

A clearly stated purpose of these criteria documents is to establish levels of "exposure from all sources, not limited to drinking water and ingesting fish" (Fed. Reg., Vol. 44, p. 15975, 1979). This has not been accomplished for beryllium. Estimates for the abundance of beryllium in the earth's crust range from 2 to 10 ppm (Merck Index, 1978). The proposed standard is 0.037 µg/l (risk level of 10^{-5}) which is ~ 0.037 ppb or ~ 10,000 times lower than the element exists in nature. No estimate of <u>total</u> dietary intake of beryllium was made. Estimates were made for shell fish consumption, but no allowances were made for other dietary sources. For example, potatoes and tomatoes contain 0.17 mg/kg and 0.24 mg/kg, respectively, of beryllium (page C-1) and contribute to overall dietary intake.

To establish a water criteria standard for beryllium, a "natural background" level for exposure must be established. The human population has been exposed to low levels of beryllium since the beginning of time, when life originated on earth. Thus, a question is raised as to the basic validity of this document. EPA clearly states (Fed. Reg., Vol. 44, p. 15977, 1979) that risk levels are based on the extrapolation from a known effect level to zero exposure level. The major point is that a zero level of beryllium has never existed. In order to set any valid criteria, a "natural background" level of beryllium must be used and not zero.

The formulation of any legal criteria should be based on the best data available. This has not been done for the proposed standard on beryllium. The calculation of a safe exposure level for man is based on the consumption of two liters of water per day; therefore, the most appropriate route of compound administration in experimental animals must be by ingestion. The

proposed water standard has been calculated as if beryllium is a carcinogen. However, there is no recorded instance of cancer being produced by the ingestion of beryllium. Definitive feeding and drinking water studies (Schroeder and Mitchener, 1975, and others C-19) have demonstrated that beryllium at 5 ppm caused no change in the growth rate of mice or rats, longevity, or incidence of tumors. This is a no effect level at ~10,000 times higher concentration than the proposed standard. These negative data are extremely important because the oral route of exposure was used and this is the route of human exposure.

SPECIFIC COMMENTS

A-2 Reeves (1965) not included in reference list on page A-5.

A-3 Oral LD_{50} of 9.7 mg/kg mentioned, but no identification of test species.

A-3 In the third and fourth paragraphs, a variety of effects of beryllium are cited, but routes of exposure are not given.

A-4 The point that ingestion of beryllium has not been shown to cause cancer is important and is not accorded enough attention. In establishing a standard for water, any information dealing with ingestion should be examined closely. This is the route by which the human population would be exposed. It is also important because the results of oral versus inhalation tend to be very different.

A-1 Methodology for detection of beryllium has improved since 1967, and the 5.4 percent cited by Kopp and Kroner (page A-1) is probably on the low side. However, for those waters containing beryllium, the mean concentration is 0.19 ug/l. To meet the highest proposed criteria level (0.087 ug/l), these average concentrations would have to be lower by one half.

B-4 The final chronic value for beryllium has been calculated using some unusual assumptions, due to the lack of adequate data. Hardness data from acute fish studies (no chronic fish data) was combined with chronic data from Daphnia magna (no hardness data available) to establish the relationship of chronic toxicity values and hardness. No extrapolation factor or error calculation was made. Data derived from an invertebrate was applied directly to a vertebrate. No supporting data for this type of extrapolation was provided. Extrapolation from one fish to another is acceptable, but to consider Daphnia and fish as equal requires substantiating evidence.

B-6 The summary is an overt misrepresentation of the facts. The toxicity values and their relationship to hardness are presented as established fact when they are only rough estimates.

D-5 Under Residues - Table 4 should be changed to Table 5.

C-1 Some foods contain rather significant amounts of beryllium (potatoes, tomatoes, etc.). These values are mentioned but are never utilized in determining a total exposure level. This is not consistent with the clearly stated purpose of these criteria documents (Fed. Reg., Vol. 44, p. 15975, 1979).

C-2 A major error has been made in calculation of the bio-concentration factor. BCF has been measured only in bluegills. The EPA erroneously assumes that "Based on data for lead and cadmium, beryllium would probably have a lower BCF for fish and decapod muscle than for fish whole body, but probably would have a higher BCF for mollusks." It is ridiculous to assume that beryllium distribution can be derived from distribution data of lead or cadmium. I am not aware of any evidence that supports this assumption. In fact, data indicate that beryllium will behave more like magnesium or calcium. This is a critical error, since the BCF is used to calculate exposure.

C-19 IMPORTANT POINT: No record of any evidence of cancer due to beryllium ingestion.

C-25 Current levels of beryllium exposure are not correct, due to lack of incorporation of data concerning dietary sources other than seafood.

C-29 The use of a "one-hit" extrapolation model is inappropriate on two counts:

1. A zero level of beryllium has never existed.
2. Beryllium is not an established carcinogen orally.

The latter point may be related to a lack of absorption of beryllium in the gut.

Comments on the Aquatic Toxicity Section of the EPA Water Quality Criteria Document (March 15, 1979) on

Cadmium

Summary

It is important that the relationship of cadmium toxicity to water hardness has been used in establishing the freshwater criterion. The freshwater criterion values are properly derived under the proposed guidelines and appear to be approximately protective of aquatic life under laboratory conditions.

It is possible that a relationship between cadmium toxicity and salinity should have been derived. Otherwise, the saltwater criterion values are properly derived under the proposed guidelines; both the maximum concentration and the 24-hour average concentration were established on the basis of studies of *Mysidopsis bahia*, a mysid shrimp, and should be approximately protective of all tested species under laboratory conditions.

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Proposed Criteria - Aquatic Life

For cadmium the criterion to protect freshwater aquatic life as derived using the Guidelines is $e^{(0.87 \ln (\text{hardness})-4.38)}$ as a 24-hour average (derived from the fish chronic slope and the invertebrate chronic datrum) and should not exceed $e^{(1.30 \ln (\text{hardness})-3.92)}$ (the final fish acute value) at any time.

The following table illustrates the criterion for representative hardness values.

Hardness mg/l	24-hour average µg/l	Maximum µg/l
20	0.17	0.97
40	0.31	2.4
100	0.68	7.9
500	1.76	33.

For cadmium the criterion to protect saltwater aquatic life as derived using the Guidelines is 1.0 µg/l (the final invertebrate chronic value) as a 24-hour average and the concentration should not exceed 16 µg/l (the final invertebrate acute value) at any time.

Our Conclusions

It is important that the freshwater criterion values were adjusted for the apparent relationship between cadmium toxicity and water hardness.

In the freshwater criterion, the maximum concentration is derived properly according to the proposed guidelines, but this involves a considerable downward extrapolation of the slope from the range of cadmium concentrations for which it was derived. The maximum concentration appears to be at realistic excursions above the 24-hour average concentration in most of the range of water hardness. The 24-hour average concentration is set as high as the available data will permit, and appears to be approximately protective under laboratory conditions for all the species tested. Although no scientific support is provided for applying the fish chronic slope to the invertebrate chronic datum, failure to extrapolate some slope would result in a much more stringent 24-hour average value at high levels of water hardness.

In the saltwater criterion formulation, it is likely that a relationship between cadmium toxicity and salinity could have been derived using published data, not all of which was tabled in the document, at least for fish acute and invertebrate acute values. The criterion formulation process was otherwise followed properly for both the maximum and the 24-hour average values. Both components of the saltwater criterion are based on studies of *Mysidopsis bahia*, a mysid shrimp. The criteria appears to be approximately protective of tested species under laboratory conditions.

General Comments

The literature on cadmium toxicity to aquatic life seems to be both extensive and difficult to summarize. The authors of this document seem to have accomplished a great deal of good work and deserve to be commended. There are, however, a number of loose ends, some of which warrant comment here. The relationship of cadmium toxicity to other water quality parameters, such as hardness, alkalinity, pH and salinity seems to warrant complex as a description. Specific comments will be addressed to several of those points.

The separate consideration of freshwater and saltwater studies tends to obscure an interesting relationship (backed up by very few data) between cadmium concentrations and the developmental stages of striped bass, which are normally anadromous, although land-locked populations exist in the United States. The available data suggest that some other anadromous fish are very sensitive to cadmium, at least in freshwater. Thus, that topic may warrant discussion in terms of use classifications for specific water bodies before any application of the criteria is made in developing water quality standards.

The document authors seemed to presume that inconsistent relationships of cadmium toxicity with other water quality parameters were "contradictory." At least in terms of logic, such relationships are merely subcontraries; as such, it is conceivable that rather different physiological mechanisms are involved in fairly distantly related taxa.

In comparing this document with the equivalent document for lead, it appears that there are inconsistencies in the flexible application of the guideline procedures for developing criteria. This perhaps warrants reconsideration of the procedural flexibility both within and between documents.

It appears that rather rigid application of the guideline procedure for rejecting literature may have been made. For example, a study of the Australian subspecies of a mussel is retained (same "species" as in North America), but a study in which deionized distilled water was used in diluting seawater (rather than as the dilution medium for the toxicant) was not included.

In summary, this is a respectable draft of the criteria document. Perhaps comments by us and others will aid the authors in developing a revised document.

Specific Comments

Introduction (ppA-1 to A-4)

The seawater value from page C-7 should be incorporated in the first paragraph.

The only values attributed to Eaton 1974 in the Aquatic Toxicology section are for chronic toxicity; Carroll et al., 1979 does not appear in the aquatic toxicology references. Perhaps better references for acute toxicity could be used here if they are needed at all.

Aquatic Life Toxicology (B-1 to B-60)

Freshwater Organisms (B-1 to B-27)

Introduction (B-1 to B-4). The discussion of the aqueous chemistry of cadmium warrants the citation of references, and perhaps some expansion to consider the work by McCarty, et al., 1978.

Acute Toxicity (B-4 to B-7)

The work by McCarty et al., 1978 and other papers warrant comment as to the relationship between toxicity and hardwater. There is some basis for suspecting that alkalinity rather than hardness is related to the mechanism of reduced hardwater toxicity. Moreover, the data suggest that, at least in static tests, the average concentration to which organisms are exposed over 96-hours is much less than the initial measured value in hardwater (perhaps less than 10% of the initial measured value). This is at least enough to question the correction factor for static tests, and perhaps also to require time averaging of the exposure concentrations for studies done in hardwater.

The studies by Hughes (1973) on early stages of striped bass do not appear to be readily accessible. It could be useful to know whether these are from an anadromous or a landlocked population.

Studies on fish which can be either landlocked or anadromous could usefully be categorized by the source population, since this also applies to steelhead. Anadromous fish may be under greater physiological stress in freshwaters, and hence

more sensitive to toxic stresses. All the very low LC_{50} values are from species which are (at least partly) anadromous, and these determine the final fish acute, which is also the Final Acute Value. The fresh acute values for cadmium are much more valuable than the guideline species sensitivity factor provide for.

In the tabulated invertebrate studies, there is no positive support relating hardness to toxicity, and the rotifer data show no evidence that this relationship would hold. Marshall (1979) reports as 48 hour EC50 for *Daphnia galeata-mendotae* which could be considered for inclusion here. The invertebrate data may be only about half as variable as the guidelines sensitivity factor suggests. The application of slopes derived for fish to invertebrates is unsupported by this document, although required by the guidelines.

Chronic Toxicity (B-7 to B-9)

The chronic fish values are very low relative to the same species in acute tests, and the tabulated range of chronic values is only a 56-fold difference, compared to several orders of magnitude in the acutes. Hence, these data reflect a very different portion of the equiblibrium chemistry of cadmium than the data for which multiple hardness values were used to adjust acute tests results. Thus, it does not seem unreasonable (nor is it contradictory) to have only a possible (but non-significant) hardness to toxicity relationship for brook trout and no apparent relationship for channel catfish. Indeed

the adjustment may not be warranted at such low cadmium concentrations, in which case there is a question as to whether an "overall relationship" can be established under the guidelines, when this is coupled with our previous concerns about the actual exposure concentrations in hard water in the fish acute studies.

Given the data and procedures used in Table 3, the species sensitivity factor of 6.7 does not appear unreasonable for the observed range of variation. It is not clear, however, how the application factor comparison is made, since section X of the guidelines is bypassed if the Final values are related to water quality.

The final invertebrate chronic value depends solely on a very low value obtained with *Daphnia magna* which may well be even further out of the range of a cadmium to water hardness relationship than the chronic fish values. We consider it to be unscientific to apply the fish chronic slope to the invertebrate chronic data, both because the change in concentrations involved modifies the thermodynamic equilibrium and because no relationship of water hardness to invertebrate toxicity has been established in this document. (Separate comments address this aspect of the guidelines.) We note that because this was one of the sensitive species in acute studies, the species sensitivity factor was not applied by the agency in determining the final invertebrate chronic value in freshwater. Marshall (1979) notes that studies on *Daphnia galeata mendotae* give results comparable to those for *Daphnia magna*.

Table 7. Some of the longer-than-acute values, such as for rainbow trout, warrant comment since they are as large as the LC_{50} value reported in acute studies, sometimes by the same authors. This is just another aspect of the overall confusing picture of cadmium toxicity. The three spine stickleback poses an opposite problem, perhaps suggesting that the final chronic may not be fully protective.

Saltwater Organisms (B-28 to B-47)

Acute Toxicity (B-28 to B-30)

The salinity to toxicity relationship is more complicated than the document indicates, in that at salinities below 20‰ (Voyer, 1975) or 15‰ (Eisler, 1971), mummichogs are also less resistant to cadmium than at 15‰ or 20‰; moreover, Middaugh and Dean (1977) did not regard the differences in cadmium toxicity from 20‰ to 30‰ salinity as meaningful for mummichogs or Atlantic silversides. Hence, it may be that high salinities are protective in more nearly an asymptotic than an exponential fashion, as would be consistent with data on *Palaemonetes pugio* (Sunda, et al., 1978). The development of additional data across the range of estuarine salinities may help to clarify whether this relationship, which could be expected on the basis of the chemistry of cadmium, can be established.

The range of 7.5-fold for only four species is not inconsistent with the species-sensitivity factor, but the document does point out that these species represent only two

families of fish. Hence the evaluation of the species sensitivity factor for this application should, as stated, await more data.

In the invertebrate data, one could question the inclusion of Ahsanullah's (1976) data on the Australian subspecies of the edible mussel, even though it is the same nominal species, but this certainly has no meaningful affect on the final invertebrate value.

The omission or exclusion of data on *Palaemonetes pugio* from Sunda, et al., 1978 is perhaps more significant in that differences in cadmium toxicity were found at different salinities; hopefully this paper was overlooked rather than excluded by a very rigid interpretation of the last sentence in Section II.E of the Guidelines. Their data do suggest that cadmium is relatively more toxic to *P. pugio* at low salinities (ca. 5‰) than at salinities near that of seawater.

The Final Invertebrate Acute Value is based on the single flow-through study by Nimmo, et al., 1977a.

Chronic Toxicity (B-30 to B-31)

The document comments on the relatively small difference found between the acute and chronic values for *Mysidopsis bahia*. However, similar small acute to chronic shifts are indicated for the very sensitive freshwater fish and invertebrates, which can perhaps be coupled with knowledge of the equilibirium chemistry of low versus high concentrations of total cadmium.

In developing the Final Invertebrate Chronic Value in freshwater, the species sensitivity factor was not used because one of the most acutely sensitive species was the basis of the chronic value. Here, in the same setting, the species sensitivity factor has been applied. It seems reasonable to evaluate the invertebrate chronic without the sensitivity factor prior to setting criterion value potentially lower than necessary for the protection of saltwater life.

Bioconcentration:

It appears from Guideline Section XIV.B that the oyster bioconcentration limit, relative to human emetic response, of 5 µg/l would be a candidate for setting the Final Chronic Value if the Final Invertebrate Chronic Value were set at 5.5 µg/l instead of at 1 µg/l.

Miscellaneous:

Dawson et al., 1977 did not regard the decrease in enzymatic activity as a toxic response, but rather as an adaptive response within the range of cadmium concentrations which would be non-toxic to juvenile striped bass in estuaries. Hence, the only potential question from Table 13 data raised below 5 µg/l is for larval fiddler crabs (Vernberg, et al., 1974); that paper suggests that most of the potential for reduced survival from exposure to 1 µg/l of cadmium would be under suboptimal temperature and salinity conditions. Perhaps that study is sufficient justification for lowering the Final

Chronic Value in saltwater from 5 µg/l to 1 µg/l, as was done by invoking the species sensitivity factor in computing the Final Invertebrate Chronic Value.

Table 8. Eisler (1971) reports additional 96-hour LC_{50} values for mummichog not given in this table.

Additional References

Sunda, W.G., et al. 1978. Effect of Chemical Speciation on Toxicity of cadmium to grass shrimp, *Palaemonetes pugio*: Importance of free cadmium ion. Environmental Science and Technology, 12(4):409-413.

Marshall, J.S. 1979. Cadmium toxicity to laboratory and field populations of *Daphnia galeata-mendotae*. Bulletin of Environmental Contamination and Toxicology, 21:453-457.

AN EVALUATION OF THE EPA AMBIENT WATER QUALITY CRITERIA DOCUMENT ON

CADMIUM

CONCLUSION: This criteria document appears to be scientifically sound and requires only minor revision.

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23 April 1979

General Comments

This document contains a number of errors. These will be addressed under the specific comments section.

The subjects of mutagenesis and carcinogenesis (C-39 to C-57) were well addressed in this criteria document. The conclusion that "the case for cadmium as a carcinogen is not persuasive when the existing data are critically reviewed" (C-62) and the recommendation that cadmium not be considered a suspect human carcinogen (C-62) appears to be scientifically sound on the basis of current data. It is also appreciated that this document recognizes that "since cadmium is an element, it will not be destroyed and may be expected to persist indefinitely in the environment in some form" (A-2). This point is often lost in regulatory activities.

Although thorough in some areas, this document has shortcomings in others. No mention has been made as to the effect of water treatment on levels of cadmium in finished water. Linstedt et al (J. Water Pollut. Control Fed. 43:1507-1513, 1971), Nilsson (Water Res. 5:51-60, 1971), Furukawa (EPA 902/9-34-001, 1973) and others have indicated that cadmium is efficiently removed (greater than 90%) under a variety of treatment conditions. Since most surface water supplies for large populations are subjected to treatment that includes coagulation, sedimentation, filtration and disinfection, it is necessary to know what effect these processes would have on the concentration of cadmium in finished water.

It is surprising that there is no mention of the recent (1977) NAS Safe Drinking Water Committee report entitled "Drinking Water and Health". Cadmium is discussed on pages 207-208, 211-213, 220-222, 236-241, 302-303, and 305-306 of this document.

This NAS report has been used and accepted as a guideline for drinking water standards. It should at least be accorded a reference in this criterion document. Other references have also been neglected and some have not been appropriately quoted. Examples of this are given in the special comments section of this report. It appears that this criterion document should be revised to insure that the data concerning cadmium is thoroughly covered.

Specific Comments

A-2 Good point. Cadmium can not be destroyed and may be expected to persist indefinitely.

B-1 First sentence reads as if no natural fresh waters have concentrations higher than 0.01 µg/l. If this is true, it should be clearly documented. In an EPA survey of 14 ground water and 69 surface water supplies, the levels of cadmium ranged from 0.2 to 12 µg/l.

C-7 Good point. Drinking water contributes relatively little to man's total daily cadmium intake (3-4 µg/d).

C-8 Only 5% of ingested cadmium is absorbed.

C-7 This page contains the only mention of removal of cadmium from drinking water in the entire document. This section clearly should be expanded. NAS' report on Drinking Water and Health and general comments section of this report should be consulted.

C-20 -24 Most of this data concerns health effects of industrial exposure to cadmium. While interesting, it should have little impact on standard formulation because it is an inappropriate route of exposure (inhalation vs oral).

C-33 Reproductive effects. I am somewhat familiar with this area of literature and, without effort, there were at least four pertinent articles concerning cadmium's effect on reproduction that were not cited or discussed.

Lee and Dixon, 187:641-652, J. Pharm. & Exp. Therap. 1973

Chiquoine, 149:23-36, Anat. Rec. 1964

Chiquoine, 10:263-265, J. Reprod. Fert. 1965

Allanson, 24:453-462, J. Endocrinol. 1962

C-40 A paragraph is accorded the Friedman and Staub (1976) in vivo mutagenic assay. The results are explained away "due to cadmium's ability to impair testicular blood supply". However, if one reads this paper, one finds in addition to the 10mg/kg acute exposures which are discussed in this document, Friedman also treated animals at 1 mg/kg for four weeks which is not mentioned in this document. Although I do not believe this discrepancy should have any significant inpact on the proposed standard, it does indicate that the document should be thoroughly revised to insure that all information from a cited reference is used and evaluated properly.

C-68 From the data presented, I feel the concluding statement of the document is appropriate. "From this analysis it appears that a water criterion needs to be no more stringent than the existing Primary Drinking Water Standard (10 ug/l) to provide ample protection for human health.

A review of proposed ambient water quality criteria for carbon tetrachloride

Recommendation: A weak supporting data base leaves the exact freshwater criterion open to debate. Data for marine life are significantly less complete and the methods utilized in developing the criterion are neither scientifically nor statistically defensible.

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A Review of Proposed Ambient Water
Quality Criteria for Carbon Tetrachloride

Freshwater and Marine Aquatic Life

The criterion to protect freshwater aquatic life for carbon tetrachloride was derived using procedures other than the recommended guidelines. The criterion is established as 620 ug/l for a 24-hour average and the concentration should never exceed 1400 ug/l at any time. The supporting data base leaves the exact criterion open to debate.

Data for marine life are significantly less complete and the methods utilized in developing the criterion are neither scientifically nor statistically defensible.

Specific Comments

Freshwater species data consist of one Daphnia and two bluegill static acute tests, and a fathead minnow embryo-larval assay. LC50 data for the two bluegill tests vary from 27,300 ug/l to 125,000 ug/l for 96 hr. exposures indicating that volatilization of the test material significantly affects results. Although the unmeasured test concentration correction factor was used for all test results, the extreme volatile nature of this compound significantly detracts from the interpretation of these data. Additionally, employing geometric means based on one or two LC50 values in the formulation of the criterion number can result in an error term approaching 200-300%.

A minimum of toxicity data indicate that carbon tetrachloride is apparently not as toxic to marine life as freshwater life, however, the procedures outlined in the criterion document for development of the Marine Final Acute Value are not defensible. Averaging toxicity data for bromoform, methylene chloride and chloroform to develop a correction factor to be applied to carbon tetrachloride is a procedure unspecified in any of the guidelines and it can be argued that the resultant criterion is in no way indicative of effects of carbon tetrachloride. We caution that even structure: activity correlations have their predictive limits.

EVALUATION OF THE HEALTH EFFECTS SECTION
OF THE CRITERIA DOCUMENT FOR
AMBIENT WATER FOR

Carbontetrachloride

Conclusions: The methodology used for the derivation of the health based criterion for carbontetrachloride may not be appropriate. The significant toxicological literature on carbontetrachloride is well reviewed.

Prepared by:

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May 10, 1979

General Comments:

The criterion document is very well written and represents an excellent review of carbontetrachloride (CCl_4) toxicity. However, the criterion developed on the basis of animal models and an extrapolation model for carcinogenic risk may not be appropriate.

Specific Comments:

Page C-5, Second Paragraph. The units describing the application rate of CCl_4 (80 mg/l) do not make any sense.

Pages C-64 to C-67. If one evaluates the proposed criteria in light of occupational exposures at the TLV level of 10 mg/m^3, the following apparent paradox occurs.

Exposure at TLV:

10 mg/m^3 (TLV) x $10m^3$ (inhaled air/8 hr) x $\frac{5}{7}$ (work week/total week) x 0.75 (assumed efficiency of absorption) = 53.6 mg/day or 53,600 ug/day.

Exposure at extrapolated risk of 10^{-5}:

2-6 ug/l (21 + 69 (BCF) x 0.0187) = 8.55 ug/day

Risk/dose = $10^{-5}/8.55 = 1.77 \times 10^{-6}$

Extrapolated risk at a rate of intake equivalent to the TLV for a life time:

$P = 1 - \exp(-1.17 \times 10^{-6} \times 53{,}600) = 0.061$

Thus, about 6% of all people exposed for long periods to CCl_4 at the TLV are extrapolated to develop cancer within their life time. Such an increase might or might not be readily detected by ordinary epidemiological methods. However, many people have

been exposed for long periods to CCl_4 at concentrations even higher than the present TLV. Also, all experimental data indicate that CCl_4 produces malignant tumors almost exclusively in the liver in all species and strains in which it has been found to be carcinogenic. However, the incidence of primary liver cancer in man is very low, even in most industrially-exposed populations. Consequently, one must conclude that an anomaly exists in either the animal model or the extrapolation model. The process selected to establish criteria for compounds found to be carcinogenic in animal models may not be directly applicable to CCl_4.

AN EVALUATION OF THE PROPOSED AQUATIC LIFE CRITERION ON CHLORDANE

The document presents criteria that are derived from a relatively large data base for aquatic organisms. A major criticism concerns the applicability of using the FDA limit for chlordane in animal feed to calculate the RLTC for both fresh and saltwater life. The final values for the 24-hour average criteria are several orders of magnitude below the reported acute and chronic values for fish and invertebrates. This information, in conjunction with the cited evidence that a rapid turnover of certain chlordane isomers occurs in aquatic organisms, suggests that the reported RLTC values may be overprotective. Until more work is reported concerning the biological half-life and toxicity of chlordane isomers, the final 24-hour average criteria should be listed as tentative or amended to include final chronic values.

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May 1, 1979

GENERAL COMMENTS

The key data used to establish the criterion to protect freshwater aquatic life (0.024 µg/ℓ chlordane as a 24-hour average) is estimated from the calculated Residue Limited Toxicant Concentration (RLTC). This RLTC value is based upon a calculation of the FDA limit for chlordane in animal feed and the bioconcentration factor of invertebrate data which was lower than the Final Fish and Invertebrate Chronic Values. The FDA limit for chlordane in animal feed applies to substances eaten by animals that may ultimately be consumed by man.

The maximum concentration (0.36 µg/ℓ) for the protection of freshwater aquatic life is based upon a calculated final acute toxicity value for invertebrates taken from several studies since values for fish were higher.

To protect saltwater aquatic life, the 24-hour average concentration of 0.0091 µg/ℓ was estimated from the calculated RLTC taken from only one fish species and no invertebrate data and should be so stated. Limitations in the data base available should also be mentioned.

The maximum concentration (0.18 µg/ℓ) for protection of saltwater aquatic life is represented by the final acute toxicity value which is taken from six species of invertebrates reported from four references. Although a final acute toxicity value (3.2 µg/ℓ) was available for fish, the invertebrate value was lower and used instead.

Specific Comments

p B-1, Paragraph 2

1) Some recent work has reported bioconcentration data of chlordane for freshwater fish (see Roberts et al. 1977, Veith et al. 1977, Moore et al. 1977).

p B-1, Paragraph 3

1) The implication that a chemical formulated as a pesticide will not be harmful to aquatic plants is unjustified. Moore et al. 1977 demonstrated that some algae (Ankistrodesmus amalloides) have a maximum bioconcentration value which greatly exceeds that of freshwater fish (5,500 vs 162, respectively). Biggs et al. 1978 showed that 10 µg/ℓ chlordane reduced algae growth rate and ^{14}C uptake per unit of chlorophyll a. Therefore it cannot be stated that the effect of chlordane on aquatic plants is "not important".

p B-3, Paragraph 3, Line 2

1) The sentence should read; ... "showing 2.5 times greater toxicity in 96 hour intermittent flow-through tests." A pulsed injection of chlordane should not be confused with a continuous application, for lethal responses would be different.

p B-3, Paragraph 3, Lines 5-8

1) This sentence needs slight modification, such as: "The adjustments for static conditions, unmeasured concentrations, and a 24-hour instead of a 96-hour test were made, which resulted

in an LC50 equal to 3 µg/ℓ for freshwater fish." The calculations from Naqvi and Ferguson 1970, which standardize the reported 24-hr LC50, varied from 7.8-436 ppb but are not presented. These values are quite important for an adequate formulation of the criteria.

p B-2, Paragraph 2

1) A recent article by Rao et al. 1975 may contribute to the knowledge concerning the susceptibility of common carp to chlordane. The 96-hr TLm of 2.9 µg/ℓ for carp is much lower than that of Ludemann and Neumann 1960. Unfortunately the journal (Anz. Schadlingskunde) was not readily available, so a comparison of methods was not possible.

p B-4, Paragraph 2, Line 15

1) The Guidelines say that bluegill "are among the less sensitive of the species acutely tested" to chlordane. However, according to Katz 1961, they are more sensitive than chinook salmon, coho salmon, rainbow trout, fathead minnow, goldfish and guppy. For reasons unknown, LC50 of 22 µg/ℓ for bluegill was omitted from Table 1 as were the last three species mentioned above. These data should be included.

p B-19, <u>Plant Effects</u>

1) There is a reference for aquatic plants, Biggs et al. 1978. In this study, 10 µg/ℓ adversely affected plant physiology. The final plant value of 1,000 µg/ℓ may therefore be too high, although the final criterion of 0.0091 µg/ℓ should provide adequate protection for aquatic plants.

p B-6, Residues

1) Roberts et al. 1977, in a study not referenced in the document, demonstrated that the tissue retention of chlordane in fish is directly proportional to the adiposity of the fish. However, it was also shown that transfer of pre-exposed fish to insecticide-free water resulted in a rapid elimination of chlordane, perhaps through the gills, feces or kidneys (Moore et al. 1977). This rapid turnover raises the possibility that an RLTC of 0.024 µg/ℓ may be overprotective. However, a radical reappraisal cannot be made until the toxicity of the different isomers, which vary in biological half-life (Roberts et al. 1977), is documented.

p B-14, Table 5

1) The 24-hour average concentration is the Final Chronic Value of 0.024 µg/ℓ. This number was based on Residue Limited Toxicant Concentrations from Cardwell et al. 1977. If one inspects Table 24 on page 67 of that study, it is difficult to understand how all the concentration factors (CF) were derived. For example, the CF factors for heptachlor were derived from the heptachlor content per measured chlordane concentration in water. However, in using the same approach for the remaining columns (chlordenes, cis-chlordane, trans-chlordane, cis-nonachlor, and trans-nonachlor) different CF values are obtained from those found in Table 24.

p B-18. 1) The statement, "The LC50 value of 0.18 µg/ℓ, which is about two times lower than the lowest value in Table 2", should be corrected in that Table 2 should be Table 8 (12-13th

lines of paragraph one).

2) On lines 13-14 of the same paragraph, the statement, "Since there are data for only four species", should be corrected to read, "Since there are data from four studies" ...

p B-20. 1) A new paper recently published by Zitko 1978 demonstrates bioconcentration in saltwater organisms; measured levels for chlordane (µg/g in lipid tissue) were reported for several organisms:

Lobster	0.078-0.1
White Shark Liver	2.6
Herring	0.039-0.114
Redfish	0.179
Atlantic Salmon	0.226

Several of these residues could exceed the accepted limit for chlordane in animal feed. However, the data are limited in that these numbers represent single determinations. It is important to note that lobster residues were similar to levels measured in commercial fish.

p B-29. 1) The volume number of the Henderson et al. 1959 reference in the Trans. Amer. Fish. Soc. should be volume 88.

p B-30. 1) The Mehrle et al. 1974 reference is incorrect. Volume 2 of the Bull. Env. Contam. Toxicol. does not include a page numbered 513.

p B-31. 1) The Naqvi and Ferguson 1970 reference is incorrect. Volume 4 should be changed to volume 99.

CRITERION FORMULATION

Guidelines for establishing a 24-hour average concentration (0.024 µg/ℓ) for protecting freshwater aquatic life were based upon the maximum permissible tissue concentrations established by the FDA in animal feed divided by the geometric mean bioconcentration factor for two invertebrate species (Daphnia magna and Hyallela aztecа). These RLTC data, which represented only one study, were one to two orders of magnitude lower than fish and invertebrate final chronic values. Although no data in Table 6 contradicted the conclusion that 0.024 µg/ℓ will adequately protect invertebrates, the final chronic value calculated for fish (0.24 µg/ℓ) was also lower than any reported effect upon aquatic biota in the studies referenced and may also protect aquatic life.

The maximum concentration (0.36 µg/ℓ) not to be exceeded at any time for the protection of freshwater aquatic life was lower for invertebrates than for fish. Data for ten fish species and five invertebrate species were available which represented several studies. This concentration appears to be reasonable from the data base present.

In developing the 24-hour average concentration of 0.0091 µg/ℓ for the protection of saltwater aquatic life, no RLTC or final chronic value information was available for invertebrates. The bioconcentration factors comprising the RLTC were taken from juvenile and adult fish of one species reported from three studies. It is recommended that these limitations in the data base be

stated.

The recommendation that the maximum concentration (0.18 µg/ℓ) to protect saltwater aquatic life, as estimated from the final acute toxicity value for invertebrates, is reasonable from the data base of fish and invertebrate studies available.

MISSING OR ADDITIONAL REFERENCES

1. Biggs, D. S., R. G. Rowland, H. B. O'Conners, Jr., C. D. Powers and C. F. Wurster. 1978. A comparison of the effects of chlordane and PCB on the growth, photosynthesis, and cell size of estuarine phytoplankton. Environ. Poll. 15:253-263.

2. Moore, R., E. Toro, M. Stanton and M. A. Q. Khan. 1977. Absorption and elimination of ^{14}C-alpha and gamma-chlordane by a freshwater alga, daphnid and goldfish. Arch. Environ. Contam. Toxicol. 6:411-420.

3. Rao, T. S., M. S. Rao and S. B. S. K. Prasad. 1975. Median tolerance limits of some chemicals to the fresh water fish "Cyprinus-carpio". Indian J. Environ. Hlth. 17:140-146.

4. Roberts, J. R., A. S. W. DeFrietas and M. A. J. Gidney. 1977. Influence of lipid pool size on bioaccumulation of the insecticide chlordane by northern redhorse suckers (Moxostoma macrolepidotum). J. Fish. Res. Bd. Canada 34:89-97.

5. Veith, G. D., D. W. Kuehl, F. A. Puglisi, G. E. Glass and J. G. Eaton. 1977. Residues of PCB's and DDT in the western Lake Superior ecosystem. Arch. Environ. Contam. Toxicol. 5:487-499.

6. Zitko, V. 1978. Nonachlor and chlordane in aquatic fauna. Chemosphere 1:3-7.

COMMENTS ON THE PROPOSED HUMAN HEALTH CRITERION FOR

Chlordane and Heptachlor

by

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CONCLUSION: The ambient water quality criterion based on the NOEL-Safety Factor approach (30 µ/l) appears to me to be more appropriate for these agents than the risk extrapolation values based on the questionable NCI mouse hepatoma study.

GENERAL COMMENTS:

The key issue in establishing a human health criterion for both chlordane and heptachlor is the question of whether either or both of these pesticides are potential human carcinogens. The NCI data which is reviewed in this document demonstrates that both agents are capable of producing hepatomas in mice, and the NAS expert pathology group convened to re-examine the pathology slides and conclusions of the NCI agreed with this effect in mice. The NAS committee concluded further, however, that neither of these agents produced liver tumors in rat studies and this, together with questions about the predictability of carcinogenesis assays in mice, raises doubts about the carcinogenicity of chlordane-heptachlor in man. If these agents are not human carcinogens, then the proposed standard is inappropriate and the human health criterion can be established using the conventional safety factor approach (a criterion of 30 µg/l is calculated in this report using this NOEL-safety factor approach). Even if chlordane and heptachlor are assumed to be potential human carcinogens, there are still questions as to how the mouse data should be extrapolated to estimate human risk. The approach used in this series of criterion documents has been discussed elsewhere and need not be repeated here.

In view of the controversy concerning the potential carcinogenicity of chlordane and heptachlor for man, it would seem to be preferable at present to use the criteria based on the NOEL for setting the chlordane-heptachlor ambient water quality criterion.

AN EVALUATION OF THE PROPOSED AQUATIC LIFE CRITERION ON CHLORINATED NAPHTHALENES

Document is of greater value than the previous document because the criterion was based on 1-chloronaphthalene and not on mixtures as was the original criterion. Major criticisms include the use of data not available for peer review and high additive errors in estimating the final criterion values because of using the "adjustment and sensitivity factors" in deriving the final numbers. Because the criterion are based on single data points without confidence limits the criterion should be listed as tentative or not listed at all.

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May 10, 1979

AQUATIC CRITERION

For 1-chloronaphthane, the criterion to protect freshwater aquatic life, as derived using procedures other than the Guidelines, is 29 µg/l as a 24-hour average and the concentration should never exceed 67 µg/l at any time.

For 1-chloronaphthalene, the criterion to protect saltwater aquatic life, as derived using the Guidelines, is 2.8 µg/l as a 24-hour average and the concentration should never exceed 6.4 µg/l at any time.

GENERAL COMMENTS

EPA is requested to read three documents previously submitted by the American Petroleum Institute (API) in response to the Water Quality Criteria "adjustment factors" published in the Federal Register (43(97):21506; 1978). These comments from API are on the public record and they address the problems in trying to correct an inadequate toxicity data base.

It is unfortunate that EPA uses data collected for an EPA contract that was not available for peer review. Further, these data lack credibility because they were not collected following published EPA methodologies (i.e., static tests and concentration of toxicant was unmeasured).

EPA should be commended for setting criteria for 1-chloronaphthane instead of for chlorinated napthalenes in general. They appear to have corrected their previous lack of adequate literature coverage.

SPECIFIC COMMENTS

Freshwater Organisms

p B-1, Introduction

The available LC50 and EC50 values for the bluegill, Daphnia,

and algae are similar only after the animal data were "adjusted." These animal data were obtained from experiments not using recommended EPA procedures. Because of the gross errors with the "adjustment factor" concept and data base, EPA should refrain from making conclusions from "corrected" data.

p B-1, Acute Toxicity

Acute toxicity data which were not available for peer review and which had to be "adjusted" should not be used to set water quality criteria for 1-chloronaphthalene. The compounded error in predicting the bluegill value is up to 128% while for the Daphnia datum it is up to 295%.

How can you have geometric means of single numbers?

p B-2, Plant Effects

Again, we are given data that were not available for peer review. This is scientifically unjustified. The use of a "lowest" plant value even though the two numbers presented in Table 3 aren't different is not justified. Are the differences significant? Given the problems in counting algae we would like to see confidence intervals for the algal data.

What happened to the datum for yeast that was presented in the earlier version? Just because the LC100 was 48.8 milligrams per liter the datum shouldn't be ignored.

p B-2, Miscellaneous

Again, the data are from an EPA document not readily available for peer review.

p B-3, Summary of Available Data

We agree that there are no data available for establishing freshwater criterion. To multiply the invertebrate acute datum (with up to 295% error) by 0.44 increases the error of prediction by up to 340%.

p B-4

It is true no adverse effects of 1-chloronaphthalene have been reported - because they haven't been studied.

p B-4, Criterion

The 24 hr average value of 29 micrograms/l has an error in prediction of up to 340%. If EPA persists in using "adjustment factors," EPA should raise the predicted 24 hr average value by the error terms. More importantly, EPA should use predicted concentrations with caution because empirically obtained data are lacking.

The maximum concentration has an error of prediction of up to 295%. If EPA persists in using "adjusted" data, then they should raise the predicted value accordingly. Reliance on data not available for peer review is scientifically unjustified.

Saltwater Organisms

p B-9, Introduction

EPA should be commended for admitting that data for commercial mixtures are not useful in setting criterion.

Again, the toxicity data for fish, invertebrates, and algae are said to be comparable but only after "adjustment." Given the errors in prediction by using the "adjustment" value it is doubtful that the numbers are comparable.

p B-9, Acute Toxicity

Again, there are geometric means of single values. The error in predicting the fish value is as high as 125%, while for the invertebrates, it may be as high as 757%.

p B-10, Chronic Toxicity

Again this study is not available for peer review. To set a criterion based on these data is academically unsound.

Because comparable MATC values were not available for saltwater fishes why did EPA persist in dividing the datum by 6.7 (See Table 5: FR 43(97):21514), which was for freshwater fish.

The possible error in dividing by a 6.7 "adjustment factor" is up to 180%.

p B-10 Plant Effects

Again the reference is not available for peer review. If there are no significant differences in the EC50 values, why was the lowest value chosen?

p B-10, Miscellaneous

The data in Table 10 indicates that EPA has reviewed the literature but if the criterion is for 1-chloronaphthalene then are these data necessary?

p B-11 and 12, Criterion

To set a criterion from one datum that is not available for peer review and that has been conducted using methods other than those recommended by EPA is academically questionable. The error in predicting

the 24 hr average value is as high as 804% and for the maximum concentration it is as high as 757%. If EPA persists in using "adjustment factors", then EPA should raise the final values accordingly.

SUMMARY

This document is of greater value than the previous document because the criterion was based on 1-chloronaphthalene and not on mixtures, etc. as was the original criterion. However, major criticisms of this document are:

a) reliance on toxicity data which were not available for peer review and were not collected using published EPA methods.

b) high compounded errors in estimating final criterion values because of the inadequate data base used to generate "adjustment factors."

CONCLUSION

EPA should not persist in using "adjustment factors" to correct an inadequate data base. The errors in their calculations and data base are scientifically incredulous and indefensible.

If EPA persists in using "adjustment factors" to correct an inadequate data base, they should increase the final criterion values by the compounded error terms. Further, EPA should support research comparing predictions of final criterion values and empirically derived data to determine if their "adjustment factors" are valid.

EVALUATION OF THE HEALTH EFFECTS SECTION
OF THE CRITERIA DOCUMENT
FOR AMBIENT WATER
FOR

Chlorinated Naphthalenes

Conclusions: The basis for the criteria is very weak. The bioconcentration factor was not appropriately derived. There are insufficient data to establish numerical criteria.

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May 10, 1979

General Comments:

The section on human health and mammalian toxicology clearly summarizes most of the known toxicology of the chlorinated naphthalenes. The paper appropriately attempts to establish criteria for five different chlorinated naphthalenes rather than to establish a categorical criterion. However, the basis for the derivation of the proposed criteria is very weak. This is especially true for the bioconcentration factor.

Another deficiency of the criterion document is the lack of an evaluation of the contribution of impurities, such as the dibenzofurans, to the observed toxicity of the chlorinated naphthalenes.

Detailed Comments:

Page C-7. A bioconcentration factor of 4,800 for Halowax 1014 is most certainly too low by more than one order of magnitude. The study in brown shrimp is inadequate to derive a meaningful bioconcentration factor.

Page C-20. There is no indication how the threshold limit values were derived and how they relate to levels of chronic exposure which have produced marginal effects and to levels which have produced no effects.

Page C-22. As a result of the uncertainties associated with the TLV's the acceptable daily intakes, which were calculated using the Stockinger-Woodward model, must be considered very tentative.

Page C-23. Because of the known deficiencies in the data for bioconcentration coefficients, it is not possible to derive believable criteria that include fish consumption. The criteria given are probably too high, but it not possible to derive more accurate criteria at the present time.

AN EVALUATION OF THE PROPOSED AQUATIC LIFE CRITERION ON CHLOROFORM

Conclusion

Due to the extreme lack of data for Chloroform in regards to aquatic toxicity testing and the fact that the meager amount of data did come from unpublished reports make it impossible to generate acceptable criteria for fresh and saltwater organisms.

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April 12, 1979

Summary Sheet

CHLOROFORM

EPA Criteria:

Freshwater - 500 µg/l as a 24-hour average and 1,200 µg/l as the maximum concentration.

Saltwater - 620 µg/l as a 24-hour average and 1,400 µg/l as maximum concentration.

Residues - Shown not be an environmental hazard to aquatic life.

Conclusions:

Due to the extreme lack of data for Chloroform in regards to aquatic toxicity testing and the fact that the meager amount of data did not from unpublished reports makes it impossible to generate acceptable criteria for fresh and saltwater organisms.

General Comments

The key data used to establish the aquatic life criteria are from unpublished EPA contracts. Until such data are published in the open literature, the criteria as proposed lack credibility.

The "fudge factors" utilized and the concept behind these "fudge factors" are rather maddening. The numbers were derived from a wide variety of tests utilizing a variety of test organisms and compounds. It is simply unscientific to apply these factors to the data presently available for chloroform.

The EPA in applying the "95% factor" often use a geometric mean derived from only one value. Not only is it silly to say a mean has been derived from one number, but statistically it is completed unsound to rely on one number. Fortunately, the geometric mean and the number are identifical.

The fact that the EPA is relying on one data point to arrive at the Final Acute Value for both fresh and saltwater and the Final Chronic Value for freshwater renders the data quite suspicious. It is conceivable that a rather low number was generated at the invertebrate tests and if more tests had been performed values similar to the unadjusted LC50 fish values may have been generated. Also, it appears that the large numbers used to divide the geometric mean of the adjusted values will insure that the invertebrate data will always generate the Final Acute Value.

Specific Comments

p. B-1. (1) The fact that the chloroform levels in all the tests were not determined reduces the credibility of the tests a great deal.

(2) The work by Bentley, et al. (1975) is not available and cannot be properly evaluated. This is true, also, for the EPA (1978) work.

p. B-3. Fish Invertebrate Acute Value should read Final Invertebrate Acute Value.

p. B-9. I find it ludicrous that EPA is attempting to formulate a criterion for chloroform in saltwater from one unpublished data point.

Criterion Formulation

Due to the extreme lack of data for chloroform in regards to aquatic toxicity testing and the fact that the meager amount of data did come from unpublished reports makes it impossible to generate acceptable criteria for fresh and saltwater organisms.

EVALUATION OF THE HEALTH EFFECTS SECTION OF
THE CRITERIA DOCUMENT FOR
AMBIENT WATER FOR

Chloroform

Conclusions: The methodology used for the derivation of the health based criterion appears to be inappropriate for chloroform. The significant toxicological literature on chloroform is adequately reviewed.

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May 10, 1979

General Comments:

The criteria document on chloroform constitutes an appropriate summary of the known toxicological information. The methodology used for the derivation of the health based criterion may be inappropriate for the reasons noted under Specific Comments.

Specific Comments:

Page C-6. The calculation of the hypothetical levels of chloroform in beef cannot be supported because it involves too many assumptions. The calculation violates many principles of pharmacokinetics, especially in ignoring excretion and compost mentalization into lipids.

Page C-23, First Complete Paragraph. This is a very significant statement. But it is presented without data on the incidence of congenital abnormalities or the identity of the anaesthetic vapors involved.

Pages C-42 to C-44. The total daily exposure for a risk of 10^{-5} is 2.1 ug/l(21 + 14(BCF) x 0.0187) = 4.75 ug. Therefore, the risk/dose is 2.11×10^{-6}.

At the current TLV of 9.8 mg/m^3, the adjusted daily exposure is $9.8\ mg/m^3 \times 10m^3 \times 0.75 \times \frac{5}{7}$ = 52.5 mg or 52,500 ug/day.

According to the risk estimate provided based on the criteria document, the single-hit model applied to life-time exposures equivalent to the TLV would result in a risk of cancer of

$$P = 1 - \exp(-52{,}500 \times 2.11 \times 10^{-6}) = 0.10$$

or a 10% chance of cancer due to TLV level exposures. It should

be considered that the TLV has been dropped to 9.8 mg/m^3 only recently, and that many people have had higher exposures than this. However, there is no evidence that chloroform has resulted in a 10% incidence of cancer in occupationally-exposed people. Consequently a discrepancy exists in the relationships between the animal model, the extrapolation model, and the human experience. The overall approach for setting criteria for substances found to be carcinogenic in animal tests may not be applicable to chloroform in the exact form that has been proposed by the EPA.

AN EVALUATION OF THE PROPOSED AQUATIC LIFE CRITERION ON 2-CHLORO PHENOL

Conclusion

For protection of aquatic life the criterion should be based on toxicity and not taste. From the data presented a value of 1800 ppb is determined to be the number that should not be exceeded in a 24 hour period. A final chronic value needs to be derived in order to finish the criteria.

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June 1, 1979

GENERAL COMMENTS

The criteria state 60 µg/L as a 24 hour average for protection of freshwater aquatic life. This is misleading as the number is based on fish taste, hence, has little or no bearing on toxicity. If taste is to be used as a limiting number, then it should be so stated in the criteria.

Basing the excursion number that should not be exceeded at any time on invertebrate data is overprotective. With the rapid generation time of freshwater invertebrates it is inconceivable that a brief excursion from the ambient level will significantly alter the quality of water.

A more defensible excursion number would be either: 1) the final fish acute value of 1800 µg/L, or 2) an invertebrate number that is designed with a safety value of 10-15% of the population rather than 95%.

COMMENTS ON THE PROPOSED HUMAN HEALTH CRITERION FOR

2-Chlorophenol

by

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CONCLUSION: Organoleptic effects are not toxic effects, and thus are inappropriate as a basis for human health criterion setting. If the toxicity data for this agent is inadequate to establish an ambient water quality criterion for 2-chlorophenol, it should be so stated. Organoleptic effects are appropriate for establishing regulatory criteria but should not be used to establish human health-related criteria based on presumed toxic effects.

GENERAL COMMENTS:

The human health criterion for 2-chloro phenol is stated to be based on the organoleptic properties of this agent because of the lack of toxicity data in animals or humans. Organoleptic effects do not constitute toxic effects and in my opinion do not provide a sound basis for establishing human health standards.

There is fairly complete data on the acute toxicity of 2-chloro phenol and there is, in addition, information on the effects of human exposure to this agent as the result of spills, etc. Thus, the statement on page C-20 that, "There are no reports of human or domestic animal toxicoses from accidental or intentional exposure to 2-chlorophenol." is incorrect. The paper by Baker et al. in the Archives of Environmental Health (March, 1978, pg. 84 to 94) refers to human health effects of a phenol spill in which other phenol derivatives were present and a similar situation has occurred in Sturgeon, Missouri, a few months ago (documented in the files of the Regional EPA office in Kansas City, Mo.). The references in the Deichman papers listed in the criterion document also contain some human exposure data. It appears that the authors of this criterion document were focusing on papers dealing with industrial exposure to 2-chloro phenol and thus did not look to the poison control or accidental spill reports in the medical literature as a source of toxicity data for 2-chloro phenol in man. Poison control reports usually are not very satisfactory for establishing toxicity standards in the absence of supportive animal toxicity studies, but in this case it is possible to make some fairly firm predictions on the basis of the documented structural-activity correlations within the phenol derivatives. Such predictions would be more meaningful than predictions based on subjective criteria such as odor and taste which have no clear relationship to injury, tissue damage or adverse effects on human health. If the animal toxicity data and the human exposure information are inadequate,

an appropriate recommendation would be to obtain additional toxicity information before attempting to establish such criteria.

SPECIFIC COMMENTS:

Page C-1. Reference to potential industrial exposure does not indicate the route.

Page C-14. Suggests that inhalation exposure is not a general population threat. Inhalation exposure is a major factor in most spill situations since dermal exposure is well documented and generally protected against. In the Sturgeon, Missouri, situation, for example, only one of the workers involved in cleaning up the contaminated track area exhibited dermal effects, but all of these workers plus the 800 people living in the town inhaled the fumes from the spill for a period of several weeks.

The document suggests that chloracne could occur as a result of exposure but there is no documentation for this and such an effect has not been reported, to my knowledge. The proposed criterion for human health is over two orders of magnitude below that proposed for aquatic life. The data referenced in this report does not support this magnitude of sensitivity for aquatic life when compared to mammals. There is a lack of consistency in the recommendations for the phenol derivatives included in this series of ambient water quality criteria documents. It would seem to be more appropriate to consider all of these agents as a group in view of their metabolic and toxicologic similarities and to make general recommendations for the group.

EVALUATION OF THE PROPOSED AQUATIC LIFE CRITERIA ON DICHLOROBENZENES

Conclusion: The alternative procedures (44 FR March 15, 1979; Appendix B-1) used to establish water quality criteria for dichlorobenzenes have not been adequately verified. Consequently, criteria based on these procedure are not scientifically defensible.

Prepared by:

Carl F. Muska

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May 23, 1979

General Comments.

Due to the general lack of aquatic toxicity data for dichlorobenzenes, EPA has relied heavily on the alternative procedures (44 FR March 15, 1979; Appendix B-1) for estimating water quality criteria for this group of compounds. The assumptions used to justify these alternative procedures have not been adequately verified. The practice of extrapolating toxicity data for one compound (in this case 1,2-dichlorobenzene) to structurally similar compounds (1,3-and 1,4-dichlorobenzene) is a questionable validity and should not be considered as a substitute for actual test data.

Specific Comments

Page B-1

When generalizations are made concerning the toxicity of a compound, the type of toxicity should be specified (i.e., acute, chronic). For example, comparable data for the bluegill, Daphnia magna and Selenastrum capricornutum suggest no appreciable differences in the acute toxicity of 1,2-, 1,3 and 1,4-dichlorobenzene. Chronic toxicity data are available for only 1,2-dichlorobenzene. Similarly, the data in Table 1 indicate that the position of chlorine atoms on the benzene ring does not appreciably influence the acute toxicity of dichlorobenzenes. The influence of chlorine atom position on the chronic toxicity of dichlorobenzenes has not been studied.

Page B-2

The document refers to the chlorinated benzene criterion document for details concerning the relationship between degree of chlorination and acute toxicity. This document was not available for review.

The adjusted 48-hour EC50 (Daphnia magna) for 1,3-dichlorobenzene (23,800 µg/l) is more than an order of magnitude greater than the adjusted 48-hour EC50 for 1,2-dichlorobenzene (2,070 µg/l). Yet, in the Introduction section (p. B-1), the document states that the data suggest ... "no appreciable differences in the toxicity of 1,2-, 1,3- and 1,4-dichlorobenzene." Order of magnitude differences in acute toxicity are generally considered "appreciable."

Page B-6

The data used to formulate criteria are from an unpublished EPA source (U.S. EPA, 1978).

The Final Acute Values are based on data for only two aquatic species - bluegill sunfish and Daphnia magna. This is an extremely limited data base; toxicity data on more species are needed.

The data used to derive the sensitivity factors for fish (3.9) and invertebrates (21) should be carefully revaluated to determine whether the difference between these factors actually reflects a greater range in sensitivities to toxic materials for invertebrates as compared to fish or is a function of the methods used in the Guidelines for calculating the sensitivity factors.

Page B-8

No Final Chronic Value for either 1,3- or 1,4-dichlorobenzene is derived using the Guidelines because no chronic toxicity data are available. The rationale used by EPA for estimating Final Chronic Values for these compounds is as follows: since the experimentally determined Final Fish Chronic Value for 1,2-dichlorobenzene (150 µg/l) is greater than .44 times the Final Acute Value, the 24-hour average criteria can be estimated for other dichlorobenzenes by multiplying 0.44 times the Final Acute Value. This procedure (44 FR March 15, 1979; p. 15973, 2.A.) implicitly assumes that because 1,2-dichlorobenzene is structurally similar to 1,3-and 1,4-dichlorobenzene it can be expected that 0.44 times the Final Acute Value will be less than a Final Chronic Value based on actual test data. There is no basis for this assumption. Criteria should not be formulated until appropriate chronic toxicity data are available.

Page B-20

No chronic toxicity data with saltwater species are available; yet, 24-hour average criteria are estimated based on alternative procedures (44 FR March 15, 1979; Appendix B-1). The assumptions used to develop these alternate procedures have not been adequately studied.

AN EVALUATION OF THE EPA AMBIENT WATER QUALITY CRITERIA DOCUMENT ON DICHLOROBENZENES

CONCLUSION: The criteria established for dichlorobenzene is too low and is not defensible based upon the paucity of experimental toxicity evidence cited.

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23 April 1979

General Comments

The present criteria document contains a very comprehensive (i.e. in terms of the published literature), although superficial, review of the specific literature on dichlorobenzenes. It is difficult to evaluate the usefulness and validity of many of the studies reported since the information presented is inadequate. For example, details of the experimental protocols (i.e. dose of DCB, duration, number of animals, route of administration, etc.) are often lacking. The data on carcinogenicity and mutagenicity is particularly noteworthy in this regard. The potential carcinogenicity or mutagenicity of DCB is significant since it may be converted to reactive intermediates. However, the data are lacking. The tests systems reported were inappropriate (compared with the current standard testing procedures), uncontrolled, and the doses used very high (greater than those used in the acute and chronic animal studies reported).

The criteria value presented is low, and probably not defensible due to the paucity of experimental details on the acute toxicity of DCB, and the lack of well-controlled chronic toxicity tests. It is important to note that the authors of this document conclude that "there is not sufficient evidence from human or animal tests to qualitatively suggest that DCBs are carcinogenic or mutagenic in mammals."

A major potential health concern might be the interaction of the DCBs with other exogenous and endogenous compounds, since DCBs can induce MFO (mixed function oxidases) in the liver. This could be a factor in setting the criteria values.

A major concern with most of the studies reported is that very high doses were required to produce toxic effects. Expected exposure levels were lower by orders of magnitude.

C-1 Although more highly halogenated benzenes have been shown to be persistent in the environment, the data suggests that this is unlikely with DCBs.

C-2 Table 2 is difficult to comprehend without more detail.

C-5 The data included on air contamination is minimal. Other pesticides appear to be a much greater problem than DCBs.

C-13 -16 There is a paucity of experimental details. Evaluations cannot be made. The doses used in these studies were very large.

C-16 A potential concern with DCBs is their lipid solubility and persistence in the body (cumulative toxicity). Concern is lessened since these compounds are metabolized extensively.

C-18 The animals were intubated with 1,2-DCB dissolved in water. It has been previously reported that these compounds are highly lipid soluble. The water solubility data are questionable.

C-22 As the authors indicate, no data are reported, just supposition. However, the fact that unmetabolized DCBs may form active nucleophilic arene oxide intermediates warrants further investigation, particularly since it is these compounds that would be involved in carcinogenicity and mutagenicity.

C-23 -24 The number of reported cases of DCB poisoning is very small (22) and these were mostly occupationally related. The toxicities resulted from acute and

chronic exposures to very high levels of DCBs. The intoxicated individuals were exposed to other substances.

C-32 -33 The details on drug metabolism presented are not relevant.

C-38 -41 The discrepancy between Hollingsworth's and Varsharskaya's data is significant. Since the route of exposure in the latter study is not mentioned, an evaluation cannot be made.

C-39 & C-42 The relevance of using subcutaneous or i.m. injections of DCBs to evaluate their health hazard is not clear, since the primary routes of exposure to these compounds are innalation and oral.

C-45 A potential toxic effect of these compounds is in their interaction with other compounds. This needs more evaluation.

C-52 -58 The available relevant data on teratology, carcinogenicity, and mutagenicity is minimal and a formultion of a criteria value based on the data presented would be limited. No information is available on teratology, and no biochemical studies on mutagenesis have been conducted. Chromosomal aberrations were only reported at very high doses of the chemicals and many of the studies appear to have been done quite crudely without regard to established scientific protocol.

C-54 1,2-DCB was not found to be mutagenic in the Ames assay (Salmonella typhimurium). This is not conclusive evidence (see recent review by M. Jacobs, J. Environ. Path. & Tox. 2:1205-1215, 1979). These compounds, in the appropriate concentration and duration of exposure may be mutagens. Furthermore, some false negatives have been reported in the Ames test. The tests reported here did not include a drug metabolizing or activating system, and since it is the reactive oxide intermediates of DCBs that are suspect of carcinogenic and

mutagenic activity, you would not expect these compounds to be positive.

C-54 The tests for carcinogenicity are also lacking. The skin test is not an appropriate test for either the tumor-producing or tumor-promoting activity of potential carcinogens.

Although the studies suggest that there is a potential for carcinogenicity, a more rigorous evaluation of the activity of the DCBs using established testing protocols is essential in order to evaluate these compounds properly and establish an appropriate criteria.

AN EVALUATION OF THE PROPOSED AQUATIC LIFE CRITERION ON DICHLOROETHYLENES

Conclusion

The only numbers that can be developed using the guidelines are the maximum concentrations. Chronic numbers need to be developed using the procedure outlined by the Agency.

Prepared by

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June 1, 1979

1,1 Dichloroethylene

The final acute value based on two experiments using Daphnia magna must be suspect until the differences between the experiments are resolved. As a general comment it is difficult to accept Daphnia magna as a representative of the total invertebrate population and using the safety factor of 21 to account for species variation. At best the final value as listed in the criteria should have a confidence interval of about 6, i.e., the 1200 could just as well be 7200.

Much more confidence can be placed on the final acute value of 16,000 µg/L.

As the guidelines indicate, no final chronic value can be estimated until the experiment is conducted. We do not agree that the factor 0.44 should be used until this factor is substantiated by further analysis.

In the case of the saltwater organisms the only value that has any degree of confidence is the 37,000 µg/L for fish. Again, if the invertebrate data on mysid shrimp is used then the associated criteria should indicate the high degree of uncertainty.

1,2 Dichloroethylene

As we indicated in our general comments, we do not believe that the alternate guidelines as expressed in Appendix B-1 of the March 15 Federal Register should be used. Accordingly, the only value that can be accepted is a final freshwater acute value of 19,000 µg/L.

Our recommended criteria would be as follows.

1,1 Dichloroethylene - The criterion to protect freshwater aquatic life should not exceed 16,000 µg/L in any 24 hour period. The ambient level will be established at a later date. For saltwater species the concentration should not exceed 37,000 µg/L in any 24 hour period.

1,2 Dichloroethylene - The criterion to protect freshwater species is a concentration of 19,000 µg/L in any 24 hour period. For saltwater species a value cannot be derived at the present time.

EVALUATION OF THE HEALTH EFFECTS SECTION
OF THE CRITERIA DOCUMENT
FOR AMBIENT WATER
FOR

DICHLOROETHYLENES

Conclusions: The evidence regarding the carcinogenicity of 1,1-dichloroethylene is overstated. The methodology used to derive the health based criterion is probably inappropriate. The significant literature on the toxicology of these compounds is adequately reviewed.

Prepared by:

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May 14, 1979

G eral Comments:

The criteria document on the dichloroethylenes cites most of the significant information on the toxicology of these three compounds. However, the evidence regarding the carcinogenicity data of 1,1-dichloroethylene seems to be overstated. The evidence for the carcinogenicity of this compound is qualitatively similar to that of selenium which was considered to be non-carcinogenic. The methodology used for the derivation of the health based criterion may be inappropriate for 1,1-dichloroethylene for the reasons noted under Specific Comments.

Specific Comments:

Pages C-19 to C-21: How were the p-values for Tables 13 and 14 derived? The incidence rates for tumors do not demonstrate a sizeable change from control values and their significance should be evaluated with the Fischer Exact Test. Thus, the p-value for the incidence of mammary adenocarcinomas at a concentration of $40mg/m^3$ is listed as p=0.068, while by the Fischer Exact Test this value should be p=0.32.

It is doubtful whether a substance should be called a carcinogen for the purpose of setting water quality criteria, if the only positive tests can be found in inhalation studies and the positive results are confined to mice. In addition, the kidney adenocarcinomas, which form the basis of the proposed criterion, are only found in male mice and not to any

significant extent in female mice. The incidence of mammary tumors in rats does not show a convincing dose response relationship (figure 14), and hamsters failed to produce any tumors in an inhalation study (Maltoni, 1977). Rats did not develop a significant incidence of tumors when 1,1-dichloroethylene was administered in the drinking water(Rampy et al. 1977). In addition Ott et al.(1976) did not find any abnormalities associated with exposures of 9 to 280 mg/m^3 in a population of 138 workers.

If one calculates the absorbed dose of 1,1-dichloroethylene at the TLV averaged over a week (see page C-24), then a worker should absorb approximately 114 mg, or 114,000 ug per day. According to the proposed criterion the risk per dose is $10^{-5}/2.77 = 3.61 \times 10^{-6}$. Therefore the estimated risk to humans exposed to the TLV level according to the single hit model can be calculated as

$$P = 1-\exp(-114{,}000 \times 3.61 \times 10^{-6}) = 0.337.$$

Considering that some of the exposures reported by Ott even exceeded the present TLV, it is astonishing that he did not find any excess cancers. It appears likely that the combination of animal models used, and the single hit extrapolation model have produced a risk estimate that is excessive.

AN EVALUATION OF THE PROPOSED AQUATIC LIFE CRITERION ON 2,4-DICHLOROPHENOL

Conclusion

For protection of aquatic life the criteria should be based on toxicity and not taste.

Prepared by

W. B. Neely

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June 1, 1979

GENERAL COMMENTS

Kirk and Othmer is not an appropriate reference source for key data. Whenever possible primary references should be used. For example, using Kirk and Othmer's encyclopedia to establish that 2,4-Dichlorophenol is a metabolic intermediate lacks the credibility that citing the original reference would have. In this same context the reference for the octanol/water partition coefficient should be given.

The introduction admits that there is little data on 2,4-DCP levels in either effluents or natural waters. In addition, it is also admitted that there is a paucity of information on aquatic toxicity. In spite of these admissions the conclusion is drawn (p. A-4) that 2,4-DCP represents a potential threat to aquatic and terrestrial life, including man. While it may be a "potential threat" (in those cases of an inadvertent loss) there certainly is not a threat under the present or past use conditions.

CRITERION FORMULATION (p B-5)

If tainting is to be used for setting a 24 hour average number, then it should be so stated in the criterion statement. Otherwise the value could be misrepresented as having some basis for toxicity which it does not have.

It is our conclusion that a chronic value needs to be established by the Guidelines to be used as the 24 hour average. The excursion as we have said before (see comments on 2-chlorophenol) should be based on either the final fish acute value (700 µg/L) or an invertebrate value designed to protect 10-15% of the population.

EVALUATION OF THE HEALTH EFFECTS SECTION
OF THE CRITERIA DOCUMENT
FOR AMBIENT WATER
FOR

2,4 Dichlorophenol

Conclusions: The criterion is appropriately formulated. The document contains some misinterpretations, but otherwise adequately reviews the significant toxicological literature.

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May 10, 1979

General Comments:

With the exception of some of the data noted below, the criterion document for health effects of 2,4-dichlorophenol is well-written and takes appropriate notice of the experimental results that are currently known. It should be noted that this criterion for human health is based on the prevention of taste and odor problems from 2,4-DCP and that the criterion for the direct protection of human health lies significantly above the taste and odor threshold.

Detailed Comments:

Pages C-1 to C-3. The dilution of a 2,4-DCP effluent in water containing 100,000 mg/liter total solids to a fresh water total solids concentration of 1,000 mg/liter constitutes only a 100-fold dilution. It is assumed that this worst case discharge after only 100-fold minimal dilution will serve as a source for drinking water and that it would be treated in a fashion that would not permit the removal of any 2,4-DCP. These assumptions are highly unrealistic and it is dubious that this example can stand even as a worst case exposure level.

Page C-11. 0.51 µg per g of kidney were found in cattle that were fed 300 µg of 2,4-D per g of feed, which corresponds to approximately 9 mg of 2,4-D per kg of body weight. A concentration of 300 µg of 2,4-D per kg of feed cannot be considered to be realistic in a field exposure.

Page C-14. The consumption of chicken liver and cattle kidney by man would result in approximately equivalent exposures to 2,4-DCP only if those cattle had been fed relatively high concentrations of 2,4-D and the chickens had been fed high concentrations of Nemacide. Whether the concentrations of these chemicals fed to chicken and cattle have any relation to normal environmental exposures is very questionable.

Pages C-14 to C-15. The worst case estimates regarding the intake of 2,4-DCP from contaminated meat and water must be questioned. It is unlikely that a human could consume 0.5 kg of kidney daily. The applicability of the estimate for 2,4-DCP levels in water has been questioned previously. It must therefore be concluded that the worst case estimate of consumption of 4 µg of 2,4-DCP per kg of body weight per day represents an over-estimate, even for a worst case.

Page C-17. The calculated bioconcentration coefficient includes so many assumptions that it must be considered to very tentative at best.

Pages C-16 to C-17. The available data do not permit an estimation of the ingested 2,4-DCP. No marketbasket surveys for 2,4-DCP are available and any estimates based on laboratory studies involving precursors for 2,4-DCP can provide only the most general indications of even a worst case incidence.

Table 7 should appear immediately after page C-26.

Pages C-25 to C-28. The promoter study by Boutwell and Bosch (1959) is clearly not designed as a carcinogenicity study.

The protocol is not remotely related to the ingestion of 2,4-DCP and the degree of emphasis given to this study is totally inappropriate. The study is not even applicable to the evaluation of the hazard of a dermal or respiratory exposure to 2,4-DCP.

Page C-28. While it is appropriate to cite the studies on taste and odor by Burtschell and by Hoak, it should also be pointed out that the protocols for the determination of taste and odor thresholds are very poorly described in both studies, even though it is well known that the determination of the thresholds is highly dependent upon the exact protocol. Regretably these poor descriptions of protocol are shared by most other publications dealing with taste and odor thresholds. Consequently, the certainties attached to taste and odor thresholds are relatively poor. In addition, it not often clear whether a taste and odor threshold refers to an unacceptable taste or odor which might affect the consumption of water.

Pages C-30 to C-33. The criterion for 2,4-DCP is appropriately formulated.

JUN 5 - 1979

EVALUATION OF THE PROPOSED AQUATIC LIFE CRITERIA ON 2,4-DIMETHYLPHENOL

Conclusion: Freshwater criteria for both maximum and 24-hour average concentrations are based on one static acute test. Basing national water quality criteria on such a limited data base is not scientifically defensible.

Prepared by:

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May 23, 1979

General Comments:

Proposed ambient water quality criteria for 2,4-dimethylphenol for the protection of aquatic life are based on data from two unpublished studies. The data base includes only three acute and one chronic test. Water quality criteria for 2,4-dimethylphenol should not be derived until more data are available.

The 24-hour average criterion is calculated by multiplying the Final Invertebrate Acute Value by a 0.44 sensitivity factor. The Final Invertebrate Acute Value is based on only one static acute test with Daphnia magna. The 48-hour LC50 is corrected by an "adjustment factor" (unmeasured to measured concentrations) and a "sensitivity factor." The end result is a proposed national water quality criterion based on one acute invertebrate toxicity test to which one "adjustment factor" and two "sensitivity factors" are applied. These mathematical procedures are used in preference to empirically derived chronic toxicity data on fish. Because of the mathematical manipulations used to derive the criteria for 2,4-DMP, the results must be regarded as unacceptable until additional aquatic toxicity data are available and until the Guidelines (44 FR March 15, 1979; Appendix B) have been thoroughly evaluated.

Specific Comments:

Page A-1

The document states that ... "its [2,4-dimethylphenol] toxicity to aquatic life, and its carcinogenic effect in mammals clearly indicate the potential hazard of 2,4-DMP to aquatic and

Page A-1 (Continued)

terrestrial life." This statement implies that 2,4-DMP is carcinogenic; however, on page C-35 of the document, a report by the Carcinogen Assessment Group concludes that ... "the data in Boutwell and Bosch regarding possible carcinogenic effects (via initiation) of 2,4-dimethylphenol are inconclusive." An apparent contradiction exists in the document concerning the carcinogenic effects of 2,4-DMP.

Page B-1

The Final Fish Acute Value (2,200 µg/l) is based on the geometric mean of only two LC50 values, both of which are from unpublished sources (Phipps, et al., manuscript; U.S. EPA, 1978). The manuscript by Phipps is not readily available and therefore could not be reviewed. The Final Invertebrate Acute Value (86 µg/l) which becomes the Final Acute Value is based on only one static acute test with Daphnia magna. The 48-hour EC50 was "adjusted" from 2120 µg/l to 1796 µg/l and then divided by the "sensitivity factor" of 21. Basing criteria on such few data is not scientifically defensible.

Page B-2

The relevance of the information on the relationship between the acute toxicity of chlorinated phenols to bluegills and the degree of chlorination should be explained. Unless these data can be related to developing criteria for 2,4-DMP, it should be deleted.

Page B-2 (Continued)

The statement that "since Daphnia magna appears to be more acutely sensitive than the fathead minnow or bluegill, a chronic test for this species would probably be lower than the Final Fish Chronic Value ..." is total speculation and has no place in a criterion document. The relationship between acute and chronic toxicity data for fish is not necessarily applicable to invertebrates such as Daphnia magna.

Page B-3

Data are presented which indicate that exposure of fathead minnows to 2,4-DMP for 192 hours does not cause any appreciable cumulative mortality as compared to the 96-hour LC50. Data of this type suggest that sensitivity or application factors as derived in the EPA Guidelines (44 FR March 15, 1979; Appendix B) may not be applicable for 2,4-DMP. Additional information, particular chronic toxicity data for invertebrate species, is necessary before defensible water quality criteria for 2,4-DMP can be established.

COMMENTS ON THE PROPOSED HUMAN HEALTH CRITERION FOR

2,4-Dimethylphenol

by

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CONCLUSION: It is not clear why organoleptic criteria are used for some phenol derivatives and not for others. Since toxicity data rather than esthetic observations should be used to establish human health ambient water quality criterion, I would agree that there is insufficient toxicity data to establish a criterion for 2,4-dimethylphenol as proposed in this document.

AN EVALUATION OF THE PROPOSED AQUATIC LIFE CRITERION ON 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN

Conclusion

We agree that there is insufficient data to develop a criteria at this time.

Prepared by

W. B. Neely

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June 1, 1979

GENERAL COMMENTS:

This document concludes that no criterion for human health effects due to exposure to 2,4-dimethylphenol can be established because of the lack of mammalian toxicity data and human health effects. It should be pointed out, however, that the document does contain organoleptic data for this agent which is, in fact, similar to that for 2-chlorophenol, and that the human health criterion for 2-chlorophenol was based on the organoleptic effects of that agent. The establishment of human health criterion for phenol and its derivatives should be consistent and should reflect the state of our toxicologic knowledge about this series of agents rather than the lack of information about specific members of the series. The aquatic organism criterion for 2,4-dimethylphenol is less than that for 2-chlorophenol, which suggests that the methyl derivative is more toxic, but comparison of the two documents does not support this difference. This document does contain information on the acute toxicity of phenol derivatives (page C-24) and subchronic data for such derivatives (page 28). This kind of information, together with our rather considerable knowledge of how these agents are metabolized, would provide a reasonable approach to making recommendations for the entire series. It is surprising, therefore, that this approach was not used.

SPECIFIC COMMENTS:

Methyl is misspelled on pages C-19, C-22 and C-23.

GENERAL COMMENTS

TCDD is not a contaminant of 2,4-dichlorophenoxy acetic acid (2,4-D) and references to 2,4-D should be removed from the document.

References to the reported persistence of TCDD of 10 years should be included as well as the reported bioaccumulation factor of 8000.

CRITERION DEVELOPMENT

Since no criteria are reported no comments can be made.

EVALUATION OF THE HEALTH EFFECTS SECTION
OF THE CRITERIA DOCUMENT
FOR AMBIENT WATER
FOR

2,3,7,8-Tetrachlorodibenzo-p-dioxin

Conclusions: The criterion for human health is appropriately derived, assuming that the single-hit extrapolation model is applicable. The significant toxicological literature is adequately reviewed.

Prepared by:

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May 10, 1979

General Comments:

The document on TCDD is, in general, well written. TCDD clearly is an extremely toxic compound. The criterion for human health is appropriately derived, if one assumes that a single-hit extrapolation model for the estimation of carcinogenic risk in man is applicable.

Detailed Comments:

Page C-4. The calculated dose for TCDD for man represents an unrealistic over-estimate. The concentration of 4 lbs 2,4,5 T per 10 gal of water per acre obviously constitutes a highly concentrated spray suitable only for aerial application. The assumption that a person would spend 8 hours continually underneath the application pattern of the spray plane is highly unrealistic.

Page C-16. The statement on carcinogenicity and fetotoxicity on the bottom of page C-16 is incomplete and does not make any sense.

Pages C-20 to C-23. The sections on the inductions of various metabolic pathways should be more appropriately incorporated into the section on metabolism rather than on mutagenicity where they are at the present time.

Page C-29. At a postulated risk level of 10^{-5}, the concentration of TCDD in drinking water combined with consumption of fish should be 4.55×10^{-7} µg per liter, rather than 455×10^{-7} µg per liter.

AN EVALUATION OF THE PROPOSED AQUATIC LIFE CRITERION ON FLUORANTHENE

Conclusion

Acceptable criteria for fresh and saltwater organisms could not be generated due to the extreme lack of data and the fact that the data is in an unpublished report.

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and

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April 12, 1979

Summary Sheet

FLUORANTHENE

EPA Criteria:

Freshwater - 250 µg/l as a 24-hour average and 560 µg/l as the maximum concentration.

Saltwater - 0.30 µ/l as a 24-hour average and 0.69 µg/l as the maximum concentration.

Residues - No steady-state bioconcentration factor (BCF) is available for this compound. An estimated BCF of 3,100 was generated.

Conclusion:

Due to the extreme lack of data (one data point per organism) for fluoranthene in regard to aquatic toxicity testing and the fact that the data came from one unpublished report, makes it impossible to generate acceptable criteria for fresh and saltwater organisms.

General Comments

The only aquatic toxicity data for fluoranthene comes from one unpublished EPA contract. Until these data are published in the open literature, the criteria as proposed lack credibility.

The EPA is attempting to establish criterion from one data point for this compound. Statistically this approach cannot be justified and scientifically it cannot be supported.

Specific Comments

p. B-1. (1) The fact that the fluoranthene level in all the tests were not measured reduced the credibility of the test a great deal.

(2) The work of the EPA (1978) has not been published and cannot be properly evaluated.

p. B-2. The document states that the bioconcentration factor (BCF) has not been measured but it goes on to state that an octanol-water partition coefficient could be calculated and indeed it does arrive at the number 79,000. However, the document does not state how this number was derived. It is assumed that the calculated octanol to water partition coefficient came from the reference sited in the Federal Register, Vol. 43 #97 p. 21509 which is "Leo, A. J., 1975. In Symposium on Structure-Activity Correlations in Studies of Toxicity and Bioconcentration with Aquatic Organism. G. D. Veith and D. E. Konosewich, eds. International Joint Commission, Windsor, Ontario, pp. 151-176. This reference is not specifically referred to, therefore, one is not sure that this was the one used.

p. B-3. Line 10 up from bottom of page states that no Final Chronic Value was obtained for freshwater organisms. However, three lines above this we find a Final Chronic Value of 54,000 µg/l. This is very confusing. Also, it appears that this 54,000 µg/l comes from plant tests, and it is not clear whether the plant tests are acute or chronic.

p. B-3. The EPA is attempting to estimate a criterion for freshwater from saltwater organism. However, they have already arrived at a criterion from the freshwater data. I assume that they are attempting to justify the freshwater criterion with the saltwater data rather than estimate it. The freshwater criterion levels are so much greater than the saltwater levels that it become very difficult to even try to justify one with the other.

p. B-8. For saltwater organisms, ie., the myrid shrimp, the Final Invertebrate Chronic Value (also the Final Chronic Value) was 3.1 µg/l while the Final Invertebrate Acute Value was 0.69 µg/l. In this instance we have a final chronic value that is higher than the Acute value (approximately 4.5 times greater). The chronic value is, also 10 times greater than the 24-hour average value. Obviously, there is a great deal of unnecessary overprotection by using these "fudge factor" derived acute values as opposed to the chronic values.

Criterion Formulation

Due to the extreme lack of data (one data point per organism) for fluoranthene in regards to aquatic toxicity testing and the fact that the data came from one unpublished report, makes it impossible to generate acceptable criteria for fresh and saltwater organisms.

AN EVALUATION OF THE EPA AMBIENT WATER QUALITY CRITERIA DOCUMENT ON FLUORANTHENE

CONCLUSION: There is not sufficient data to justify the formulation of a water quality criteria level of fluoranthene.

Prepared by:

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23 April 1979

GENERAL COMMENTS

It appears that there are not sufficient data to justify the formulation of a water quality criteria level for fluoranthene. This lack of data is further illustrated in the "Specific Comments" section of this report.

The formulation of a water quality criteria level for fluoranthene is not justifiable on two major points. First, there are not sufficient data available to scientifically set an exposure level. For fluoranthene, there are no steady state bioaccumulation data (C-16), no pharmacokinetic data (C-21), no metabolic data (C-22), no data on excretion (C-23), and no teratogenic data (C-27). Secondly, the data that are available do not indicate that fluoranthene is a hazardous material. It is not particularly toxic; the LD_{50} in experimental animals is 1-5 grams/kg (C-24). Fluoranthene has displayed no mutagenic activity in in vitro systems (C-28) and has not been shown to be carcinogenic in experimental animals (C-29). Why is it being regulated?

In the criteria document, constant reference is made to fluoranthene being a polycyclic aromatic hydrocarbon (PAH) and it is implied that it is toxic. There is a need to regulate total PAH concentrations because of the presence of known mutagens and carcinogens, such as benzo(a)pyrene. Individual PAHs should be considered separately. Fluoranthene does not appear to be a hazardous chemical. This is not true of some other PAHs. EPA should continue to regulate known carcinogens, such as benzo(a)pyrene or benz(a)anthracene.

Another point that must be addressed is the proposed figure of 200 ug/l. This limit has been recommended and calculated as a drinking water standard (C-45). However, on page C-46, it is clearly stated that "Inadequacies in the current data base prevent the formulation of a drinking water criterion . . ."

This contradiction within the document demonstrates that there are insufficient data for setting a criteria for fluoranthene. In addition, fluoranthene is effectively removed (87.5 to 100%) during the treatment of drinking water (C-5).

SPECIFIC COMMENTS

B-1 Acute data in fresh water organisms were collected using static test procedures and unmeasured concentrations. Data from static tests are questionable. For meaningful data, these tests should be repeated in flow-through systems with a known concentration of fluoranthene.

B-2 There are no data on the chronic effects of fluoranthene on fresh water organisms.

B-2 There are no data on the steady state bioconcentration of fluoranthene.

B-3 "No fresh water criterion can be derived for fluoranthene using the guidelines - ESTIMATE of criterion calculated through data from salt water organism." The fact that these criterion are estimates has been overlooked in many sections of the document, and these numbers are erroneously presented as being soundly established. This can be demonstrated in the abstract, Page B-1 and B-3.

B-9 There is no measured steady state bioconcentration factor available for fluoranthene.

C-3 Removal of fluoranthene from water by conventional sewage treatment 91-99% effective.

C-5 Removal of fluoranthene during drinking water treatment 87.5-100% effective.

C-2 There are no data available concerning the pharmacokinetics of fluoranthene.

C-22 There are no data on the metabolism of fluoranthene.

C-23 The statement, "It is reasonable to assume that fluoranthene is metabolized in a manner which is consistent with the general biochemical scheme for biotransformation of PAHs." This may indeed be possible, but there is no evidence to indicate that this is so.

C-23 There are no data available concerning the excretion of fluoranthene.

C-25 Fluoranthene presents relatively low degree of toxicity.

C-27 There are no data available on the potential teratogenic effects of fluoranthene.

C-28 Fluoranthene displayed No Mutagenic Activity in the Ames assay. Duplicated in separate laboratories.

C-29 Fluoranthene has been tested for carcinogenic activity in several studies with negative results.

C-33 -35 The data review does not indicate that fluoranthene is either an inhibitor or tumor promoter.

SUMMARY

There are not adequate data to establish a water quality criterion for fluoranthene, either on the basis of effects on human health or fresh water organisms.

An Evaluation of the Aquatic Life Toxicology Section of the EPA Ambient Water Quality Criteria Document (March 15, 1979) on

Heptachlor

Summary

The Freshwater criterion to protect aquatic organisms is based on dubious chronic and bioconcentration data and should not be considered as completely formulated.

The Saltwater criterion to protect aquatic organisms is correctly formulated, but the recommended 24-hour average concentration is not detectable in saltwater with current technology.

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May 1979

Proposed Criteria

For heptachlor, the criterion to protect freshwater aquatic life as derived using the proposed guidelines is 0.0015 µg/l (Residue Limited Tissue concentration derived from the FDA maximum heptachlor concentration for animal feed and the freshwater bioconcentration factor) as a 24-hour average and the concentration should not exceed 0.45 µg/l (the final invertebrate acute value) at any time.

The criterion to protect saltwater aquatic life as derived using the proposed Guidelines is 0.0036 µg/l (Residue Limited Tissue concentration derived from the FDA maximum heptachlor concentration for animal feed and the saltwater bioconcentration factor) as a 24-hour average and the concentration should not exceed 0.05 µg/l (final invertebrate acute value) at any time.

Our Conclusions

We find that the Criterion Formulation for freshwater aquatic life is faulted by the inclusion of dubious chronic toxicity data and an inappropriate bioconcentration factor. It appears that no Final Chronic Value or estimated Final Chronic Value can be derived uder the Guidelines or published alternative procedures.

We find that the Criterion Formulation for saltwater aquatic life is apparently in proper form, with a minor correction (0.44 x Final Acute Value is 0.022 µg/l), but we note that the recommended 24-hour average concentration is at a level below that detectable in saltwater with current technology.

General Comments

The section on aquatic life toxicology is clearly documented and relatively easy to review. In general the studies which were included correspond to those which ought to have been retained in the process of screening the data base (Guidelines, Section III); we do find one significant exception, which is discussed below.

We find that the Criterion Formulation for freshwater aquatic life is faulted by the inclusion of dubious chronic toxicity data and an inappropriate bioconcentration factor. It appears that no Final Chronic Value or estimated Final Chronic Value can be derived under the Guidelines or published alternative procedures.

We find that the Criterion Formulation for saltwater aquatic life is apparently in proper form, with a minor correction (0.44 x Final Acute Value is 0.022 µg/l), but we note that the recommended 24-hour average concentration is at a level below that detectable in saltwater with current technology.

While we agree with the expressed concern that this recommended 24-hour average concentration may not afford fully adequate protection to penaeid shrimp, that value is less than the unmeasured concentration reported to cause only 15% mortality in penaeid shrimp and perhaps is sufficiently small to protect all but 0-10% of penaeid shrimp in accordance with the Guidelines. We see no immediate need to modify the Guidelines in this case.

Specific Comments

Freshwater Organisms

Chronic Toxicity

The chronic toxicity study by Macek, et al.(1976) with heptachlor and the fathead minnow should probably be regarded as unavailable under the Guidelines because it was subject to the same analytical difficulties in measuring heptachlor concentrations in water as other studies in that report which were not regarded as available for the criteria document. Further, the available statistical information on heptachlor concentrations in Table 10 of Macek et al. (1976) shows that there has been some erroneous compilation of the heptachlor data in that table; specifically, some of the standard deviations are numerically impossible if the means, sample sizes and ranges are correct. The exclusion of this study would then mean that no valid chronic test data were available for any fish species.

Residues

The doubts regarding the heptachlor concentrations in water in the fathead minnow chronic study extend to the bioconcentration factors computed for the fish residue levels, which depend on accurate concentration measurements. Further, the concentration data from day 210 to 276 are stated to be unknown, and hence the last 28 days (the minimum period of interest for a bioconcentration study under the guidelines) has no available measurements of exposure concentrations in test water. Therefore the bioconcentration factors, even if correctly recalculated from Table 27 of Macek, et al. (1976), are unavailable under the Guidelines. Further the Residue Limited Tissue Concentration (RLTC), if it were to be based on the FDA animal feed action-level (0.03 mg/kg), would require residue measurements of whole fish, not eviscerated fish. Thus, the RLTC is apparently not available.

Miscellaneous

Perhaps the *Daphnia magna* study by Macek, et al. (1976) warrants mention here, and in Table 5, even though the concentrations can only be reported as nominal.

Criterion Formulation

Freshwater -Aquatic Life

Final Fish Chronic Value should be treated as not available Residue Limited Toxic Concentration should be treated as not available. Final Chronic Value should be treated as not available.

It does not appear that any of the published alternative procedures can be satisfied as a means for estimating a Final Chronic Value for freshwater. Thus, the freshwater criterion cannot be completed under the Guidelines or the published alternative procedures.

Saltwater Organisms

Acute Toxicity - The last paragraph discusses the frequent appreciable reductions of measured heptochlor concentrations relative to nominal concentrations. It is true that most tests

show markedly lower measured (than nominal) concentrations on average, but there are counter-examples, e.g., a few tests run by Schimmel, et al. (1976a, b), in which mean measured concentrations exceeded nominal. Thus, it may not be warranted even to consider deriving an adjustment factor specific to heptachlor for measured versus unmeasured concentrations.

Chronic Toxicity

Presumably the next to last sentence of page B-24 (beginning "No other fish...") refers to the current absence of alternative saltwater fish for which life cycle tests have been developed.

Residues

Schimmel et al. (1976b,) although only a 24-day study of spot, achieved steady-state bioconcentration values and is indeed available.

Miscellaneous

Concern was expressed over the adequacy of protection offered to pink shrimp at the Final Chronic Value. This appears to be a possible issue, but as Stephan (1977) has pointed out, a generally different level of effort in testing would be required to obtain adequate LC_{50} values. This may qualify as a case in which the species sensitivity factors warrant review. With other toxins, examples of concern in the other direction can be found.

Criterion Formulation

0.44 x Final Acute Value = 0.022, not 0.22 µg/l.

Additional Reference

Stephan, C.E. 1977. Methods for calculating an LC_{50}. pp. 65-84 in Mayer, F.L. and J.L. Hamelinch (eds.). Aquatic Toxicology and Hazard Evaluation. ASTM STP 652.

EVALUATION OF THE PROPOSED AQUATIC LIFE CRITERIA ON HEXACHLOROBUTADIENE

Conclusion: Available data do not support the derivation of numerical water quality criteria.

Prepared by

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May 23, 1979

General Comments:

No criterion for the protection of either freshwater or saltwater aquatic life was derived for hexachlorobutadiene 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 (p. B-3; p. B-9)." Given the general lack of aquatic toxicity data for this compound, the criterion statement is appropriate. The criterion of 0.9 µg/l derived in the first draft of the EPA water quality criteria document for hexachlorobutadiene was not scientifically defensible. This conclusion is supported by the current document. Additional aquatic toxicity data are required before a numerical criterion for hexachlorobutadiene can be formulated.

EVALUATION OF THE HEALTH EFFECTS SECTION
OF THE CRITERIA DOCUMENT FOR
AMBIENT WATER
FOR

Hexachlorobutadiene

Conclusions: The health based criterion for hexachlorobutadiene is defensible, assuming that a single-hit extrapolation model is applicable. The significant toxicological literature on hexachlorobutadiene is adequately reviewed.

Prepared by:

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May 10, 1979

General Comments:

In general, this document is well written. The survey of the available data is reasonably complete and the criterion which has been derived for protection of human health is appropriate, assuming that a single-hit model is applicable for this extrapolation.

Specific Comments:

Page C-25. The statement on mutagenicity in S. typhimurium is misleading. Taylor (1978) classified HCBD as not proven to be mutagenic because of the low number of induced reversions. The existence of a slight dose-response relationship in the number of reversions, which did not reach twice the number of background reversions at the highest dose level tested, is insufficient to establish the mutagenic potential of HCBD.

An Evaluation of the Aquatic Life Toxicology Section of the EPA Ambient Water Quality Criteria Document (March 15, 1979) on

Hexachlorocyclopentadiene

Summary

The freshwater criterion for the protection of aquatic life is properly derived, but based on data for only one species, *Pimephales promelas* (fathead minnow). There are insufficient data for a saltwater criterion to be derived for the protection of aquatic life, and none was attempted.

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Proposed Criteria - Aquatic Life

For hexachlorocyclopentadiene, the criterion to protect freshwater aquatic life, as derived using the Guidelines is 0.39 µg/l (based on the final fish chronic values) as a 24-hour average and the concentration should not exceed 7.0 µg/l (based on the final fish acute value) at any time.

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

Our Conclusions

The freshwater criterion is based entirely on data for fathead minnow. The recommended maximum concentration is properly derived and is presumably protective of fathead minnow under laboratory conditions. The 24-hour average concentration has been adjusted well below the no-effect level for fathead minnow, but we have no basis for evaluating this as an extrapolation to other organisms or to field conditions.

No suitable data are available for saltwater criterion formulation.

Hexachlorocyclopentadiene

General Comments

The freshwater criterion for hexachlorocyclopentadiene is based essentially on the work of Spehar, et al. (in press), much of which was reported by Spehar et al. (1977). The work gives evidence of careful quality control, as did the earlier work by Henderson (1956).

Specific Comments

Freshwater

Chronic Toxicity

The third sentence here should begin "The Final Fish Chronic" (not "Acute").

Admittedly there is limited evidence for hexachlorocyclopentadiene, but this seems to be a case in which the guideline sensitivity factor is perhaps excessively stringent. This is much more stringent than necessary to protect the tested organisms, so we cannot evaluate the suitability of the final chronic value for other organisms and conditions.

Additional Reference

Spehar, D.L., et al. (1977). A rapid assessment of the toxicity of three chlorinated cyclodiene insecticide intermediates to fathead minnows. Ecological Research Series, Report EPA-600/3-77-099. 30pp.

AN EVALUATION OF THE EPA AMBIENT WATER QUALITY CRITERIA DOCUMENT ON HEXACHLOROCYCLOPENTADIENE

CONCLUSION: It is evident that the information needed to accurately establish a criterion for HEX is lacking.

Prepared by:

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23 April 1979

GENERAL COMMENTS

The only relevant study of chronic effects was a 6-month study in rats involving 3 dosage levels. Neutropenia and a tendency toward lymphocytosis were the only adverse effects observed and only at the highest dose.

Longer term studies and adequate evaluation of carcinogenic potential are lacking.

Since the limited toxicity observed by Naishtein and Lisovskaya described in the document (C-79) as being possibly attributable to the compound, selecting the higher value of the proposed range does not seem inappropriate. Thus 4.0 µg/l appears to be as reasonable a figure as 0.4 µg/l, bearing in mind that the data for establishing a criterion is totally inadequate at the present time.

SPECIFIC COMMENTS

C-1 "Many commercially important organochlorine pesticides" - This is no longer true. Compounds have been banned or use severely restricted. Main use now is in manufacture of flame retardants. Thus present exposure potential is considerably less than implied here.

C-2 It is not clear from the single reference (Bell, 1978) whether use of HEX is declining or not. It is stated that use in pesticide manufacture is declining, but use in manufacture of flame retardants is increasing. Is overall use (and hence environmental exposure potential) of HEX increasing or decreasing? It is assumed the latter is true, but this should be made clear.

C-3 "Scores of workers" - Granted this section is intended to be a brief description of the Louisville problem, but a more quantitative term than "scores" would be appropriate. "Scores" is a dramatic term "indicating indefinitely large numbers" (Funk and Wagnall's Dictionary). This implies a massive disaster.

C-4 Chemical properties are described on page A-1. No need to repeat here.

C-5 Were lines or words left out of last sentence? Meaning is unclear as it now appears.

C-9 Discussion of Spehar study is extremely vague. First, are sentences 2-4 in the 2nd paragraph related to the Spehar reference? (There is no other here). Sentences 2-4 raise such questions as: What percentage of fish contained HEX? What were the exposure levels? What were the HEX levels found in fish?

C-13-15 The Kommineni study is not really a pharmacokinetic investigation. Devoting 3 pages to gross and histopathological observations under the heading of pharmacokinetics is inappropriate, incorrect, and contributes to the excessive length of this document.

C-19-25 These acute toxicity findings have no bearing on the criterion. They should have been summarized briefly.

C-28 As noted, the deaths in the 1972 IRDC study were not necessarily due to HEX.

C-30-31 Dermal study. It is unclear how many concentrations of HEX were used in this study. Apparently, only two were involved which is unfortunate since the lower level was toxic, especially to mice.

C-54 Item 4? Where are items 1-3?

C-69 Elevations . . . in what?

C-77 8 hr. resp vol of $10M^3$ too high; Int. Comm Radiol. Protect. says 7.6 M^3.

C-78 0.7857 mg/day should be termed ADI (is 0.60 if 7.6 m^3 is used). Assumption of 100% resp. absorption - real value almost surely less. Criterion is calculated in very confusing and perhaps incorrect manner. The relevant formula from the "Guidelines and Methods" is:

$$CR = ACI/WC + (R \times F) \text{ where}$$

CR = criterion

ADI = acceptable daily intake (0.7857 mg/day)

WC = daily water consumption (2 liters)

R = Bioconcentration factor for fish (3.2)

F = Avg. wt. of fish consumed/day (0.0187g)

$$CR = \frac{.7857}{2} + 0.06$$

$$CR = 0.45 \text{ mg/l}$$

Thus the figure should be 15% higher than shown, when derived from the TLV value.

Comments on the Aquatic
Toxicology Section of the EPA
Ambient Water Quality Criteria
Document (March 15, 1979) on

Lead

Summary

The modification of the proposed guidelines permitted proper adjustment for lead toxicity as a function of hardness in freshwater. The freshwater criteria are properly derived and reasonably valued under tested conditions.

The data base is insufficient to complete saltwater criterion formulation.

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Proposed Criteria - Aquatic Life

For lead, the criterion to protect freshwater aquatic life as derived using the Guidelines is "e(1.51 ln (hardness)-3.37)" as a 24-hour average (based on the slope for fish acute studies and the adjusted mean intercept for fish chronic studies) and the concentration should not exceed "e(1.51 ln(hardness)-1.39)" (based on the slope for fish acute studies and the adjusted mean intercept for invertebrate acute studies) at any time.

The following table illustrates the meaning of this criterion for waters at specified hardness.

Hardness (mg/l)	24-hour Average (µg/l)	Maximum (µg/l)
20	3.2	25
40	9.0	65
100	36.	261
300	189.	1370

Our Conclusions

It is important that the proposed guidelines have been modified to permit adjusting the criteria for hardness or related water quality parameters. The application of the fish acute slope to other kinds of data, although required by the proposed guidelines, is an extrapolation without scientific support in the document.

The 24-hour average and maximum concentrations have been properly derived under the proposed guidelines. The 24-hour average appears to be properly protective of aquatic life under laboratory conditions.

There are insufficient data to complete the saltwater criteria formulation process.

General Comments

This document generally makes full use of the available data on the toxicity of lead to aquatic life. Our comments are generally concerned with the adequacy of the data base for criterion formulation, particularly since water quality standards, for particular uses and bodies of water, may be established on the basis of section 304(a) criteria.

Lead is one of the metals with highly variable toxicity in different freshwaters; this variability has usually been associated with the protection afforded to aquatic life by increased water hardness. It is at least plausible that alkalinity, rather than hardness, is directly responsible for (and predictive of) the reduced toxicity of lead in freshwaters of high hardness or high alkalinity. The data summarized in the criteria document do not provide sufficient information to distinguish between these two correlated water quality parameters in freshwaters.

The supposed relationship of toxicity to dissolved lead, to the extent that this had been or might become clearly documented, deserves some treatment in the criteria document, even though the criteria themselves are to be based on total lead.

Specific Comments

Introduction (pp. A-1 to A-5) - The third sentence is not a very useful summary of the solubility of ionic lead, since pH is not the only major influence; also, Durum, 1973, is not in the list of references.

Perhaps the low lead concentration reported in seawater deserves more comment, since the usual table (reprinted from Sverdrup, et al. (1942)) gives the average lead concentration in seawater as 4-5 µg/l.

It might be useful to summarize the Kopp and Kroner (1967) data, perhaps by plotting them against hardness as an indication of how well water quality conforms to the recommended freshwater criterion for lead for the protection of aquatic organisms.

Perhaps the Davies et al. (1976) paper should be referenced on the second line of p. A-2 by way of providing a thermodynamic explanation for the reduced toxicity of total lead in hard water.

The acute and chronic toxicity to vertebrates mentioned on p.A-1 are not cited in the aquatic toxicology section.

Freshwater. (B-1 to B-20)

Acute Toxicity (B-1 to B-5)

On page B-3, line 9, the "test water" should be the soft test water.

The question can be raised, on the basis of the aqueous chemistry of lead, as to whether alkalinity might be more predictive than hardness in selecting a water quality measurement on which to form a dependent relationship for lead toxicity. This would permit a partial evaluation of the exponential relationship, since rainbow trout have been studied at four alkalinities (30, 105, 228 and 267 mg/l). (Hale, 1977; Davies, et al., 1976), three of which have measured concentrations. For bluegill and fathead minnow, no intermediate values of hardness are available, and the criterion document did not list alkalinities (since these are not needed if hardness is retained).

The Davies, et al. (1976) data for hard and soft-water measured total lead compared with nominal total lead suggest that the guideline value of 0.77 may be inappropriate for lead for converting unmeasured to measured concentrations, at least in static tests.

The reported (p.B-4) 14-fold range in species sensitivity appears to be in general agreement with the approximately 11-fold range which can be crudely estimated by back-calculating from the guideline value of 3.9.

The calculated log intercepts for invertebrates, the ranges of which was given as a measure of relative species sensitivity, shows approximately a 300-fold difference which is in general agreement with the species sensitivity factor of 21, from which back-calculations suggest a typical 260-fold difference from most to least sensitive.

Chronic Toxicity (B-6 to B-8).

Davies, et al. (1976) give additional chronic data, mentioned on p.A-1, but not reported in this section in Table 7.

Using the guidelines sensitivity value for freshwater fish chronic studies of 6.7 results in a much greater reduction in computing the Final Fish Chronic Value than would seem to be warranted by the 2.2-fold range after adjustment for hardness in relative species sensitivities in Table 3, especially since the rainbow trout value (the most sensitive species in Table 1) Is right in the middle of the available fish chronic values. If the application factor were invoked, the estimated final fish chronic value would have been e(1.51. ln (hardness)-1.40), which is very close to the value before adjusting by 6.7, namely e (1.51. ln (hardness)-1.47). The above reasoning seems to be in line with the document's rationale for not using the species sensitivity value for the final invertebrate chronic value (p. B-7). (It is noteworthy, however, that data in Table 7, suggest that adverse effects occur at concentrations very little higher than those given by the final fish chronic value. Those data should be discussed here or under Miscellaneous.)

Table 1.

The first entry (rainbow trout in hardwater) combines the results of two tests at two different hardnesses (333 mg/l is neither the arithemetic nor the geometric mean) with the arithmetic mean of the two LC_{50} values given; moreover, measured lead concentrations were published for both of these tests. The tests should be shown separately as were the multiple soft water tests on fathead minnow by Pickering and Henderson (1966).

Saltwater (pp. B-21 to B-28)

Criterion Formulation - The RLTC and Final Chronic Value entries presumably should be deleted (p.B-24). We cannot locate the source of the 8.5 ug/l values.

COMMENTS ON THE PROPOSED HUMAN HEALTH CRITERION FOR

Lead

by

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CONCLUSION: The ambient water quality criterion recommended in this document for lead (50 µg/l) appears to be appropriate on the basis of the animal and human toxicity data.

GENERAL COMMENTS:

The human health criterion recommendation in this report for lead (50 ug/l) is based primarily on the EPA air quality criteria for lead document (which is listed four times in the reference), and on the WHO document (Environmental Health Criteria 3, lead). Other recent important documents dealing with the setting of standards for lead have been reviewed, including the NAS Safe Drinking water report and the NAS report on Airborne lead in perspective (which is included twice in the reference list). The proposed recommendation is consistent with the recommendations for lead standards proposed by other agencies and organizations, although, the NAS Safe Drinking Water Committee suggested that consideration be given to lowering the limit if additional research demonstrates that the current levels do not provide a safe limit for fetuses and growing children.

The toxicology of lead in man and animals has been extensively reviewed in a number of recent documents, criteria reviews, committee reports and books,. and this document appears to have covered essentially the same ground and to have reached similar conclusions about the human health hazards associated with lead in our environment. Comparison of the ambient water quality criteria document for lead with the air quality criteria document for lead, suggests that the criterion formulation section of the water report could have been appended to the air quality document or even to one of the many NAS reports on lead without losing any of the important toxicologic studies or missing any of the current controversies involving environmental lead. In the case of this metal, at least one has the impression that we are spending more time evaluating the toxicologic data available for lead than we are in generating new data which is needed to resolve some of the remaining problems associated with lead in our food, air, and water. Other than the fact that it generates a distinct feeling of deja vu in this reviewer, there is nothing wrong with this document or its conclusions regarding the human health criterion for lead in ambient water.

Comments on the Aquatic Toxicology Section of the EPA Ambient Water Quality Criteria Document (March 15, 1979) on

Nitrosamines

Summary

No criteria for the protection of aquatic life were derived for N-nitrosodiphenylamine under the proposed guidelines since there are insufficient data in both freshwater and saltwater. N-nitrosodiphenylamine is an appropriate test compound in this class.

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Proposed Criteria - Aquatic Life

N-nitrosadiphenylamine

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

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

Our Conclusions

No criteria for the protection of freshwater aquatic life were formulated since a final chronic value for N-nitrosodiphenylamine could not be derived under the guidelines. If the final chronic value were to be established in the vicinity suggested by available data, it would lie within the ambient range for total nitrosamines of natural origin. The selection of N-nitrosodiphenylamine for tests of toxicity to aquatic organisms is reasonable in view of the statement that this is the most prevalent anthropogenic nitrosamine.

There are inadequate data to derive a criterion for the protection of saltwater aquatic life under the proposed guidelines.

Nitrosamines

General Comments

The primary concerns with nitrosamines (and therefore available data) seem clearly to be in terms of human health rather than the immediate protection of aquatic life. Moreover, the evidence presented suggests that nitrosamines of natural origin are likely to predominate over anthropogenic nitrosamines in ambient water.

The introduction (p.A-2) does mention very low concentrations of nitrosamines ("less than 0.1 µg/l") in industrial pipe sources. Hence, it would be desirable if data can be developed to establish at least the freshwater criterion values. The tentative upper bound to a Final Chronic Value in freshwater is based on very recent testing the report of which we have not seen.

The current separation of this group into individual compounds for criteria consideration is far more desirable than lumping them together as was previously done.

Specific Comments

Introduction - The use of N-nitrosodiphenylamine for acute tests of aquatic toxicity seems reasonable in view of the statement (p.A-2) that this is the most prevalent anthropogenic nitrosamine.

Chronic Toxicity

Apparently the second clause of the first sentence should read, "but adverse effects were observed at every test concentration, even the lowest at 48 µg/l (Table 3)."

The suggested Final Invertebrate Chronic Value of "less than 9.4 µg/l" is certainly in the range reported for ambient stream measurements, "less than 10 µg/l" (p.A-2). If an MATC value is eventually established which yields a definitive Final Chronic Value in this range, there may be some question as to what a regulatory agency could accomplish on the basis of such a criterion value, given that most exposure to nitrosamines is not anthropogenic in origin (p.A-2).

Miscellaneous

Ferraro, et al. (1977) cite histopathology work on a nearctic crayfish reported by Harschbarger et al. (1971); perhaps this should be considered for possible citation.

Additional Reference

Harshbarger, J.C., et al. 1971. Effects of N-nitrosodimethylamine on the crayfish, *Procambarus clarkii*. *In* Proceedings of the Fourth International Colloquium on Insect Pathology with the Society for Invertebrate Pathology, College Park, Maryland, August 25-28, 1970, pp. 425-430.

COMMENTS ON THE PROPOSED HUMAN HEALTH CRITERION FOR

Nitrosamines

by

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CONCLUSION: Despite some reservations on the rationale for transferring data calculated for food intake to the ambient water quality situation, the use of the risk extrapolation approach to setting criteria for nitrosamines appears to be justified.

GENERAL COMMENTS:

The decision of the authors of this document to include both the nitrosamides and the various nitrosamines in a single criterion document is appropriate in view of the present state of development of the toxicity data for these agents. It is probable, in fact, that the final decision on the human health criterion for this group of agents will also need to consider nitrites, nitrates and amines in the ambient water supply in order to establish satisfactory criteria recommendations. The data on page C-7 concerning the short half-life of nitrosamines is reassuring as is the intake data for food versus water, etc. In this respect the statements on C-9 concerning percentage intake should be referenced. It would also be helpful if the authors would expand the statements regarding the analytical difficulties in detecting nitrosamines and nitrosamides (page C-10). Most of the data in this report relate to the nitrosamine content of foods, and there is some question as to the transferability of such data to a water situation. The use of the risk-extrapolation procedure to set ambient water quality criteria on this type of data needs to be evaluated carefully since it appears from this document that there are important chemical and physical-chemical considerations for which definitive data is lacking.

AN EVALUATION OF THE PROPOSED AQUATIC LIFE CRITERION ON PENTACHLOROPHENOL

Conclusion

Chronic values for freshwater species need to be developed. At this time the only valid number is the final acute number.

Prepared by

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June 1, 1979

Freshwater

The only acceptable value for criteria formulation is the final fish acute value of 25 µg/L. The invertebrate value is based on three experiments with the Tubificid worm at three different pH's and for a 24 hour period. To extrapolate this to 96 hours is unreasonable, further to assume that the three values represent three different species for purposes of the guidelines is also unreasonable. Until further work has been done the only value that should be used is the fish acute.

Since chronic studies have not been performed, it is impossible to derive a final chronic value. The value based on Chlorella pyrenoidosa must be reserved until a decision can be made on both the importance and the sensitivity of this species to reflect the aquatic plant world.

Saltwater

The value of 25 µg/L appears to be reasonable for a final fish acute value. Since we do not accept the data base for the safety factor of 49 in converting invertebrate acute to a value for protecting 95% of the species, we cannot accept 8.5 µg/L as a reasonable acute value. In this connection it is interesting to note that the final fish value of 25 µg/L is more than adequate to represent the acute toxicity for the invertebrate species studied in Table 7 (p. B-27).

The criterion for pentachlorophenol to protect saltwater aquatic life should be 9.6 µg/L as a 24 hour average not to exceed 27 µg/L.

COMMENTS ON THE PROPOSED HUMAN HEALTH CRITERION FOR

Pentachlorophenol

by

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CONCLUSION: The ambient water quality criterion proposed in this document (140 µg/l) is appropriate for PCP itself but is probably too high for dioxin containing PCP. Since a separate criterion is being proposed for dioxin, it is probably acceptable to establish a criterion for "pure" PCP, and the value recommended in this document is reasonable.

GENERAL COMMENTS:

The human health criterion for pentachlorophenol recommended in this document is 140 ug/l, which is roughly 7 times the no-adverse-effect level suggested by the Safe Drinking Water Committee in 1977. The difference is primarily due to the use of a safety factor of 100 in this document in contrast to the use of a safety factor of 1000 in the NAS document. Although it is stated in this document that the data of Schwetz et al. and that of Innes et al. were apparently not available or not considered by the NAS committee (which is incorrect in both assumptions), the major reason for the use of the large uncertainty factor by the NAS committee was the concern about the presence of dioxin as a contaminant in commercial samples of pentachlorophenol. The NAS committee was justifiably much more concerned about the chronic toxic effects of dioxin as a contaminant in PCP than the possible chronic toxic effects of PCP itself and reflected this concern in their choice of an uncertainty factor for this agent. There is almost no data in this document to support the argument that the human health criteria for PCP should be established on the toxicity of the pure chemical PCP rather than on the toxicity of PCP as it is likely to be found in the "real world". This would be appropriate if an ambient water quality criterion were also being established for the various dioxins which occur as contaminants of commercial PCP samples.

TABLE VI-55. Summary of Chronic Toxicity Data for Pentachlorophenol

Species	Duration of Study	Dosage Levels and No. of Animals per Group	Highest No-adverse effect Level or Lowest Minimal-effect Level	Effect Measured	Reference
Rat	12 weeks	0-200 ppm in diet, 20 animals per group	25 ppm (1.25 mg/kg/day)	No toxic effect	Knudson et al., 1974
Hamster	days 5-10	1.25-20 mg/kg/day orally	2.5 mg/kg/day	No fetotoxic or embryotoxic effects	Hinkle, 1973
Rat	90 days	0-30 mg/kg/day in diet[a]	3 mg/kg/day[c]	No toxic effect	Johnson et al., 1973
Rat	90 days	0-30 mg/kg/day in diet[b]	3 mg/kg/day	Increased organ weights, serum enzyme changes	Johnson et al., 1973
Rat	days 6-15	0-50 mg/kg/day, orally, 20-20 animals per group[a]	5 mg/kg/day	Teratogenic effects	Schwetz et al., 1974
Rat	8 months	0-50 ppm in diet, 20 animals per group[b]	100 ppm (5.0 mg/kg/day)	No toxic effect	Kimbrough and Linder, 1975
Rat	8 months	0-500 ppm in diet[a]	500 ppm (25 mg/kg/day)	No toxic effect	Goldstein et al., 1976

Using an uncertainty factor of 1,000, suggested no-adverse-effect level in drinking water is calculated as follows:

$$\frac{3}{1{,}000} = 0.003 \text{ mg/kg/day (ADI)}, \quad 0.003 \times 70^{c} \times 0.1^{d} = 0.021 \text{ mg/liter}.$$

[a] pure pcp

[b] Technical pcp

[c] Assume average weight of human adult = 70 kg.

[d] Assume average daily intake of water for man = 2 liters, and that 20% of total intake is from water.

[e] Test study from which to calculate suggested no-adverse-effect level.

Comments on the Aquatic Toxicology Section of the EPA Ambient Water Quality Criteria Document (March 15, 1979) on

Selenium

Summary

The freshwater criterion is derived under one of the proposed alternative procedures, using unpublished data to permit criterion formulation. The freshwater criterion appears to be fully protective of all tested species under laboratory conditions.

The saltwater criteria is properly derived under the proposed guidelines, but is numerically based on a single acute study of *Mysidopsis bahia*, a mysid shrimp. The saltwater criterion is fully protective of all tested species.

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May 1979

Proposed Criteria - Aquatic Life

For selenium the criterion to protect freshwater aquatic life, as derived using procedures other than the Guidelines, is 9.7 µg/l (derived as 0.44 times final invertebrate acute value) as a 24-hour average and the concentration should never exceed 22 µg/l (the final invertebrate acute value) at any time.

For selenium the criterion to protect saltwater aquatic life as derived using the Guidelines is 4.4 µg/l (derived as 0.44 times the final invertebrate acute value) as a 24-hour average and the concentration should not exceed 10 µg/l (the final invertebrate acute value) at any time.

Our Conclusions

The freshwater criterion was derived according to the first of the published proposed alternative procedures since a fish or invertebrate chronic value could not be derived under the proposed guidelines. These chronic values did not directly affect the criterion values, but other unpublished data was used to modify the final invertebrate value, raising this concentration significantly. The most important determinants of the criterion components are the species sensitivity which cannot be directly evaluated in this case. The freshwater criterion appears to be fully protective of all tested species under laboratory conditions, but does not address ambient conditions.

The saltwater criterion is properly derived according to the proposed guidelines, but is numerically based on a single study of *Mysidopsis bahia*, a mysid shrimp, and the species sensitivity factor for invertebrate acute studies. The criterion appears to be fully protective of all tested species; further evaluation is not currently possible.

Selenium

General Comments

The available data indicates that selenium can be acutely toxic to aquatic invertebrates and fish. The criterion document does not indicate the levels of selenium concentrations encountered in ambient waters; the discussion of health effects permits the inference that selenium concentrations in freshwaters are highly variable. An old value (which may not be reliable in view of analytic improvements) gives the average concentration in seawater as 0.004 mg/l, or 4 µg/l (Sverdrup, et al. (1942)).

The introduction (p.A-1) indicates that the major sources of environmental selenium are natural rather than anthropogenic. The health effects data suggest that dietary selenium is essentially in low concentrations for most species (p.C-46) and that there are significant interregional differences in ambient selenium concentrations (p.C-47); this could suggest that native or naturalized populations of aquatic organisms could be adapted to different ambient concentrations of selenium. Those points suggest that it might be unreasonable to establish a nationwide selenium criterion for the protection of aquatic life if such criterion values were to be in the range ordinarily encountered by aquatic life in the absence of anthropogenic sources.

A similar pattern of reasoning would suggest that the proposed 24-hour average value for selenium in seawater is very possibly within the range ordinarily encountered by marine organisms, and that marine organisms in some coastal regions may be adapted to higher concentrations of selenium than the proposed 24-hour average concentration.

The aquatic life criteria were not developed using bioconcentration data, presumably because it is difficult to establish an appropriate limit for selenium concentrations in food. (pp.C-48, 49).

Specific Comments

Freshwater

Acute toxicity

On p.B-2, the text refers to "two test results with *Daphnia magna*," but Table 2 indicates that one of these is with *Hyalella azteca* instead; therefore, the comments on Guideline adjustment factors should not be inserted at this point.

Selenium

Criterion Formulation

The first attempt failed for lack of a suitable fish or or invertebrate chronic value; when these were supplied from very new data, a second attempt was made. There is one computational error in the second attempt, namely, that the geometric mean of the two available fathead minnow (juvenile) flow-through tests with measured concentrations should have been used instead of the single lowest value; since this geometric mean does not indicate different sensitivity for fry and juveniles, the geometric mean for fry and juveniles should be taken, and this yields a Final Fish acute Value of 2100 µg/l. The correct procedure was followed for recomputing the Final Invertebrate Acute Value, and these two *Daphnia magna* tests do not clearly support the Guideline adjustment factors.

Although the Final Fish Chronic Value is less than 1% of the Final Fish Acute Value, the reduction does not seem unreasonable in view of the long-term studies presented in Table 5.

Saltwater

All the available marine data are from studies just completed for EPA. Tests have been completed on only one fish, one invertebrate and one algal species.

Acute Toxicity

The Guideline sensitivity factor of 49 for saltwater invertebrates results in a Final Invertebrate Acute Value much lower than the equivalent calculation, with a sensitivity factor of 5.1, for the same invertebrate, in arriving at the Final Invertebrate Chronic Value. The saltwater criterion values are both based on the Final Invertebrate Acute Value. This sensitivity factor is subject to review as more sets of data become available.

Criterion Formulation

Page B-14 was omitted in our copy of the criterion document, but the information should be identical to that presented in the Federal Register (44:15962, 3rd column). The 24-hour average concentration of 4.4 µg/l is uncomfortably close to the reported average of 4 µg/l in seawater (Sverdrup, et al., 1942). This

suggests that the sensitivity factor may be unnecessarily large in this case.

Additional References

Sverdrup, H.U., et al. 1942. The Oceans. Prentice-Hall.

EVALUATION OF THE HEALTH EFFECTS SECTION
OF THE CRITERIA DOCUMENT
FOR AMBIENT WATER
FOR

Selenium

Conclusions: The health based criterion selected for selenium is appropriate. The significant toxicological literature on selenium is adequately reviewed.

Prepared by:

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May 10, 1979

General Comments:

The proposed criterion for the protection of human health is approximately 10 µg selenium per liter, which is similar to the recommendation made by the NAS Committee on Drinking Water and Health and is identical with the present EPA drinking water standard. The document is, in general, very well written and takes account of most of the known literature on selenium. The document discusses the role of selenium as a required trace element, its toxicity at elevated levels, and the known information on the possible carcinogenicity of selenium. For selenium, the experimental data on cancer are equivocal. There clearly are data that argue for both sides of the question of carcinogenicity or non-carcinogenicity. It is interesting to note that in this case EPA chooses the position to call selenium non-carcinogenic and does not employ the carcinogenicity extrapolation model for selenium, while for other chemicals it takes any indication for carcinogenicity as a sufficient basis to label a chemical a carcinogen.

If such a position were chosen for selenium, then the resulting criterion for selenium would be less than the concentrations required to prevent deficiencies.

Detailed Comments:

Page A-2. The statement regarding the FDA position on selenium appears to be out of date. In fact, as indicated on page C-42, the FDA has ruled that sodium selenite may be used as a feed additive with certain restrictions.

Page C-1. The units utilized to express the selenium contents in foods differ significantly between different food commodities. The concentration of selenium in eggs is quoted incorrectly from the NAS document; the concentration should be 10 µg per gram rather than 10 µg per liter.

Page C-25. The dilutions cited for the various tests done in tissue culture are meaningless because no units are given.

Comments on the EPA
Water Quality Criteria For Silver
For the Protection of Aquatic Life

(FR 44, pg. 15964, March 15, 1979)

Prepared by:

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May 14, 1979

Conclusions

On the basis of the data and discussion given in the Silver Criteria Document (PB 292 441), the criteria to protect freshwater aquatic life of 0.000009 parts per million total silver as a 24-hour average, and 0.0019 parts per million total silver as a maximum, cannot be justified. The 24-hour number is based on one egg-fry sub-chronic fish bioassay in which water of a hardness of only 26 mg/l, as $CaCO_3$, was used, and the test chemical was silver nitrate. The aquatic toxicity of this soluble silver salt is unrepresentative of the toxicities of silver species actually present in most silver-bearing wastes discharged to the environment, and the dilution water used is unrepresentative of most natural waters.

General Comments

It is disturbing to read in this criteria document the way in which the EPA has repeatedly ignored considerations of silver toxicity as a function of the environmental chemistry of silver. The EPA's treatment of all silver species which could be present in the environment, as if these species were soluble, uncomplexed (free) silver ion, disregards volumes of published research on the inorganic chemistry of silver. The criterion document avoids the important facts in the scientific literature (Terhaar et al, 1972, 1977; Bard et al, 1976; and Cooper and Jolly, 1970) that point to the effects of silver on aquatic organisms as being a function of the concentration of free silver ion, not a function of the concentration of total silver.

The method used by the EPA to develop the silver water quality criteria for the protection of aquatic life, described in the May 18, 1979 Federal Register, is long on statistics, short on biology, and lacking in environmental chemistry. The method used to calculate water quality criteria concludes that the analytical chemistry, physico-chemical properties, and aquatic effects, as functions of biological species exposed and chemical species of silver present, can be determined with "statistical validity" from the results of previous studies on a random set of unrelated chemical compounds. Such conclusions by the writers of the EPA method are incorrect.

The criteria numbers for total silver should be subjected to a very important test: reasonableness. One good test for reasonableness would be: are the numbers put forth consistent with what is found in natural unpolluted waters where the aquatic species to be protected are known to flourish? The numbers proposed by the EPA for total silver criteria fail this simple test of reasonableness. Significant data exist in EPA's own STORET data base which show that concentrations of total silver more than two orders of magnitude greater than the proposed 0.000009 parts per million criterion value are present in natural waters, with no measurable adverse effects on aquatic life. In fact, many of these same natural waters are recommended by the respective local wildlife and conservation groups as being excellent fishing areas. However, a strict interpretation of the EPA criteria for total silver would be that nature has erred by placing harmful concentrations of total silver in natural waters.

To be scientifically valid, the criteria for silver must be written in terms of free silver ion, not total silver. The method for calculation of water quality criteria, as set forth in the May 18, 1978 Federal Register, is inappropriate to use for the establishment of criteria on silver.

Specific Comments (Page numbers refer to the criteria document)

A- 1 Only those silver salts which readily dissolve to give appreciable free, soluble silver ion concentrations, such as silver nitrate and silver sulfate, are toxic to a large number of microorganisms. Silver compounds of environmental significance, such as silver sulfide and silver thiosulfate complex, have been shown by Terhaar et al, (1972, 1977) and Bard et al (1976) to be without significant toxicity to aquatic life.

A- 1 Free silver ion, not "silver salts", combine with sulfhydryl groups on biological molecules. Free silver ion, not "many silver salts", can be absorbed into the human circulatory system resulting in argeria. Such effects caused by silver ions are discussed by Cooper and Jolly (1970).

A- 2 Effects on aquatic organisms have been demonstrated by free silver ion at concentrations > 1ppm. Effects have not been shown by silver species in which the silver ion is tightly complexed (see Bard, Terhaar, above).

A- 2 The reference by the EPA to Kopp's finding that silver concentrations in well and surface waters ranged from 0.1 to 38 ppb, with a median of 2.6 ppb, is interesting in light of EPA's 24-hour average criterion value in fresh water of 0.009 ppb. A reasonableness test should be applied here.

B- 1 The statement that " ... there are no data available on the toxicity of different forms of silver." points up the inadequacy of the literature search on silver effects on aquatic organisms. Data on the effects of silver species are found in such journals as the Journal of the Water Pollution Control Federation (Bard et al, 1976) and Water Research (Terhaar et al, 1977).

B- 1 The acute and chronic effect data on fish, specifically rainbow trout, are from Davies et al (1978). It should be noted that the chloride content of the water used in the Davies studies represents about 5% of the water in the U.S. supporting a good fish fauna (McKee and Wolf, 1963); 95% of all such waters have > 170 mg/l of chloride ion present. Thus, the criterion value of 0.009 ppb may be valid only to protect rainbow trout in Colorado-like mountain streams from the adverse effects of silver nitrate.

B- 3 The use of the lowest plant toxicity value instead of a geometric mean of all data when calculating the final plant value seems statistically inconsistent with the manner in which the other values were calculated.

B- 5-10 Tables 1-6 contain some studies performed with silver species other than silver nitrate (free silver ion). All of these chemical species should not be lumped together as "silver" when reporting out effects.

B- 6 Table 2. Only the extremes of the data are reported here, showing that there is little correlation of toxicity between two invertebrate species.

B- 7 Table 3. Davies et al (1978) reported the "no-effect" limit as 0.09 µg/l based on adjusted control mortality. However, actual control mortalities were never reported. If the control mortalities exceeded 10%, by the EPA's own definition, this test would be considered invalid.

B-10 Table 6. Data from this table were evidently not used for the criterion calculation. Terhaar et al (1972) is quoted incorrectly; the 96-hour mortality to fathead minnows using silver thiosulfate at 250 mg/l, as Ag, is 25%, not 75%.

It should be noted in this table that Coleman and Cearley (1974) exposed bluegills to 70 µg/l silver as $AgNO_3$ for six months with no effects.

B-13 It is an indication of a problem with the method when the Final Acute Value is less, 0.58 µg/l, (based on invertebrate data) than

the Final Chronic value, 3.6 µg/l (also based on invertebrate data). A reasonableness test should be applied here.

References

Bard, C. C., Murphy, J. J., Stone, D. L. and Terhaar, C. J., "Silver in Photoprocessing Effluents", J. Water Pollution Control Federation 48, 389-394 (1976).

Coleman, R. L. and Cearley, J. E., "Silver Toxicity and Accumulation in Largemouth Bass and Bluegill", Bulletin of Environmental Contamination and Toxicology 12, 53-61 (1974).

Cooper, C. F. and Jolly, W. C., "Ecological Effects of Silver Iodide and Other Weather Modification Agents: A Review", Water Resources Research 6, 88-98 (1970).

Davies, P. H., Goettl, J. P. Jr., and Sinley, J. R., "Toxicity of Silver to Rainbow Trout", Water Research 12, 113-117 (1978).

Kopp, J. F. "The Occurrence of Trace Elements in Water", 3rd Annual Conference on Trace Substances in Environmental Health, D. Hemphill, ed., V. of Missouri, Columbia, Mo.

McKee, J. E. and Wolf, H. W., "Water Quality", California State Water Resources control Board, Pub. 3-A (1963).

Terhaar, C. J., Ewell, W. S., Dziuba, S. P. and Fassett, D. W., "Toxicity of Photographic Processing Chemicals to Fish", Photographic Science and Engineering 16, 370-377 (1972).

Terhaar, C. J., Ewell, W. S., Dziuba, S. P., White, W. W., and Murphy, P. J., "A Laboratory Model for Evaluating the Behavior of Heavy Metals in an Aquatic Environment", Water Research 11, 101-110 (1977).

COMMENTS ON THE PROPOSED HUMAN HEALTH CRITERION FOR

Silver

by

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CONCLUSION: The proposed ambient water quality criterion for silver appears to be justified on the basis of the animal and human toxicity data presented in this document. The use of a safety factor between 10 and 100 is rather unusual, but the proposed criterion (10 µg/l) seems to be a reasonable criterion for this metal.

GENERAL COMMENTS:

This document provides a great deal more information than is needed to establish a human health criterion for silver in ambient water supplies. The first 20 pages of the human health section, for example, could be appropriately summarized in a few paragraphs with short tables listing the levels of silver in foods, human tissues, and geographical locations. Most of the rest of the human health section of this report (160 pages) is also unnecessarily redundant, repetitive and full of extraneous material.

The toxicity data, which is on page 68, demonstrates that both the acute and chronic toxicity of silver has been extensively investigated in a variety of species, including man. The synergism/antagonism section appears to be more focused on selenium than on silver, although the silver-selenium interaction is well characterized. The mutagenesis and carcinogenesis sections provide good research reviews of the work done with silver but contribute little to the criterion-setting requirements for toxicity data. In the criterion formulation section of this report, considerable emphasis is given to the derivation of the existing guidelines and standards for silver in drinking water and work place air. The dependence of these criteria on argyria is described and the problems associated with the use of a cosmetic effect rather than a toxic effect as the basis for criterion-setting is discussed. Evaluation of the reported toxic effects in rats chronically exposed to silver in their drinking water leads to the conclusion that the NOEL for chronic exposure to silver would be about 400 µg/l and, using a safety factor of 10 to 100, the criterion level was calculated to be 10 µg/l (1.6 to 16 µg/l). The recommendation of the NAS Safe Drinking Water Committee for silver was to give consideration to taking silver off of the list of substances to be included in primary drinking water standards in view of the low natural concentrations of this agent in public water supplies.

AN EVALUATION OF THE PROPOSED AQUATIC LIFE CRITERIA ON TETRACHLOROETHYLENE

Conclusion

The data base on fish toxicity is more credible than the data on *Daphnia magna*, hence it should be used for criteria setting. Using the guidelines, a value of 2600 ppb should not be exceeded in a 24 hour period. A final chronic value cannot be derived at the present time.

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June 1, 1979

GENERAL COMMENTS

A partition coefficient of 339 indicates that tetrachloroethylene has a modest affinity for lipids. I believe that the statement that PCE has a "high affinity" should be changed (p A-1).

The data base for freshwater organisms p B-1 indicates that the invertebrate data on one species is unpublished and should not be used for criteria development. The more credible data is the toxicity on fish. Since there is no chronic data, then no chronic criteria can be established at this time. The use of the alternate guidelines as suggested on p B-4 is not acceptable.

The data base on saltwater organisms (B-11) is also very weak. To use one value for mysid shrimp using 96 hour unmeasured, static conditions is inconsistent with the guidelines. Since this value was determined in 1978 under an EPA contract, the experimental procedure should have called for a flow-through protocol where the concentration was measured.

EVALUATION OF THE HEALTH EFFECTS SECTION
OF THE CRITERIA DOCUMENT FOR
AMBIENT WATER
FOR

Tetrachloroethylene

Conclusions: The criteria document contains some misinterpretations, and the methodology used for the derivation of the health based criterion is probably inappropriate for tetrachloroethylene. The significant toxicological literature is adequately reviewed.

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May 10, 1979

General Comments:

In general, the document covers the literature on tetrachloroethylene (PCE) well. However, the criteria document contains some questionable interpretations, and the method for deriving the criteria is probably inappropriate as noted under the specific comments.

Specific Comments:

Page C-3. Some data on concentrations found in dry-cleaning establishments and other occupational settings should be cited here. The present TLV for PCE is 670 mg/m^3.

Page C-11. The significance of electrical impedance measurements on the cerebral cortex is obscure to me. Was this information gleaned from an abstract of the Russian paper or from a full translation?

Page C-14. It is very questionable that PCE is "closely related to vinyl chloride"; there are significant differences in physical, chemical and toxicological properties between these two substances.

Page C-15. The last full sentence on this page is purely speculative, and appears to reveal a bias on the part of the original author, especially when read in context with the last paragraph on Page C-14.

Page C-16. Mixtures whose effects are less than additive are defined as being antagonistic by the joint action model. In order for potentiation to occur the components of the mixture must cause greater than additive effects according to a joint

action model. These mixtures can be called synergistic only according to an independent action model which expects that the damage produced by one chemical has no influence whatever on the effects produced by the second chemical in the mixture. Since non-specific interactions usually occur, the independent action model scores the interactions of most chemicals as synergistic.

Page C-22. The application of the Stockinger-Woodward model to derive a "safe level" for ingested PCE in humans from a rat inhalation study is probably inappropriate. This is especially true for an effect such as "altered electrical impedance of the cerebral cortex" whose significance is questionable.

Pages C-23 to C-24. If one calculates the amount of PCE inhaled at the TLV, assuming the inhalation of $10m^3$ per 8-hour day, a ratio of absorption by ingestion vs inhalation of 0.57, and adjusts from a 5-day work week to a full week, then the estimated daily intake per 70 kg person would be

$$670\ mg/m^3 \times 10m^3 \times 0.57 \times \frac{5}{7} = 2728\ mg/day.$$

At an extrapolated risk of 10^{-5}, the daily exposure according to the criteria document would be

$$2.0\ ug/l(21 + 110(BCF) \times 0.0187) = 8.11\ ug/day.$$

This would result in a risk/dose of $10^{-5}/8.11 = 1.23 \times 10^{-6}$. This can be applied to estimate the risk from exposure at the TLV using the single-hit model.

$$P = 1 - \exp(-2{,}728{,}000 \times 1.23 \times 10^{-6}) = 0.9653$$

The single-hit model predicts the occurrence of cancer in virtually all people exposed to PCE at the equivalent to a TLV exposure for a life-time.

However, PCE has been used for a long time, and many people have been exposed to it without any obvious exposure-related cancers being noticed. There is an obvious discrepancy between the animal model, the extrapolation model and the human experience! The conclusion must be that the use of the EPA approach to developing water quality criteria for compounds that have been found carcinogenic in animal testing is inappropriate for PCE.

AN EVALUATION OF THE PROPOSED AQUATIC LIFE CRITERION ON THALLIUM

The recommendation that no criterion for thallium can be derived for freshwater or saltwater aquatic life is justified from the scarcity of data in the literature. Chronic toxicity data for freshwater fish were presented from a U.S. EPA study that had limited peer review and circulation and was not clearly referenced in the text. No recommendation is justified at the present time from the additional studies found and added to this document.

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May 1, 1979

GENERAL COMMENTS

The recommendation that no criterion for thallium can be derived for freshwater aquatic life is justified. There are insufficient data to estimate a criterion, and only a few general references on thallium studies have been cited in the criterion document.

Specific Comments

p A-1. 1) The 13th line, "of trivalent" should read "or trivalent".

p A-3. 1) In the 2nd sentence, the authority or reference that reported chronic toxicity to fish at thallium concentrations as low as 20 µg/ℓ and to bioconcentrate by a factor of up to 130 is missing. It is assumed to be U.S. EPA (1978) as referenced in Table 3 (p B-7). If so, it is difficult to evaluate the methodology and potential mortality between controls and treated groups because of the limited distribution of this study.

2) Additional studies that may be incorporated into the introduction section include Mathis and Kevern 1975 ("Distribution of mercury, cadmium, lead and thallium in a eutrophic lake"), Eisler and LaRoche 1972 ("Elemental composition of the estuarine teleost Fundulus heteroclitus L."), Norris et al. 1976 ("Toxicity and accumulation of thallium in bacteria and yeast"), and Nehring 1962 ("Experiments of the toxicological effect of thallium ions on fish and fish-food organisms").

p A-5. 1) In the last reference, Zitko 1975 is cited twice on p A-1, but not as Zitko et al. 1975. Which of these references is Zitko et al.?

p B-1. 1) In the 2nd sentence, again, what is the reference to chronic toxicity of thallium to fish at 20 µg/ℓ? The same question applies in the next sentence at 100 µg/ℓ for algae.

p B-4. 1) The summary of available data for freshwater aquatic life is basically represented from the U.S. Environmental Protection Agency (1978) which has limited peer review and circulation. A similar trend is observed on p B-13 for saltwater aquatic life. Since this unpublished EPA document is not a primary reference, it is recommended that the methodology be made available for review before evaluation of the data is completed.

CRITERION FORMULATION

The guidelines for establishing a final acute fish toxicity number may have been erroneously calculated. The geometric mean of adjusted LC50 values of 2,000 µg/ℓ should be readdressed to see if 16,012 µg/ℓ is correct.

No formulation of criteria for freshwater or saltwater aquatic life should be attempted for thallium at this time until sufficient data are generated in the literature.

MISSING AND ADDITIONAL REFERENCES

1. Eisler, R. and G. LaRoche. 1972. Elemental composition of the estuarine teleost Fundulus heteroclitus (L.). J. Experimental Marine Biol. and Ecol. 9:29-42.

2. Mathis, B. J. and N. R. Kevern. 1975. Distribution of mercury, cadmium, lead and thallium in a eutrophic lake. Hydrobiologia 46:207-222.

3. Nehring, D. 1962. Experiments on the toxicological effect of thallium ions on fish and fish-food organisms. Z. Fisch. 11:557-562.

4. Norris, P., K. M. Wing, M. N. Hughes and D. P. Kelly. 1976. Toxicity and accumulation of thallium in bacteria and yeast. Arch. Microbiol. 110:279-286.

COMMENTS ON THE PROPOSED HUMAN HEALTH CRITERION FOR

Thallium

by

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CONCLUSION: Although the safety factor used to calculate the ambient water quality criterion for thallium seems to be higher than justifiable, I would have no serious objection to the final criterion proposed in this document (4 µg/l).

GENERAL COMMENTS:

In following the arguments, assumptions and calculations used to calculate the human health criterion for thallium in ambient water supplies, it is evident that the recommended level of 4 µg/l provides a generous margin of safety. The rat subchronic study (Downs et al.) is reported to demonstrate a NOEL of less than 12 ppm in the diet (calculated to be less than 1.6 mg/kg/day). Reducing the dose by 1/3 results in no symptoms or adverse effects, which suggests a NOEL of about 1 mg/kg. Using the NAS Safe Drinking Water Committee approach for data of this type (no 2-year chronic, scanty subchronic, no acute human data) with a safety factor of 1000, the calculation would be as follows:

$$\frac{1}{1000} = 1.0 \text{ µg/kg/day (ADI)} \times 70 \times 0.1 = 7 \text{ µg liter}$$

In the case of thallium, this safety factor seems large since there is rather good data on the acute lethal dose for thallium in children and adults, and the toxic effects of thallium are similar following single or fractionated doses. The human health criterion calculated in this document includes a further reduction (additional safety factor) to take care of the differences in intake required by the rat and man to attain a steady state condition. In the NAS SDW approach, such additional factors are not included since they are assumed to be more than adequately provided for by the use of the 3-fold safety factor approach. Thus, the human health criterion calculated in this document is lower than the NAS SDW toxicologists would have recommended. However, the difference is not large and there are some arguments for recommended levels in this document, which are not directly related to the safety factor approach. In addition, the data in this report indicate that this level will be reasonable in terms of detection methodology and the "real world" situation.

This report demonstrates one of the current concerns of many toxicologists in the use of safety factors by regulatory agencies to establish hazard standards. When safety factors are applied sequentially or "pyramided," the

net result is often a gross exaggeration of the level of protection. For agents with a steep dose-response relationship, this approach is almost invariably inappropriate, both from a toxicologic viewpoint and for maximizing benefits and minimizing the risks associated with a specific chemical entity.

AN EVALUATION OF THE PROPOSED AQUATIC LIFE CRITERION ON TRICHLOROETHYLENE

Conclusion

A more defensible number for the maximum concentration that should not be exceeded is 7900 ppb. A chronic number needs to be developed.

Prepared by

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June 1, 1979

GENERAL COMMENTS

The key data used to establish the aquatic life criterion are from unpublished EPA documents. Until such data is published in the open literature, the criterion as proposed lack credibility.

The criterion to protect freshwater aquatic life is based on invertebrate species and should be so stated.

Specific Comments

p A-1. 1) Trichloroethylene is not used as an inhalation aesthetic at this time and the statement indicating such a use should be deleted.

2) The paper by Pearson and McConnell is a general overview paper and should not be used as primary reference.

3) The paper by Radding et al on bioconcentration was not available for review. Again, this is an internal EPA document and is not suitable as a primary reference. The statement "may bio-accumulate" implies a potential problem. At the expected water concentration it is inconceivable that bioconcentration will be a problem. Hence, this statement implying bioaccumulation should be deleted.

CRITERION FORMULATION B-5

The guidelines for establishing a final acute invertebrate toxicity number suggest that the geometric mean of all acute values be estimated. Since there is only one acute value, it is impossible to determine a mean. Hence, this method should not be used.

A more defensible number is 7900 ug/L based on the fish acute studies.

EVALUATION OF THE HEALTH EFFECTS SECTION
OF THE CRITERIA DOCUMENT
FOR AMBIENT WATER
FOR

TRICHLOROETHYLENE

Conclusions: The evaluation of the carcinogenic effects of trichloroethylene is compromised and the derived criterion is very questionable. The significant toxicological literature on trichloroethylene is adequately reviewed.

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May 14, 1979

General Comments:

The criterion document on trichloroethylene (TCE) covers the available literature relative to toxicology and health effects well. The evaluation of the carcinogenic effects of TCE is compromized and the derived criterion is very questionable.

Specific Comments:

Page C-2 (top) What is trichloroethylene chloride?

Page C-21 (bottom) The interactions of TCE with CNS stimulants or depressants are speculative.

Page C-22. Considering the weakness of the mutagenicity data the introductory statement in the teratogenicity section is inappropriate.

Pages C-23 to C-24. The last sentence of the mutagenicity section should be used to introduce this section. The occurrence of impurities in the TCE samples tested has so compromized many mutagenicity studies and the carcinogenicity study, that it should be treated as a major point of discussion.

Page C-24 (center). The reported concentration of 1M TCE in tissue culture is either reported in error, or the resulting changes bear no relationship to any real world changes.

Pages C-24 to C-25. Since the proposed criterion is for TCE and not for epichlorohydrin or epoxibutane, the NCI carcinogenicity data cannot be used to establish a criterion for TCE