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Methodology for Assessing Hazards of

Contaminants in Seafood 80 pp

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Narragansett Bay Estuary Program

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Final Report to the Narragansett Bay Project for the year 1986-87

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FOREWORD

The United States Congress created the National Estuary Program in 1984, citing its concern for the "health and ecological integrity" of the nation's estuaries and estuarine resources. Narragansett Bay was selected for inclusion in the National Estuary Program in 1984 and designated an "estuary of national significance" in 1988. The Narragansett Bay Project (NBP) was established in 1985. Under the joint sponsorship of the U.S. Environmental Protection Agency and the Rhode Island Department of Environmental Management, the NBP's mandate is to direct a five-year program of research and planning focussed on managing Narragansett Bay and its resources for future generations. The NBP will develop a comprehensive management plan by June 1991 , which will recommend actions to improve and protect the Bay and its natural resources.

The NBP has established the following seven priority issues for Narragansett Bay:

* management of fisheries
* nutrients and potential for eutrophication
* impacts of toxic contaminants
* health and abundance of living resources
* health risk to consumers of contaminated seafood
* land-based impacts on water quality
* recreational uses

The NBP is taking an ecosystem/watershed approach to address these problems and has funded research that will help to improve our understanding of various aspects of these priority problems. The Project is also working to expand and coordinate existing programs among state agencies, governmental institutions, and academic researchers in order to apply research findings to the practical needs of managing the Bay and improving the environmental quality of its watershed.

This report represents the technical results of an investigation performed for the Narragansett Bay Project. The information in this document has been funded wholly or in part by the United States Environmental Protection Agency under assistance agreement #CX812680 to the Rhode Island Department of Environmental Management, and by the Rhode Island Toxics Integration Project. It has been subject to the Agency's and the Narragansett Bay Project's peer and administrative review and has been accepted for publication as a technical report by the Management Committee of the Narragansett Bay Project. The results and conclusions contained herein are those of the author(s), and do not necessarily represent the views or recommendations of the NBP. Final recommendations for management actions will be based upon the results of this and other investigations

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FOREWORD

The methodology and results obtained from it for assessing hazards from seafood contamination in Narragansett Nay presented in this report were developed in the academic year 1986-7. The project was supported by the Narragansett Bay Project. Since the submission of this report to the Bay Project in the summer of 1987 and its publication in Regulatory Toxicology and Pharmacology, January 1988 (Brown *et al.*, 1988) the report has been reviewed extensively, and we have spent another year applying the methodology. We have not, unfortunately, had any resources or opportunity to update the methodology or to make substantive changes in some of the directions recommended by the reviewers or from our own experience in using the methodology. We do stand by the methods and the conclusions as presented here: we have made minor changes in the original text of the final report.

In lieu of an update of the methodology, we include here excerpts from the draft final report of our 1987-88 project, which indicate how such an update might proceed.

The objective of the 1986-7 project was to develop a methodological tool for assessing the hazards of contaminants in Narragansett Bay Seafood which would have the following properties:

- it would be accessible and useful to Rhode Island officials in Narragansett Bay planning issues, who did not not necessarily have extensive toxicological training;
- it would not be used to provide a legal basis for regulation, but would be used to inform the planning process for Bay development;

- consistent with the objective of making the methodology accessible, it would capture the diversity and some of the complexity of the spectrum of possible contaminants and the range of possible effects on human health;
- it would take into account the large differences between people in the amount of seafood they consume;
- it would be based on up-to-date reviews of the relevant toxicological information.

While the proposed methodology broadly meets the objectives set, there are a number of problems with its use which have been identified by us in the course of our work this year and last, and by reviewers of the methodology. These problems have been only partly addressed in the work performed in 1987-88 and must be considered still unresolved. They include the following concerns:

- while the method is primarily intended to be used by State officials as a part of their preparation for incorporating health concerns in Bay management, not many people have tried to use it, and there has been little feedback about what aspects are informative/uninformative and convenient/inconvenient in use;
- while the method implicitly recommends the use of new compendia of information (such as the IRIS Data Base) by recommending the use of EPA reference doses when they are available, it does not include specific directions for obtaining the most up-to-date information;
- the secondary literature on reproductive and developmental hazards is in poor shape (partly reflecting problems with the primary literature) and we were forced to compromise among objectives for this dimension of hazard; this is an area where building in an updating capability would be particularly desirable;
- there is still extremely little information available for basing estimates of seafood consumption;
- the method does not provide for any explicit consideration of hazard management alternatives.

Further Use of the Methodology

With regard to the use of the methodology we have a number of observations: some pertain to the information base on which the methods rest; others concern the effective incorporation of the methodology, or something like it, into Rhode Island's planning.

- The available information for making exposure estimates is still woefully incomplete: the monitoring information on contaminants is still quite limited, and there are as yet no reliable data on seafood consumption patterns in the Narragansett Bay area, nor information about how seafood from particular areas is likely to be distributed. The first step needed in this regard is a proper local survey of fish consuming habits.
- The national regulatory review of reproductive/developmental toxicity is still incomplete and inconsistent when compared with the reviews of systemic toxicity and carcinogenicity. This and the previous set of problems will plague any assessment methodology, not only the one we recommend.
- Risk assessment data bases are changing very rapidly and it is a major challenge, which we have not addressed, to show explicitly how to keep these methods up-to-date, using the latest secondary sources. (The recent issue of the IRIS data compendium after the preparation of our report is an illustration of this problem.)
- The methodology has not adequately been tested to see whether it meets its principal objective (and to identify ways in which it can be better directed toward that objective), which is to serve as a learning device for State Officials who are not trained as toxicologists, but need a general understanding of health hazards to incorporate in planning for Bay management; we need to know better whether the emphasis on diversity in health effects, qualitative characterizations, and simply structured numerical analysis (which follows current regulatory practice) is helpful in practice during policy formulation.

- Perhaps the major challenge is to explicitly relate health effects analyses to planning options for Bay development and management.

INTRODUCTION

The tragedy of fish contamination with mercury in Minimata Bay brought to public attention the dangers of human exposure to toxic chemicals via consumption of contaminated aquatic organisms (WHO, 1976). In this country, numerous surveys conducted since the mid-seventies demonstrated the presence of trace levels of metals, synthetic pesticides, and other toxic organic compounds in a variety of aquatic organisms. The 1976 National Marine Fisheries Service survey reported the presence of mercury, lead, cadmium, chromium, and arsenic in sea and fresh water fish at concentrations ranging from 0.12 ppm for mercury to 2.6 ppm for arsenic (Zook *et al.*, 1976). Some of the same metals, as well as additional ones (silver, cobalt, iron, manganese, nickel, and zinc) were found in several surveys of fish and shellfish in the New England waters in concentrations ranging from 0.1 ppm for cobalt to 53 ppm for zinc (Eisher *et al.*, 1978; Capuzzo *et al.*, 1987). Polychlorinated biphenyls (PCBs) are particularly ubiquitous contaminants of aquatic organisms because of their widespread presence in the environment and their persistence and ability to bioconcentrate. PCBs have been found in the organisms from various New England waters (Capuzzo *et al.*, 1987) and in other locations along the U.S. coastline (Farrington *et al.*, 1982) as well in Lake Ontario (New York State, 1982), in the Great Lakes, and in the Hudson River (New York State, 1985). Concentrations of PCBs were as high as hundreds of parts per million in extreme cases.

In addition to PCBs several of the surveys reported the presence of organic pesticides such as DDT, DDE, aldrin, endrin, mirex, hydrochlorobenzene, dieldrin, kepone, chlordane, and toxaphene in concentrations of 1 ppm or less.

In the United States the Federal Food and Drug Law requires the Food and Drug Administration to set action levels for contaminants in fish and seafood designated for interstate commerce (US FDA, 1982). The action levels are based on both the toxicity to people of

chemicals and on the economic impact of such regulation. To date, action levels have been set for 11 chemicals and chemical classes, clearly leaving a large number of contaminants known to be present in aquatic life unregulated.

Increasing evidence of the presence of chemical contaminants in seafood, continuing public and institutional concerns over the potential hazards of consuming contaminated seafood, and mounting pressure on state regulatory agencies to respond to these concerns all have created a need for a methodology to characterize and judge these hazards. To be useful as a risk assessment tool such a methodology would have the following characteristics: (1) it would be capable of addressing a large number of chemicals within limited resources, yet be based on a reliable, comprehensive, and readily accessible data base; (2) it would be sensitive to a unique spectrum of the hazardous properties of each chemical and to the attendant scientific uncertainty, yet be simple enough to allow relative ranking of these properties; (3) it would be capable of separating chemical contaminants into categories according to the degree of hazard; and (4) it would provide the basis for setting priorities and making hazard management decisions.

In this paper we describe the results of our efforts to develop such a methodology. The results of assessment of seven chemicals identified in quahog clams from Narragansett Bay, using our methodology, are also presented.

PHASE I ASSESSMENT

Central to our system is a two-phased risk assessment of chemicals. In Phase I a profile of hazardous properties, broadly defined as a function of toxicity and exposure, is generated. On the basis of this profile, chemicals are sorted into two potential hazard categories, high and low, according to the degree of concern they raise for public health. Chemicals classified into high potential hazard category undergo Phase II assessment which is more detailed than Phase I assessment and focuses only on those hazardous characteristics of an agent that, according to the profile generated in Phase I, may contribute to a public health hazard. Chemicals classified into low potential hazard category are considered to present no current threat to public health and are

excluded from further consideration.

The Phase I assessment is conceptually related to a previously developed methodology for assessing hazards of air contaminants (Brown *et al.*, 1987). Each chemical is assessed under five categories, four of which are related to health effects: carcinogenicity, mutagenicity, developmental/reproductive toxicity, and systemic toxicity. The fifth category is exposure. The product of the assessment is a relative score, a to e (a to d for exposure), plus ND designation (for no data) in each category for each chemical, where "a" denotes the greatest hazard. Thus, the hazard profile for each chemical is described in a five-letter code.

Three elements were considered in developing scores for each health effect category, weight of evidence, severity of effect, and potency.[1] The first two elements are the qualitative component of the assessment and can be expressed in arbitrary symbols or verbal descriptors. Potency is the quantitative element and is expressed in units unique to a particular health effect category. Under such a system each score would thus reflect the degree of confidence that the effect noted is real, the magnitude of response, and the severity of the effect observed. Our initial goal was to consider all three elements for each of the four health effect categories. However, as shown later, for some health effect categories this approach was not practical because there are no satisfactory methods for scoring some of the three elements.

For the exposure category, two elements are used to derive a score: the average concentration of the contaminant and a qualitative measure of variability in exposure. Derivation of scores is described in more detail in the following sections for each of the categories.

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[1]The term "weight of evidence" refers to the amount or strength of evidence that a particular effect will occur in humans. It describes how much data exist, and the degree of confidence that the effects noted are genuinely associated with the chemical being evaluated. "Potency" refers to the size of dose which elicits a particular response and "severity of effect" pertains to the seriousness of health implications of a particular effect.

Table 1

SOURCES OF TOXICITY DATA USED FOR EACH HEALTH EFFECTS CATEGORY

Title
SYSTEMIC TOXICITY
° Verified Reference Doses of the U.S. EPA (US EPA, 1985a)
° National Primary Drinking Water Regulations, Federal Register November 13 (US EPA, 1985b)
° Draft Superfund Health Evaluation Manual (US EPA, 1985c)
° EPA Health Assessment Documents (chemical-specific)
° National Academy of Sciences, Drinking Water and Health, Vols. 1-5 (NAS, 1977-1983)
CARCINOGENICITY
° See above
° See above
° See above
° IARC Monographs on the Evaluation of Carcinogenic Risks of Chemicals to Humans (IARC, 1982)
° Carcinogen Assessment Group
° National Toxicology Program. Technical Reports on the Toxicology and Carcinogenicity of Chemicals
MUTAGENICITY
° See above
° See above
° See above
° EPA Gene-Tox data base (Office of Pesticides and Toxic Substances)
REPRODUCTIVE/DEVELOPMENTAL TOXICITY
° Primary literature strongly recommended
° See above
° See above
° Chemical Hazards to Human Reproduction (CEQ 1981)
° Catalog of Teratogenic Agents (Shepard, 1980)
° Reproductive Hazards of Industrial Chemicals (Barlow, Sullivan, 1982)

Table 2

SCORING MATRIX FOR CARCINOGENICITY[a]

Weight of Evidence Category[b]	Potency Index $(\mu g/kg\text{-}day)^{-1}$			
	$10^{-2}<PI$	$10^{-3}<PI\leq10^{-2}$	$10^{-4}<PI\leq10^{-3}$	$PI\leq10^{-4}$
A, Human Carcinogen	a	a	a	a
B1, Probable Human Carcinogen	a	b	b	b
B2, Probable Human Carcinogen	a	b	b	c
C, Possible Human Carcinogen	b	b	b	c
D, Not Classifiable	d	d	d	d
E, Evidence of Non-Carcinogencity	e	e	e	e

[a]Scores "d" and "e" are derived on the basis of weight of evidence alone.

[b]Weight of evidence categories, A, B1, B2, C, D, E, have been previously defined by the Environmental Protection Agency (US EPA, 1986)

Data Base

As shown in Table 1 the assessment methodology in Phase I is designed to rely on secondary sources of data on health effects, wherever possible, mainly in recognition of the limited resources available to most of the potential users. Only for the developmental/reproductive toxicity information do we recommend going directly to the published literature. The methods for using the primary and secondary literature for scoring this category have been described previously (Brown *et al.*, 1986). A simplified version of that methodology is shown in Appendix A.

The mutagenicity category heavily relies on the EPA Gene-Tox data base but is also supplemented by other sources, as indicated in Table 1.

For the toxicity category only data derived from oral administration of chemicals is used. The specific sources are lited in Table 1 in descending order of preference. This order is largely related to the level of detail provided by each one of these documents.

For the carcinogenicity category, we rely mostly on the data summarized and evaluated by the EPA Cancer Assessment Group (CAG). References where the CAG data can be found are listed in Table 1. The CAG data can also be supplemented by other sources, in particular the reports of the National Toxicology Program carcinogenicity bioassays.

The categorization of exposure is to be based on ongoing measurements of concentration of toxic substances in seafood. The choice of categories based in part on fish consumption data derived from National Marine Fisheries Service and other surveys, as discussed later.

Health Effect Scores

Tables 2 through 6 show the matrices used to derive scores under the specific health effect categories. Three of the four matrices use qualitative and quantitative components to derive a score. For carcinogenicity and developmental/reproductive toxicity the qualitative element--the weight of evidence--is used in such a way that a lower degree of confidence that the effect is real requires an increasingly greater potential magnitude of that effect (potency) in order to assign a

particular score. This assures that poorly tested but potentially hazardous chemicals are not overlooked. As shown in Table 2 the weight of evidence classification for carcinogenicity is based on six categories: A, human carcinogens: B1 and B2, probable human carcinogens; C, possible human carcinogens; D, not classifiable as to human carcinogenicity; E, evidence of noncarcinogenicity for humans. These are adopted unchanged from the guidelines for carcinogen assessment recently issued by the Environmental Protection Agency (US EPA, 1986a). The potency index (PI) is defined in terms of a unit risk: PI is the 95% statistical upper bound estimate of the probability of contracting cancer by experimental animals per unit dose, where unit dose is one µg/kg-day administered orally. Table 2 also shows that greater significance is attached to qualitative than to quantitative data. Thus, the weight of evidence classification determines the minimum score. This is especially evident for the human carcinogens category which receives "a" score, regardless of potency.

As defined previously (Brown *et al.*, 1986) reproductive toxicity refers to any effect resulting from parental exposure to a substance which interferes with conception, gestation, birth, or development of offspring to health adult life. Developmental toxicity refers to adverse effects on the fetus and consists of three types of abnormalities; teratogenicity, embryo/fetal toxicity, and postnatal and perinatal developmental toxicity. As shown in Tables 3 and 4 weight of evidence is classified into five categories, separately for developmental and reproductive toxicity. For developmental toxicity, there is a further division into subcategories I, II, and III based on the severity of effect. The categories and the method for ranking the weight of evidence have been previously described (Brown *et al.*, 1986). Two indices for quantitative assessment are used: lowest observed effect level (LOEL) and risk ratio (RR). LOEL is the lowest dose at which statistically significant effects are observed. It is not synonomous with potency because it is not related to the dose-response curve, but is used here as a measure of potency. LOEL is chosen as a key quantitative measure of the magnitude of effect for practical reasons: no observed effect level (NOEL) and potency values for reproductive and developmental toxicity are rarely reported in the literature.

Table 3

SCORING MATRIX FOR REPRODUCTIVE TOXICITY

WEIGHT-OF-EVIDENCE[a]	LOEL	SCORE
Confirmed Evidence	NA	a
Substantial Evidence	$0 < LOEL \leq 50$	a
Suggestive Evidence	$0 < LOEL \leq 5$	a
Substantial Evidence	$50 < LOEL \leq 200$	b
Suggestive Evidence	$5 < LOEL \leq 100$	b
Substantial Evidence	$200 < LOEL \leq 400$	c
Suggestive Evidence	$100 < LOEL \leq 325$	c
Substantial Evidence	$400 < LOEL \leq 500$	d
Suggestive Evidence	$325 < LOEL \leq 500$	d
Insufficient Evidence	$500 < LOEL$	e
No Data		ND

[a]Weight-of-Evidence categories have been previously defined (Ref)

Table 4

SCORING MATRIX FOR DEVELOPMENTAL TOXICITY

WEIGHT-OF-EVIDENCE[a]	LOEL mg/(kg-day)		RISK RATIO	SCORE
Confirmed Evidence	NA		NA	a
Substantial Evidence				
Group I	$0 < LOEL < 50$	or	$100 < RR$	
Group II	$0 < LOEL \leq 25$	or	$150 < RR$	a
Suggestive Evidence				
Group I	$0 < LOEL < 5$	and	$200 < RR$	
Group II	$0 < LOEL \leq 2$	and	$250 < RR$	a
Substantial Evidence				
Group I	$50 < LOEL < 200$	or	$20 < RR < 100$	
Group II	$25 < LOEL \leq 150$	or	$30 < RR \leq 150$	b
Suggestive Evidence				
Group I	$5 < LOEL < 100$	and	$40 < RR < 200$	
Group II	$2 < LOEL \leq 75$	and	$50 < RR \leq 250$	b
Substantial Evidence				
Group I	$200 < LOEL < 400$	or	$2 < RR < 20$	
Group II	$150 < LOEL \leq 350$		$3 < RR \leq 30$	c
Suggestive Evidence				
Group I	$100 < LOEL < 325$	or	$4 < RR < 40$	
Group II	$75 < LOEL \leq 300$	or	$5 < RR \leq 50$	c
Group III	$LOEL \leq 25$		NA	
Substantial Evidence				
Group I	$400 < LOEL < 500$	or	$1 < RR < 2$	
Group II	$350 < LOEL \leq 500$	or	$1 < RR < 3$	d
Suggestive Evidence				
Group I	$325 < LOEL < 500$	or	$1 < RR < 4$	
Group II	$300 < LOEL \leq 500$	or	$1 < RR < 5$	d
Group III	$25 < LOEL \leq 500$		NA	
Substantial or Suggestive Evidence (Groups I, II, or III)	$500 < LOEL$	or	$RR < 1$	e
Insufficient Evidence	NA		NA	e
No Data				nd

[a]Weight-of-Evidence categories and subcategories (I, II, III) have been previously defined (Ref)

A second component in the scoring system for developmental toxicity is the risk ratio. The RR provides a quantitative estimate of the degree to which a chemical can exert toxicity to the fetus or embryo without producing maternal toxicity. It does not apply to reproductive effects. It is defined here as a ratio of an adult toxic dose LD_{50} or LC_{50}) to the fetal toxic dose (LOEL) in the same species and route of absorption. A large risk ratio is of concern because it means that developmental toxicity occurs at doses far lower than toxicity to the mother. As with LOEL, the choice of LD_{50} or LC_{50} rather than maternal LOEL is dictated by the availability of data. The scores for developmental/reproductive toxicity of 110 chemicals, and details of their derivation, have been previously reported (Brown *et al.*, 1986).

For purposes of the assessment, a mutagen is defined as a chemical capable of inducing alterations in the genetic material of either somatic or germinal cells. The term "mutation" encompasses a broad spectrum of genotoxic events, including mutations affecting one or more nucleotides of DNA, several genes, large segments of chromosmes, or entire chromosomes. Mutagenic endpoints of concern include point and gene mutations, structural or numerical chromosome aberrations, other genotoxic effects, cellular transformation, and abnormal sperm morphology. Thus, while experimental data demonstrate a correlation between mutational events and carcinogenicity, the mutagenicity assessment is designed to evaluate a range of genotoxic endpoints of potential significance to humans and is not merely a substitute for, or an adjunct to, the carcinogenicity assessment. As shown in Table 5 the mutagenicity score is based only on the weight of evidence that a chemical may produce effects in humans. This is because of lack of widely accepted units of potency applicable to all bioassays considered here and because of inability to distinguish the severity of different types of genetic events in relation to human health. The score is derived after considering the result of testing in any of 76 different short-term and long-term screening assays, which are grouped into categories I, II, and III in a decreasing order of their relevance to humans. A detailed discuion and rationale for deriving the scores for 100 chemicals have been described previously (Brown *et al.*, 1986a).

Table 5

SCORING CRITERIA FOR MUTAGENICITY

CATEGORY	TEST TYPE AND NUMBER OF POSITIVE RESULTS[a]	LETTER SCORE
Sufficient Evidence	Group I: Two or More	a
	or	
	Group II: Four or More	a
	or	
	Group III: Six or More	a
	or	
	Group I:	
	and	a
	Group II: One or More	
	or	
	Group I: One	
	and	a
	Group III: Two	
Substantial Evidence	Group I: One	b
	or	
	Group II: Three	b
	or	
	Group III: Four or Five	b
	or	
	Group II: One or Two	
	and	b
	Group III: Three	
Suggestive Evidence	Group II: One or Two	c
	or	
	Group II: Two or Three	c
	or	
	Group II: One or Two	
	and	
	Group III: One or Two	c
Limited Evidence	Group III: One	d
Inadequate Evidence	Inconclusive Data (results equivocal)	
	or	e
	Non-positive results only	
No Data	Chemical not tested	ND

[a]Screening assays classified into Groups I, II and III have been previously defined (Ref)

The scoring matrix for systemic toxicity, defined here as all adverse effects not covered by the other three categories, is shown in Table 6. Two elements define the score: quantitative, represented by a value of the acceptable daily human dose, and qualitative, in the form of a severity factor. The value of acceptable daily human dose (ADD) is selected from one of the following quantitative toxicity indices: verified reference doses (RfD; US EPA, 1985a), acceptable intake (ADI; US EPA, 1985b), suggested no adverse response level (SNARL;[2] NAS, 1977-1983), and acceptable intake for chronic exposure (AIC; US EPA 1985c). Despite different names, these four indices are essentially equivalent in that they represent a daily human dose (in μg/kg-day) which is not expected to produce adverse health effects upon chronic exposure. It is derived from no observed adverse effect level (NOAEL) by applying an appropriate uncertainty factor. If more than one value of such acceptable daily dose exists, we recommend the following order of preference: RfD > ADI > SNARL > AIC. This order of preference is based on the currency, extent of peer review, and level of detail provided by each source.

Based on the health effects documented in the references used to derive ADD, a rating factor of 1, 2, or 3 is assigned, representing the severity of those effects, as well as potential reversibility. Only the effects associated with the acceptable daily dose are described by the severity factor and both toxicity descriptors are derived from the same study. Evidence of carcinogenicity, mutagenicity, developmental, and reproductive toxicity are not considered in assigning the toxicity score since they are evaluated separately. Severity factors are assigned as follows:

one point: mild or transient irritant effects (e.g., runny nose, eye irritation, headache, coughing).

two points: moderate to severe irritant effects; mild to moderate transient systemic effects; effects generally considered to be reversible (e.g., anoxia, incoordination, fatigue, dizziness).

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[2]An alternative term used by EPA is Health Advisory, HA. Health Advisories, like SNARLs, are issued by the Office of Drinking Water.

Table 6

SCORING MATRIX FOR SYSTEMIC TOXICITY BY ORAL ROUTE

Acceptable Daily Dose (ADD) (mg/kg-day)	Severity Factor 1	2	3
ADD≤0.001	c	b	a
0.001<ADD≤0.01	c	c	b
0.01<ADD≤0.1	d	c	b
0.1<ADD≤1	e	d	c
1<ADD	e	d	c

three points: irreversible or serious systemic effects; chronic or persistent effects; cumulative effects; or effects involving multiple sites or organ systems (e.g., epilepsy, cirrhosis, peripheral nerve damage).

The matrix for toxicity is such that at a lower severity of effect higher potency is required to arrive at a particular score. This assures that the highest scores are reserved only for agents for which the daily dose protects against severe adverse health effects.

No weight of evidence classification for systemic toxicity is used for two reasons: the level of detail offered by the sources of data used is insufficient; there are no generally agreed upon methods to do so, although the current efforts in that area may change that (US EPA, 1987).

Exposure Scores

The scoring matrix for exposure is shown in Table 7. Two elements define a score; a quantitative element, the average concentration in seafood (in ppm or µg/g of wet weight); and a qualitative element, defined here as an index of variation. The choice of scale for concentrations reflects four criteria: (1) to be consistent with the rough treatment of quantitative variables in the health effects it is defined in orders of magnitude; (2) it covers the most likely range of observed concentrations for a wide variety of substances; (3) it allows for the possibility that there may be substantial variation in the concentration of a particular substance found in particular types of seafood and takes account of the effect such variation might have on the distribution of exposures; and (4) the top categories for exposure are such that chemicals that may score "c" or lower in all health effect categories, but are present in high concentration in seafood, and are not excluded from further assessment.

The third criterion is met by using the index of variation in the matrix. The index accounts for the possibility that the average concentration might seriously underestimate the exposure to some individuals and reflects possible uncertainties in the data due to (1) the variation in concentration among organisms collected for analysis and (2) the variation introduced by handling and sample analysis. The index is defined in Table 7. It uses the ratio of maximum to average

Table 7

MATRIX FOR SCORING EXPOSURE CATEGORY

Measured Average Concentration	Score	
ppm (µg/gm - wet)	Typical Variation[a]	Potentially High Variation
> 30	a	a
3 - 30	b	a
.3 - 3	c	b
< .3	d	c

[a]Variation is defined by three numbers: the average concentration, the maximum concentration measured, and the number of samples;

Typical Variation

More than 100 samples *and* Maximum/Average < 20

or

20 - 100 samples *and* Maximum/Average < 10

Potentially High Variation

Fewer than 20 samples

or

Fewer than 100 samples *and* Maximum/Average > 10

or

Maximum/Average > 20

values as a measure of *observed* variability and uses sample size as an indicator of how much *opportunity* there has been to observe variation. The assumption of "typical" variability is that at most a few percent of individual samples will exhibit values greater than 10 times the average value. "Potentially high variation" defines cases where either the data exhibit great variation or the average is poorly determined so that the possibility of a few percent of samples exceeding 30-100 times the measured average value cannot be ruled out.[3] Once the index of variability is determined, the exposure score for a particular average concentration is given by the matrix in Table 7. "Potentially high" variability shifts the score one letter (one order of magnitude in concentration), since average scores may be a more serious underestimate in this case.

The results of applying the fourth criterion for the scale of concentrations in Table 7 are shown later on.

Hazard Profiles

The scores produced for 20 sample chemicals under each of the five categories are listed in Table 8. Of these, only seven metals were assigned exposure scores based on the data collected for quahog clams from Narragansett Bay. Measurements for other contaminants were not available. The chemicals were not selected on the basis of hazardousness but rather as a representative sample of contaminants likely to be detected in seafood. As shown in Table 8 the results of assessment in Phase I for each substance are described in a five-letter code. The code reflects the types of adverse health effects associated with a given chemical, the severity and potential magnitude of these effects at certain doses, the magnitude of potential human exposure, the characteristics which may contribute the most to the hazard to humans, and gaps in the data

[3]These assumptions can be described more precisely in terms of a mathematical model in which concentration measurements are assumed to obey a log-normal distribution. "Typical" variability corresponds to a geometric standard deviation of 3 or smaller. "Potentially high" variability is represented by a geometric standard deviation of 5 to 10. The particular choice of indicators in Table 7 is based on that model.

Table 8

HEALTH EFFECTS AND EXPOSURE SCORES FOR 20 SAMPLE CHEMICALS

Chemical name	Toxicity			Carcinogenicity			Mutagenicity score	Reproductive/developmental toxicity				Exposure
	ADD[a]	Severity factor	Score	PI	WOE	Score		LOEL	WOE	RR	Score	
Arsenic and compounds	0.2	3	a	1.5×10^{-2}	A	a	b	—	a	—	a	ND
Barium and compounds	50	2	c		D	d	e				ND	ND
Benzo[*a*]pyrene				1.1×10^{-2}	B2	a	a				ND	ND
Cadmium and compounds	0.55	3	a		D	d	ND	1.25	Subst.	—	a	d
Chlordane	0.9	3	a	1.7×10^{-3}	B2	b	d	0.16	Sug.	—	b*[b]	ND
Chromium and compounds	5	3	b		D	d	ND				ND	c
Copper and compounds	40	1	d		D	d	e				ND	b
DDT	20	1	d	3.4×10^{-4}	B2	b	e	50	Sug.		b	ND
Epichlorohydrin	2	3	b	1.8×10^{-6}	B2	c	a	80	Sug.	—	b	ND
Heptachlor	0.07	2	b	3.4×10^{-3}	B2	b	d		Insuf.		e	ND
Heptachlor epoxide	0.03	2	b	5.4×10^{-2}	B2	a	d		Insuf.		e	ND
Lead and copper	0.6	3	a		D	d	d	0.11	Subst.	—	a*	c
Lindane	0.3	2	b	1.3×10^{-3}	C	c	ND		Insuf.		e	ND
Mercury (org)	0.1	3	a		D	d	ND		Suff.		a	d
Methoxychlor	50	2	c		D	d	e				ND	ND
Nickel and compounds	10	2	c		D	d	ND	0.5	Sug.		b*	b
PCBs	2	1	c	4.3×10^{-3}	B2	b	ND	0.06	Subst.	—	a	ND
Pentachlorophenol	30	3	b		D	d	d	5	Sug.	27	a	ND
Selenium and compounds	3	2	c		D	d	ND		Insuf.		e	ND
Zinc and compounds	200		e		D	d	ND				ND	a

[a] Abbreviations and units used: ADD, acceptable daily dose (μg/kg-day); PI, potency index $(\mu g/kg\text{-}day)^{-1}$; WOE, weight of evidence; RR, risk ratio; LOEL, lowest observed effect level (mg/kg-day).

[b] Astersk signifies that the score was assigned on the basis of qualitative evidence only.

base. The methodology does not produce a cumulative score because its aim is to capture the complexity of hazardous properties of chemicals and the associated uncertainty, rather than to rank order them. Despite the simplicity of the five-letter code, the elements of each score, and the underlying data base, are sufficiently informative to be interpreted in terms of risks to the population consuming the contaminated seafood. This is demonstrated later on.

Seafood Consumption

In order to interpret the significance of the hazard profiles shown in Table 8 to human health the scores under the health effect categories, and especially their quantitative components, must be viewed in terms of the oral intake of the contaminants in seafood. Oral intake of a substance from seafood is a function of concentration and seafood consumption, and is commonly expressed as a daily dose in relation to human body weight, as shown:

$$\text{Intake } (\mu g/kg\text{-day}) = \frac{\text{Concentration } (\mu g/kg \text{ wet weight}) \times \text{Consumption } (kg/day)}{\text{Body weight } (kg)}.$$

In order to estimate the intake, not only must the data on concentration of toxic substance in seafood samples be interpreted, but also the seafood consumption by the exposed population must be estimated. Both elements have a range of uncertainty, although their origins are different. As discussed before, for concentration the uncertainty comes from limitations in the number and representativeness of samples and the variation among organisms collected for analysis along with any variation introduced by handling and analysis of the samples. For consumption, the uncertainty is related to the definition of the seafood consuming population, to the quality of the data on seafood consumption, and to the differences between people in the amount and rate at which they eat. In addition, particular rates and durations of intake are relevant to some but not other adverse health effects. For example, developmental and some toxic effects are most likely to occur as a result of exposure to high concentrations over a period of 1 or 2 months while for other types of chronic effects, including cancer, chronic exposure over years may be of primary concern.

This becomes an important consideration in risk assessment when intake data is evaluated in light of the toxicity profile, as we show later on.

For the purpose of this work we define the hypothetical exposed population as those individuals (1) whose consumption of seafood is typical for New England; (2) who obtain a large fraction of their seafood from Narragansett Bay; and (3) who consume the species that are of concern for assessment. The population is "hypothetical" in a sense that we know very little about how many people consume seafood from Narragansett waters and what fraction it is of their total seafood consumption. It would therefore not be possible to calculate the total number of adverse health outcomes by multiplying individual risks by the number of people in the reference population. This definition is adequate, however, for other regulatory aspects of risk assessment such as evaluation of individual risks to the members of the representative hypothetical population.

Our assumptions about seafood consumed by an average member of a hypothetical exposed population are listed in Table 9. Three averaging time periods are used: 24 hr for acute exposures, 1 month for intermediate exposures, and 1 year for long-term exposures. We take as a basic unit of consumption a nominal "meal" of 200 g of fish flesh. This is an arbitrary amount, but one consistent with the fish consumption data of Hu (1985) who summarized the results of four major seafood consumption surveys.[4,5] Although the Hu data provide mostly annual averages and therefore are not suitable for assessing the variability in consumption over shorter periods of time, they are broken down by major regional populations in the U.S., including New England, and by the types of fish and shellfish. According to Hu, average yearly consumption of all types of

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[4] (1) The 1969-70 Consumer Panel Survey funded by the National Marine Fisheries Service (NMFS) and conducted by Market Facts, Inc.
(2) The 1973-74 Seafood Consumption Survey funded by the Tuna Research Institute and conducted by NPD Research, Inc.
(3) The 1977-78 National Food Consumption Survey conducted by the U.S. Department of Agriculture (USDA).
(4) The 1981 National Consumer Panel, funded by NMFS conducted by Marketing Research Corp. of America.

[5] For comparison, Minnesota Department of Health assumes 227 g per meal for sportfishermen (Minnesota DNR, 1985). Others have used 150 g per meal (US EPA, 1986b).

Table 9

ASSUMPTIONS ABOUT SEAFOOD CONSUMED BY MEMBERS OF HYPOTHETICAL EXPOSED POPULATION

Size of a meal: 200 g (wet) of cleaned seafood

AVERAGE CONSUMER

Annual consumption: 7.2 kg = 20 g/day = .1 meal/day

Monthly during peak month: 2.4 kg = 80 g/day = .4 meal/day

Daily during peak 24 hrs: 400 g = 2 meals

HIGH CONSUMER

1 - 3% of population may consume 3 x these values

Assumptions based on data from Hu (1985)

seafood by New Englanders ranges from 10 to 25 g per day where the difference reflects different definitions of waste, differences in sampling methods, and differences in the data and averaging periods of the samples. We choose 20 g/day as the representative annual average consumption of fish by the hypothetical exposed population; this is consistent with the data of Hu and others (Minnesota DNR, 1985; US EPA 1986b). At 200 g per meal that corresponds to 0.1 meal per day or 36 meals per year. For the representative maximum 1 month exposure we assume 12 meals or 80 g/day, and for 24 hr we assume 2 meals or 400 g. According to our definition of the "exposed" population those consumption assumptions apply to that portion of the fish consuming population for which the relevant species is a substantial fraction of their annual seafood diet, that is, those at highest risk because they consume particular species of seafood.

As a simple model for the individual variability in eating habits (frequency and amount) among the hypothetical exposed population we assume that it roughly follows a log-normal distribution with a geometric standard deviation of approximately 2-3. A few percent (1-3%) of the individuals, those in the upper two standard deviations from the mean, will then consume amounts greater than 2-3 times the average. The assumption of a log-normal distribution gives a consumption estimate greater than 5-10 times the average for 0.1% of the subpopulation (3 standard deviations from the mean).

Variations in exposure can result both from variability in consumption patterns and from variability in the concentration in seafood. For "typical variation" as defined in Table 7, variation in consumption is most important for monthly and yearly exposures. For "potentially high" variation a high monthly exposure may result from one meal. In Table 10 we show the amount of variation in exposure that will be exceeded for only 1-3% of the exposed population from both effects combined.

Because the amount and quality of toxicity and exposure data generally available rarely support more than two standard deviation estimates, it is usually not appropriate to go beyond that point in our individual variability assumption. We therefore define the "high consumers" as those in the upper 1-3% of the hypothetical exposed population. This definition is consistent with that

Table 10

FACTOR BY WHICH INTAKE OF A TOXIC SUBSTANCE MIGHT EXCEED AVERAGE INTAKE FOR THE HIGHEST CONSUMING 1-3% OF THE HYPOTHETICAL EXPOSED POPULATION

	TYPICAL VARIATION	POTENTIALLY HIGH VARIATION
Day	10X	100X
Month	3X	10X
Year	3X	6X

The variation in intake, expressed as a factor X average intake, depends on the time period over which it occurs, variation in fish consumption behavior of the population, and the expected variability in concentrations found in fish.

currently adopted by EPA (US EPA, 1986b). Naturally, this definition of high-risk population should be adjusted upward or downward for individual contaminants according to the policy of a regulatory agency and according to the consumption and toxicity data available. For example, knowledge about a particular ethnic group consuming significantly above 3-fold the average value may alter that assumption. Similarly, concern for a specific hypersensitive subpopulation may lead to a redefinition of the "high risk population." In general, the ADD vaues derived from the sources listed in Table 1 are based on an assumption of a 10-fold variability in response to toxic substances among humans and are designed to protect about 99% of those within that group (Dourson and Stara, 1983). Others have argued that the variability is greater (Calabrese, 1985; Hattis, 1986) and that the size of the population outside the 10-fold range of individual response may be between 5 and 20% (Calabrese, 1985). Specific knowledge of a hypersensitive population may alter the assumptions for risk assessment for a particular chemical. These adjustments would be performed in Phase II of the assessment.

FIRST DECISION POINT: INTERPRETATION OF HAZARD PROFILES

Hazard profiles generated in Phase I have two functions: (1) to provide a basis for sorting the chemicals into two hazard categories, only one of which will be a subject of a more detailed health assessment in Phase II; and (2) to identify those health effect categories which may contribute to the health hazard the most and therefore be the focus of the assessment in Phase II.

The second function is efficiently fulfilled by the letter scores under the five categories where a's and b's clearly require more attention than c's, d's, and e's. The first function is an important element in hazard management because substances classified into a lower hazard category are excluded from further assessment on the assumption that they do not present a significant health hazard. The classification criteria must therefore be based on reasonably strong grounds. Our criteria are as follows:

High potential Hazard category: one or more "a" or "b" scores

Low potential Hazard category: no "a" or "b" scores.

The greatest concern in applying these criteria is that a substance that receives no "a" or "b" scores, and therefore is excluded from further consideration, may in fact present a significant health hazard. We tested that hypothesis on a hypothetical example of a chemical that receives scores "c" under toxicity, carcinogenicity, reproductive/developmental toxicity, and exposure categories.

As shown in Table 7, score "c" in the exposure category implies an average concentration of no more than 3 μg/g and 0.3 μg/g for typical and high variation, respectively. For a 1-month exposure that gives an average daily intake of 3 μg/kg-day and 0.3 μg/kg-day, respectively ([3 μg/g X 80 g/day]/70 kg = 3 μg/kg-day). A similar calculation for an annual exposure would give an average daily intake of 1 μg/kg-day and 0.1 μg/kg-day, respectively.

An acceptable daily dose for a substance classified as a "c" in systemic toxicity, with a severity factor 3, would be in the 100-1000 μg/kg-day range (Table 6). That is about 30-fold higher than the intake by an average member of the hypothetical exposed popualtion on a monthly basis and about an order of magnitude higher than the intake of a high consuming individual (Tables 9 and 10). Using the annual average consumption, instead of a monthly, would make the safety margin appropriately greater.

A lowest observed effect level for a substance classified as a "c" in developmental toxicity is at least 75 mg/kg-day. This is about four orders of magnitude greater than the average intake on a monthly basis (most appropriate for developmental toxicity) by a high consuming member of a hypothetical exposed population. If we further assume that the acceptable human dose for a developmental toxicant should be two to three orders of magnitude lower than the LOEL observed in animal experiments (uncertainty factor of 100-1000) (Dourson and Stara, 1983), the daily intake would still be significantly lower than such a dose.

From Table 2, for a substance classified as "c" in carcinogenicity the potency index associated with C weight of evidence (based on one animal bioassay whose reliability is open to question) is less than 10^{-4} kg-day/μg. Using body surface as a basis for conversion from an animal to human model would generally reduce that potency unit by approximately an order of

magnitude, to about 10^{-5} kg-day/µg (US EPA 1986a; Dourson and Stara, 1983). For an annual exposure (the most appropriate for carcinogenic risk) that implies an individual lifetime risk of 10^{-5} for an average member of a hypothetical exposed population, and between 10^{-4} and 10^{-5} for the a high consumer.

Whereas it is not possible to perform a similar quantitative analysis for mutagenic effects, it is nonetheless reassuring to note that substances classified as "c" in this category have only suggestive evidence of potential genotoxicity to humans.

The example presented here shows that no significant hazards are associated with exposure to substances that receive no "a" or "b" scores and justifies their exclusion from further assessment. The example also provides additional explanation for our particular choice of the scale for the exposure matrix (Table 7) and specifically the fourth criterion for the selection of the concentration scale in that matrix.

Applying the above criteria to the chemicals listed in Table 8 produces the following stratification of chemicals:

High potential hazard category	Low potential hazard category
Arsenic and compounds	Barium and compounds
Benzo[*a*]pyrene	Methoxychlor
Cadmium and compounds	Selenium and compounds
Chlordane	
Chromium and compounds	
Copper and compounds	
DDT	
Epichlorohydrin	
Heptachlor	
Heptachlor epoxide	
Lead and compounds	
Lindane	
Mercury and compounds	
Nickel and compounds	
PCBs	
Pentachlorophenol	
Zinc and compounds	

While it may perhaps seem disappointing that so few of the 20 chemicals can be classified as "low potential hazard," it is not surprising. The chemicals selected were all ones known to be of concern, and the nature of the regulatory responsibility is such that reasonably strong grounds are necessary to limit further consideration for a potential health hazard. Thus, this initial sorting is not an insignificant accomplishment.

In addition to performing the two functions, that of sorting out and that of highlighting the health effect categories requiring further analysis, the hazard profiles generated in Phase I provide sufficient qualitative and quantitative information about toxicity and exposure for a decision regarding which chemicals in the high potential hazard category may be of more urgent concern. This is described in the next section.

SECOND DECISION POINT: INTERMEDIATE ASSESSMENT

As illustrated by the example of a hypothetical chemical, a comparison of oral intake of a chemical, for some preselected exposure period, with the quantitative elements of each health effect score provides the basis for an initial decision about the nature and magnitude of a hazard associated with its presence in seafood. Such comparisons, based on the data listed in Table 11 are presented in Table 12 for seven metals measured in the Narragansett Bay clams. Because one set of management options is keeping open (or closed) selected areas in the Bay, we present in Table 11, mean values for each location. All of the measurements satisfied the requirement for "typical" variation (Table 7).

Only systemic toxicity and developmental/reproductive toxicity categories are included in Table 12 because neither of the seven metals received scores higher than "d" in the carcinogenicity or mutagenicity categories. In the table, the range of daily intake of each agent, calculated from the range of mean concentrations in clams collected from various sampling stations in the Bay (Table 11) and using a 1-month averaging period, is compared with the corresponding ADD and LOEL values. For copper, chromium, and zinc, the intake is well below the acceptable daily intake and

Table 11

CONCENTRATIONS OF SEVEN METALS IN QUAHOGS CLAM MEATS FROM NARRAGANSETT BAY[a] (ppm)

	Cadmium		Chromium		Copper		Mercury		Nickel		Lead		Zinc	
Location	Mean[b]	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Fall 1985														
Q-GR1	0.12	0.03	0.31	0.19	3.44	0.82	0.02	0.01	2.52	1.19	0.17	0.01	27.50	3.39
Q-MH55	0.14	0.04	0.99	0.42	3.29	0.70	0.08	0.04	3.17	1.19	0.59	0.24	31.54	10.71
Q-MH61	0.15	0.06	0.67	0.32	3.35	0.46	0.09	0.01	2.95	0.59	0.47	0.25	35.11	8.75
Q-MH62	0.09	0.05	0.73	0.22	2.81	0.61	0.11	0.03	2.76	0.29	0.42	0.11	30.47	1.74
Q-MH63	0.10	0.03	0.52	0.24	4.11	0.97	0.09	0.01	3.33	0.50	0.42	0.13	25.47	2.13
Q-MV1	0.19	0.07	0.82	0.68	4.14	1.60	0.04	0.02	3.26	1.28	0.18	0.05	25.97	6.17
Q-OL1	0.14	0.02	0.77	0.50	3.22	0.80	0.03	0.02	3.14	1.30	0.43	0.15	31.31	8.90
Q-PR13	0.18	0.01	0.48	0.27	5.54	0.69	0.03	0.02	4.04	0.77	0.76	0.34	41.13	6.10
Q-PR2	0.18	0.03	1.17	0.50	9.27	3.92	0.06	0.02	4.18	1.82	0.97	0.47	47.46	14.94
Q-PR30	0.38	0.18	0.74	0.54	7.04	3.60	0.03	0.02	4.29	1.48	0.85	0.60	52.60	29.18
Q-PR47	0.21	0.02	1.33	1.61	4.22	1.40	0.04	0.03	4.06	1.02	0.25	0.13	29.04	5.02
Q-PR49	0.19	0.05	1.53	0.41	6.04	1.20	0.07	0.01	6.43	2.29	0.62	0.33	43.10	6.87
Spring 1986														
Q-GR2	0.11	0.01	0.18	0.01	3.45	0.56	0.02	0.01	2.25	0.30	0.23	0.06	30.90	9.00
Q-MH55	0.15	0.04	1.07	0.57	5.37	1.22	0.10	0.01	5.19	1.31	0.83	0.45	40.17	12.71
Q-MH61	0.15	0.01	0.57	0.40	3.10	0.50	0.12	0.09	2.70	0.64	0.68	0.15	34.00	6.30
Q-MH62	0.15	0.01	1.58	0.10	3.85	0.01	0.15	0.02	4.01	1.33	1.03	0.23	46.40	18.40
Q-MH64	0.15	0.01	1.73	0.36	4.43	0.57	0.14	0.03	3.34	0.81	0.77	0.16	35.93	3.65
Q-MV1	0.09	0.02	0.31	0.21	3.54	0.54	0.03	0.02	2.68	0.70	0.39	0.13	27.40	8.12
Q-MV2(1)	0.32	0.09	1.50	0.50	11.12	1.55	0.13	0.03	11.54	3.63	1.51	0.31	82.23	5.35
Q-MV2(2)	0.08	0.07	0.18	0.01	3.90	0.54	0.02	0.01	2.81	0.57	0.69	0.19	29.30	6.56
Q-OH1	0.17	0.06	0.53	0.21	5.18	0.72	0.04	0.04	3.77	1.12	1.24	0.19	39.44	7.43
Q-PR15	0.13	0.02	0.45	0.16	6.41	1.12	0.03	0.01	4.46	0.91	0.99	0.34	49.52	15.03
Q-PR1	0.21	0.05	0.98	0.03	9.92	3.44	0.07	0.03	5.07	0.99	1.03	0.33	49.87	6.60
Q-PR30	0.21	0.04	0.41	0.36	3.96	0.42	0.03	0.01	3.26	0.65	0.52	0.14	40.11	7.37
Q-PR47	0.15	0.03	0.59	0.32	4.74	0.43	0.03	0.01	4.15	1.00	0.55	0.18	26.78	4.75
Q-PR49	0.15	0.06	0.85	0.39	7.51	3.73	0.06	0.01	4.75	1.22	0.67	0.38	47.36	24.87

[a] From Thibault/Bubly Associates (1985).

[b] Mean of between 4 and 10 measurements taken at the same location where each measurement represents a composite of four clams.

Table 12

COMPARISON OF TOXICITY INDICES WITH DAILY INTAKE OF METALS THROUGH CONSUMPTION OF QUAHOG CLAMS FROM NARRAGANSETT BAY[a]

	ADD (score)[b] ug/kg-day	LOEL (score)[b] ug/kg-day	Daily Mean Intake from Clams, ug/kg-day	Suggested Action
Cadmium	0.5 (a)	1250 (a)	0.1 - 0.45	Detailed assessment. No urgency
Chromium	5 (b)	—	0.2 - 2.0	No further analysis
Copper	40 (d)	—	3.0 - 13	No further analysis
Mercury	0.1 (a)	— (a)	0.02 - 0.17	Detailed assessment. No urgency
Nickel	10 (c)	500 (b*)	2.5 - 13	Detailed assessment. No urgency
Lead	0.6 (a)	113 (a)	0.2 - 1.7	Detailed assessment. Priority
Zinc	200 (e)	—	30 - 60.0	No further analysis

[a]Assuming 80g of clams per day. 1-3% of the population may consume two- to three-fold quantity.

[b]ADD, Acceptable Daily Dose to protect from chronic toxicity (see Table VI); LOEL, Lowest Observed Effect Level for developmental/reproductive toxicity (see Tables III and IV).

therefore no further action is suggested. Daily intake of mercury exceeds the ADD for chronic toxicity in some quahog samples by less than 2-fold. Daily intake of nickel in quahogs from some areas of the Narragansett Bay exceeds the ADD for chronic toxicity by less than 2-fold and is less than 100-fold below the daily dose at which developmental toxicity was observed in experimental animals. This margin of safety may not be sufficient or be only marginally so if we require a 5 to 10-fold uncertainty factor for LOEL and NOEl extrapolation and a 10-fold factor for interspecies extrapolation. Daily intake of cadmium approaches the ADD in some quahogs. Daily intake of lead exceeds the acceptable daily dose for chronic toxicity 3-fold in some areas of the Bay. On the basis of these comparisons we conclude that mercury, nickel, cadmium, and lead require a detailed assessment but that priority should be given to lead.

PHASE II ASSESSMENT

The purpose of the detailed assessment in Phase II is to perform a comprehensive review of the adverse health effects which received scores of "a" and "b" in the preliminary assessment. Such assessments are presented here for two chemicals identified in Table 12 as priority contaminants, lead and cadmium.

The detailed assessment for an agent consists of three steps. First, the quantitative dose-response relationship for a health endpoint in question is characterized. Second, based on the first step for noncarcinogens, a no observed adverse effect level is identified, and from that an allowable daily oral intake of a chemical from seafood is calculated for each health endpoint included in the detailed assessment. For carcinogenic agents this step is based on a quantitative risk estimation for a range of daily doses. The risk level which corresponds to such an acceptable daily oral intake must be decided by the agency but it is likely the range between 10^{-3} and 10^{-6} for a lifetime exposure (Travis *et al.*, 1987). Third, the daily oral intake value from the second step is converted to a corresponding concentration of that agent in seafood.

The allowable daily oral intake from seafood is the *incremental* daily oral dose which, when combined with the average daily burden of the chemical from other sources, would not produce

adverse health effects. The second step requires therefore the consideration of other sources of exposure to the particular agent. Recognizably, this approach is limited by the quality of information on the multiple sources of exposure of the population to chemicals. For the two chemicals considered here, lead and cadmium, we use average concentrations in food, air, and drinking water.

Our approach to the third step is to assume seafood consumption patterns that best match the exposure period associated with a particular health effect under consideration. Thus, for systemic toxicity, the annual or monthly average seafood consumption pattern may be the most significant. For developmental toxicity of cadmium, monthly consumption levels may be most appropriate. For carcinogenic effects the annual consumption patterns would be used.

We recommend that for systemic toxicity, carcinogenicity, and mutagenicity EPA Health Assessment Documents be used as a principal source of toxicological data. For developmental and reproductive toxicity, the original reports of experimental studies should be reviewed.

Cadmium

Preliminary assessment of cadmium toxicity indicates that chronic toxicity and developmental effects may be of concern. Thus, the detailed assessment is focused on these two health effect categories.

The analysis of chronic toxicity presented here is based on the information compiled in the *Final Draft Criteria Document for Cadmium* prepared by the EPA Office of Drinking Water (US EPA, 1985d). This source was selected for two reasons: (1) it is a comprehensive and fairly current (April 1985) review of the literature; and (2) it concerns itself mainly with the gastrointestinal route of exposure.

Chronic toxicity. The kidney is the principal target of cadmium toxicity in animals and humans. Signs of renal malfunction are observed when the cadmium burden reaches a critical level in the renal cortex. Proteinuria is the early sign of toxicity. Based on studies with cadmium workers, it has been estimated that the critical concentration of cadmium in the renal cortex which

would cause toxicity in 10% of the population is between 180 and 220 µg/g (wet weight). This value is referred to as population critical concentration-10 (PCC-10). PCC-50 may be about 25% higher in this case.

Friberg used the PCC-10 of 200 µg/g in renal cortex as a human low observed effect level to calculate daily intake of cadmium (as repred by US EPA, 1985d). Assuming a daily excretion rate of 0.01% of total body burden and a daily absorption of 4.5% he calculated that daily ingestion of 352 µg Cd for 50 years would lead to accumulation of 200 µg of Cd/g in the kidney cortex. The model assumed that 33% of the body burden of cadmium would be accumulated in the kidney. Using the same model, a daily ingestion of 88 mg of cadmium would lead to the renal burden of 50 µg/kg after 50 years. That number is consistent with the observed exposures and body burdens in the U.S. population. Thus, observed concentrations of cadmium in kidney cortex among U.S. adults are between 25 and 50 µg/g. Using Friberg's model that burden can explained by the EPA estimates of a daily oral intake of cadmium, which would be between 39 and 49 µg/day for individuals whose drinking water contained between 5 and 10 ppb of cadmium (US EPA, 1985d).

If we take the 352 mg/day to be LOAEL for 10% of the population, then the NOAEL is

$$\frac{352\ \mu g/day}{5} = 70\ \mu g/day,$$

where 5 is an uncertainty factor for extrapolating from LOAEL to NOAEL (Dourson and Stara, 1983).

According to the EPA Health Assessment Document an average total daily dietary intake of cadmium from food and water (assuming cadmium concentration in water to be at a current drinking water standard of 10 µg/liter) is 49 µg/day in the United States (the contribution from ambient air is less than 1% of that and can be ignored). Subtracting that from 70 µg/day gives an incremental allowable increase of 21 µg/day from other non-average food sources.

Using the average seafood consumption data, on an annual basis, this value is converted to cadmium concentration in the clams as follows:

$$\frac{21\ \mu g/day}{20\ g/day} = 1\ \mu g/g\ (ppm).$$

For high consumers that concentration should be lowered by a factor of 2 to 3, to 0.5-0.3 ppm.

Developmental toxicity. The study by Webster (1978) was selected for qualitative and quantitative evaluation of developmental hazards of cadmium, for three reasons: (1) it was no worse in quality than the other seven reports on developmental toxicity of cadmium; (2) it used oral route of exposure to animals to cadmium; and (3) the dose range was relatively low, and therefore more applicable to environmental risk assessment.

In this study, mice were exposed to cadmium in drinking water throughout pregnancy at concentrations of 0, 10, 20, and 40 ppm. Dose-dependent decreases in fetal weights were found in all treated groups at a statistical significance of $P < 0.001$. In addition, severe anemia was observed among the pups in the highest exposure group. The weakness of the study is that preanemic conditions were also observed in pregnant and nonpregnant females, but not among controls, which indicates that the effects on the fetuses may have been secondary only to the effects of the mothers and not frank fetal toxicity. However, because of consistent evidence from other studies that cadmium leads to fetotoxic and teratogenic effects, and because of lack of evidence to the contrary, we will assume that cadmium is a fetal toxicant. The calculations of the threshold dose for humans are based on the assumption that the absorption rate is equal among rats and humans.

The lowest observed effect level for cadmium-induced developmental toxicity in mice is 10 ppm in drinking water. Using the body weight of 0.025 kg for a female mouse and daily water intake of 5 ml, the daily dose of cadmium is

$$\frac{10\ \mu g/ml\ X\ 5\ ml/day}{0.025\ kg} = 2000\ \mu g/kg\text{-day (LOEL)}.$$

Applying an uncertainty factor of 500 to the LOEL (10 for interspecies variablity, 10 for intraspecies variability, 5 for LOEL to NOEL extrapolation, as in Ref. 19a) we obtain an equivalent

human NOEL:

$$\text{NOEL (human)} = \frac{2000\ \mu\text{g/kg-day}}{500} = 4\ \mu\text{g/kg-day}.$$

For a 60-kg female, that corresponds to 240 µg/day oral intake to protect from developmental toxicity. As before, if we subtract 49 µg/day from food and water, the incremental increase allowed from seafood is 191 µg/day.

Using average seafood consumption, on a monthly basis, this value is converted to seafood concentration as follows:

$$\frac{191\ \mu\text{g/day}}{80\ \text{g/day}} = 2.4\ \mu\text{g/g (ppm)}.$$

For high consumers this value should be between 0.8 and 1.2 ppm.

Lead

Chronic systemic toxicity and developmental effects are of greatest concern for lead. Our analysis of lead toxicity is based mostly on two EPA documents: the 1986 *Air Quality Control Document for Lead* (US EPA, 1986c) and the 1984 *Draft Drinking Water Criteria Document for Lead* (US EPA 1984). Additional references for developmental effects of lead are also used, as cited in the text.

Chronic toxicity. Lead at relatively low levels interferes with erythrocyte synthesis and is associated with adverse effects to the central nervous system. Children below the age of 6 are particularly susceptible to lead both because of increased absorption and because of their vulnerable developmental stage. Subtle effects of lead neurotoxicity on children may manifest themselves by delayed development or impaired school performance. The quantitative relationship between blood lead concentration and the magnitude and nature of toxic effects has been studied extensively. The current consensus is that blood lead levels at which no toxicity to either the nervous system or the

heme-synthesizing system would be expected in 99.5% of children is 15 µg/dl or less. The current EPA ambient air standard for lead is based on the presumed safe concentration.

Developmental toxicity. It has been known for some time that lead readily crosses the placental barrier and causes fetal effects ranging from delayed developmental to mental retardation. These earlier studies have also shown that concentrations of lead in maternal venous blood, umbilical cord blood, and fetal capillary blood are highly correlated, and that the ratio of lead in maternal to cord blood is approximately 1:1. More recently, quantitative relationships between maternal blood levels and effects on the fetus have been extensively studied by Bellinger, Rabinowtiz, Needleman, and others (Bellinger *et al.*, 1984). These workers have shown that mean cord blood levels of 14.6 µg/dl at birth were associated with early developmental disadvantage at 6 months of age as measured by the mental development index of the standard infant development test, the Bayley Scales (Bellinger *et al.*, 1984, 1985). Another follow-up study by the same researchers also showed that the difference between the high and low exposure groups (mean cord levels of 1.8 and 14.6 µg/dl, respectively) observed at 6 months persisted at 12 months of age (Bellinger *et al.*, 1986). These researchers also showed that the scores in the Bayley test did not correlate well with the lead levels in the infants at the time the test was administered which underscored the importance of the past prenatal exposure to lead. Although it is not known what, if any, effects these early developmental disadvantages may have on the future mental development of the infants, or whether or not they are reversible, these studies nevertheless show that maternal exposure to lead can have a measurable effect on fetal development and that the effects are observed at the levels currently considered safe to mothers or to small children (between 10 and 15 µg/dl).

Our choice of the critical toxic effect of lead is that demonstrated in infants exposed *in utero*. We justify the choice in two ways: (1) because of potentially critical lifelong irreversible damage to the central nervous system of a developing fetus; and (2) the effects on fetal development appear to occur at blood lead levels lower than toxic effects in children and adults exposed to lead. Assuming that the ratio of maternal blood to cord blood is 1:1, desired

concentration of lead in maternal blood can be used as a basis for calculating an acceptable incremental daily dose from fish consumption, as follows:

$$\text{Incremental daily intake from fish consumption } (\mu g/day) = \frac{\text{NOAEL - Background } (\mu g/dl)}{\text{Slope X Uncertainty factor}},$$

where

NOAEL is concentration of lead in maternal blood to protect from developmental effects (10 µg/dl)

Slope is the increase in blood consumption of lead per 1 µg/day of ingested lead, for a 60-kg female (0.023 (µg/dl)/(µg/day); determined by Steik, as reported in US EPA, 1984)

Background is the average concentration of lead in blood in U.S. adults;

Uncertainty factor used in the EPA *Draft Drinking Water Criteria Document* is 5, to account for variability between individuals.

According to the *Air Quality Control Document for Lead* average levels of blood lead among U.S. adults ranged from 9 to 12 µg/dl, depending on the source of data, in 1980. For 9 µg/dl, the incremental allowable intake from fish consumption would be

$$\frac{10 - 9 \text{ } (\mu g/dl)}{0.023 \text{ } (\mu g/dl)/(\mu g/day) \text{ X } 5} = 8.7 \text{ } \mu g/day.$$

Using an annual consumption that value is converted into a seafood concentration as follows:

$$\frac{8.7 \text{ } \mu g/day}{20 \text{ } g/day} = 0.4 \text{ } \mu g/g \text{ (ppm)}.$$

For high consumers the concentration would be 0.1-0.2 ppm.

For the population with blood lead levels ranging from 10 to 12 µg/dl no incremental intake of lead would be allowed.

THIRD DECISION POINT: INTERPRETATION OF MONITORING DATA

The concentrations of seven metals in the composite clam samples collected at 14 locations and in two seasons are listed in Table 11 (Thibault/Bubly Associates, 1986). For cadmium, with the exception of two samples (0.32 and 0.38 ppm) all are below the allowable concentration to protect from chronic toxicity (0.3 to 0.5 ppm). All of the samples are below the allowable concentration to protect from developmental toxicity (0.8-1.2 ppm). It is reasonable to conclude, therefore, that the presence of cadmium in the clam meat does not present a significant hazard to public health, at the present. Further reduction in cadmium levels would, however, be desirable.

For lead the conclusions are different. Most of the samples exceed the 0.1-0.2 ppm calculated previously. The management problem is further complicated if we assume that the average concentration of lead in blood is above 10 µg/dl in the exposed population. In this case no incremental exposure to lead would be then allowed. One managerial solution to this paradox could be to define the allowable incremental daily dose of lead from clams as that not exceeding a certain fraction of the average adult dietary intake of lead in the United States (35.8 µg/day). Choosing 10% (not an unreasonable increment) would give 3.6 µg/day or 0.18 ppm concentration in clams, based on an average annual consumption pattern. As shown in Table 10, most samples exceed that value.

DISCUSSION

One of the difficulties that regulatory agencies face in managing the hazards of environmental toxicants is the conflict between the need to respond quickly to a myriad of potential hazards and the desire to base that response on firm scientific grounds. Whereas the first objective requires a fast judgment, based on a readily accessible and previously compiled and interpreted data base, and often must be performed by individuals with limited expertise in toxicology, the second one requires just the opposite: sophisticated expertise, utilization of a broad data base, and time. One approach to reconciling this inherent conflict is to utilize a decision tree which permits

making a series of judgments, each requiring greater expertise and more effort than the previous one, but for progressively fewer chemicals and adverse effects. The methodology for assessing hazards of contaminants in seafood, presented here, allows for construction of such a decision tree.

As shown in Fig. 1, a unique feature of our system is a two-phased risk assessment and three or more decision points. In Phase I a hazard profile of each chemical is generated using five letter symbols "a" to "e", which describe the magnitude of exposure and the nature, severity, and magnitude of four types of health effects. The letter codes not only reflect the average values for exposure and the consensus on the potential adverse health effects, but also the range of attendant uncertainty. In concept, the score for each of the five categories is equivalent to a geometric mean of qualitative and quantitative evidence. The system thus represents a mixture of several possible approaches to assessing the potential consequences of exposure to a particular agent: one which gives the highest rank to those that are most likely to produce adverse effects in humans (strong weight of evidence); another that ranks the highest those that may produce adverse health effects at the lowest dose (high potency); the third, that ranks the highest those that may produce the most debilitating disease or defect (high severity); the fourth, that ranks the highest those that appear to be at the highest concentration. This approach presents several advantages; (1) it makes a maximum use of data and therefore chemicals which appear hazardous on either count are not missed; (2) it avoids overreliance on some highly uncertain procedures such as interspecies or low-dose extrapolation of toxicity data, subjective ranking of severity of effects, determination of no effect levels, or chemical analysis of limited numbers of seafood samples; and (3) it emphasizes the uncertainty in qualitative and quantitative data on toxicity and exposure.

Several messages are instantly communicated through the five-letter code for each chemical: the types of adverse health effects anticipated, the magnitude of exposure, the effects which may produce the greatest degree of hazard to humans, and gaps in the data base. The data base for the risk assessment in Phase I consists mostly of reviews, reports, and previously established exposure guidelines. While it is not appropriate in most cases for the derivation of allowable

Figure 1

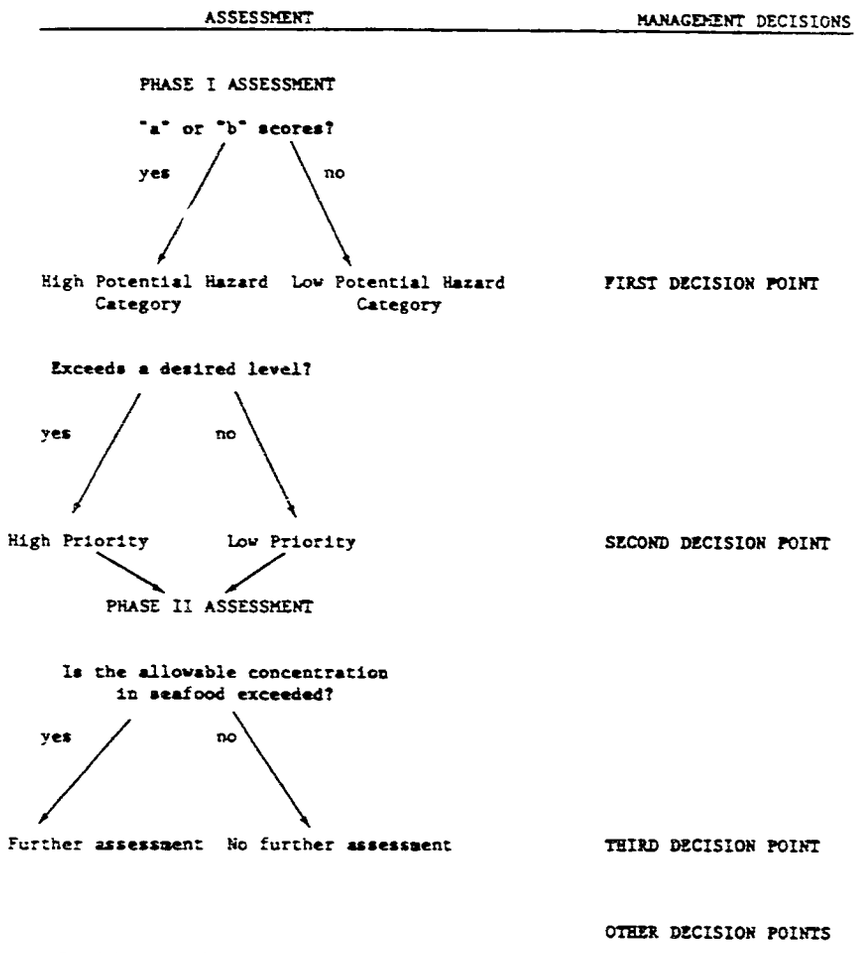

FIG. 1. Decision tree for hazard management on the basis of phase I and phase II assessment.

concentrations in seafood, this data base provides sufficient information on the nature and potential magnitude of hazards to support two hazard management decisions that follow. First, on the basis of the hazard profiles some chemicals are judged to present no significant health hazard and are eliminated from further consideration (low potential hazard category). Second, the remaining chemicals (high potential hazard category) undergo an intermediate assessment and are further sorted into one of three groups: those eliminated from further assessment, those requiring further assessment or a priority basis, those for whom further assessment is recommended but not urgent.

The principal goal of the risk assessment in Phase II is to derive an allowable concentration of contaminants in seafood, which would be used by a regulatory agency to judge the results of chemical analysis of seafood. In contrast to Phase I, the emphasis is not on a large number of chemicals or on the full spectrum of health effects. Rather, a small number of chemicals are examined in depth, with a focus on the adverse health effects previously identified in Phase I. The analysis requires interpretation of published toxicologic literature and is therefore time-consuming and resource intensive. In the two examples presented in this report, lead and cadmium, two types of data were used: primary literature and governmental criteria documents. The derivation of allowable concentrations followed the procedures previously applied by regulatory agencies (see, for example, EPA recommended maximum contaminant levels for drinking water (US EPA, 1985b)).

It is not our intention to argue in this paper whether or not the allowable concentrations of lead or cadmium derived here best reflect the hazardous properties of these agents. Clearly, a different selection of a data base or the uncertainty factors, or different assumptions about other sources of exposure or fish consumption patterns, would lead to different results. In the regulatory field, issues such as these are best resolved by peer-review or consensus-seeking groups. Rather, we use these to illustrate the application of the decision tree shown in fig. 1 to a particular hazard management problem: *interpretation of the data on concentrations of seven metals in quahog clams from Narragansett Bay.*

On the basis of the hazard profiles generated in Phase I, all seven metals were assigned into high potential hazard category. The lack of stratification of the chemicals into two hazard categories is not an indication that the method lacks sensitivity at this stage. Instead, it reflects two other ongoing phenomena: (1) the selection bias in designing most monitoring programs which tend to concentrate on chemicals with high potential health hazards and those anticipated to be present in high concentrations; and (2) our attitude in choosing the stratification criteria that it is better to err on the side of safety. At the second decision point, the seven metals were stratified into three groups: three were judged to require no further assessment; three were judged to require further assessment sometime; and one (lead) was judged to require further assessment on a priority basis. The allowable seafood concentrations derived for cadmium and lead in Phase II became the basis for the third decision point: when compared with the concentration in the quahog samples from the Bay, cadmium was judged to present no threat to public health and no further assessment was recommended, which confirmed the preliminary decision based on the intermediate assessment. Concentration of lead, on the other hand, exceeded the allowable level in most samples. For the regulatory agency that would mean a need for further work on lead. This might include a more detailed look at the most contaminated areas of the Bay (possibly with more monitoring), identification of the sources of discharge, a survey of the eating habits of the high-risk populations, or reassessment or other sources of exposure to lead. Following such an analysis, another evaluation of the lead data would be called for.

CONCLUSIONS

Judging by the results of our work on the seven metals, the decision tree, and the two phases of assessment which supported it, accomplished its principal goals: it allowed for making several explicit and well-informed decisions with regard to the potential health hazards of the contaminants and for a gradual narrowing down of the management problem. Thus, the hazard management problem was reduced from potentially seven metals to one, lead, that may present a health hazard to some consumers of the quahog clams from Narragansett Bay. Although more

work is required before additional decisions are made regarding the present of lead in the clams, defining its scope and accomplishing it with some modest resources should be a manageable task.

Like all systems of this nature, ours is based on a set of simplifications and assumptions. Despite that, we believe that our methodology is a useful tool for assessing and managing hazards of seafood contaminants, one that allows for consistency in judging relative hazards of chemical contaminants and for informed priority setting in their management.

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APPENDIX A

EPA Classification System for Categorizing Weight of Evidence for Carcinogenicity From Human and Animal Studies (Adapted From IARC)*

A. Assessment of Weight of Evidence for Carcinogenicity From Studies in Humans

Evidence of carcinogenicity from human studies comes from three main sources:

1. Case reports of individual cancer patients who were exposed to the agent(s).
2. Descriptive epidemiologic studies in which the incidence of cancer in human populations was found to vary in space or time with exposure to the agent(s).
3. Analytical epidemiologic (case-control and cohort) studies in which individual exposure to the agent(s) was found to be associated with an increased risk of cancer.

Three criteria must be met before a causal association can be inferred between exposure and cancer in humans:

1. There is no identified bias that could explain the association.
2. The possibility of confounding has been considered and ruled out as explaining the association.
3. The association is unlikely to be due to chance.

In general, although a single study may be indicative of a cause-effect relationship, confidence in inferring a causal association is increased when several independent studies are concordant in showing the association, when the association is strong, when there is a dose-response relationship, or when a reduction in exposure is followed by a reduction in the incidence of cancer.

The weight of evidence for carcinogenicity [1] from studies in humans is classified as:

1. Sufficient evidence of carcinogenicity, which indicates that there is a causal relationship between the agent and human cancer.
2. Limited evidence of carcinogenicity, which indicates that a causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding, could not adequately be excluded.
3. Inadequate evidence, which indicates that one of two conditions prevailed: (a) there were few pertinent data, or (b) the available studies, while showing evidence of association, did not exclude chance, bias, or confounding and therefore a causal interpretation is not credible.
4. No data, which indicates that data are not available.
5. No evidence, which indicates that no association was found between exposure and an increased risk of cancer in well-designed and well-conducted independent analytical epidemiologic studies.

B. Assessment of Weight of Evidence for Carcinogenicity From Studies in Experimental Animals

These assessments are classified into five groups:

1. Sufficient evidence [2] of carcinogenicity, which indicates that there is an increased incidence of malignant tumors or combined malignant and benign tumors: [3] (a) in multiple species or strains; or (b) in multiple experiments (e.g., with different routes of administration or using different dose levels); or (c) to an unusual degree in a single experiment with regard to high incidence, unusual site or type of tumor, or early age at onset.

Additional evidence may be provided by data on dose-response effects, as well as information from short-term tests or on chemical structure.

2. Limited evidence of carcinogenicity, which means that the data suggest a carcinogenic effect but are limited because: (a) the studies involve a single species, strain, or experiment and do not meet criteria for sufficient evidence (see section IV. B.1.c); (b) the experiments are restricted by inadequate dosage levels, inadequate duration of exposure to the agent, inadequate period of follow-up, poor survival, too few animals, or inadequate reporting; or (c) an increase in the incidence of benign tumors only.
3. Inadequate evidence, which indicates that because of major qualitative or quantitative limitations, the studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect.
4. No data, which indicates that data are not available.
5. No evidence, which indicates that there is no increased incidence of neoplasms in at least two well-designed

[1] For purposes of public health protection, agents associated with life-threatening benign tumors in humans are included in the evaluation.

[2] An increased incidence of neoplasms that occur with high spontaneous background incidence (e.g., mouse liver tumors and rat pituitary tumors in certain strains) generally constitutes "sufficient" evidence of carcinogenicity, but may be changed to "limited" when warranted by the specific information available on the agent.

[3] Benign and malignant tumors will be combined unless the benign tumors are not considered to have the potential to progress to the associated malignancies of the same histogenic origin.

*Federal Register 51, 33992-34003 (1986).

and well-conducted animal studies in different species.

The classifications "sufficient evidence" and "limited evidence" refer only to the weight of the experimental evidence that these agents are carcinogenic and not to the potency of their carcinogenic action.

C: Categorization of Overall Weight of Evidence for Human Carcinogenicity

The overall scheme for categorization of the weight of evidence of carcinogenicity of a chemical for humans uses a three-step process. (1) The weight of evidence in human studies or animal studies is summarized; (2) these lines of information are combined to yield a tentative assignment to a category (see Table 1); and (3) all relevant supportive information is evaluated to see if the designation of the overall weight of evidence needs to be modified. Relevant factors to be included along with the tumor information from human and animal studies include structure-activity relationships; short-term test findings; results of appropriate physiological, biochemical, and toxicological observations; and comparative metabolism and pharmacokinetic studies. The nature of these findings may cause one to adjust the overall categorization of the weight of evidence.

TABLE 1.—ILLUSTRATIVE CATEGORIZATION OF EVIDENCE BASED ON ANIMAL AND HUMAN DATA [1]

Human evidence	Animal evidence				
	Sufficient	Limited	Inadequate	No data	No Evidence
Sufficient	A	A	A	A	A
Limited	B1	B1	B1	B1	B1
Inadequate	B2	C	D	D	D
No data	B2	C	D	D	E
No evidence	B2	C	D	D	E

[1] The above assignments are presented for illustrative purposes. There may be nuances in the classification of both animal and human data indicating that different categorizations than those given in the table should be assigned. Furthermore, these assignments are tentative and may be modified by ancillary evidence. In this regard all relevant information should be evaluated to determine if the designation of the overall weight of evidence needs to be modified. Relevant factors to be included along with the tumor data from human and animal studies include structure-activity relationships, short-term test findings, results of appropriate physiological, biochemical, and toxicological observations, and comparative metabolism and pharmacokinetic studies. The nature of these findings may cause an adjustment of the overall categorization of the weight of evidence.

The agents are categorized into five groups as follows:

Group A—Human Carcinogen

This group is used only when there is sufficient evidence from epidemiologic studies to support a causal association between exposure to the agents and cancer.

Group B—Probable Human Carcinogen

This group includes agents for which the weight of evidence of human carcinogenicity based on epidemiologic studies is "limited" and also includes agents for which the weight of evidence of carcinogenicity based on animal studies is "sufficient." The group is divided into two subgroups. Usually, Group B1 is reserved for agents for which there is limited evidence of carcinogenicity from epidemiologic studies. It is reasonable, for practical purposes, to regard an agent for which there is "sufficient" evidence of carcinogenicity in animals as if it presented a carcinogenic risk to humans. Therefore, agents for which there is "sufficient" evidence from animal studies and for which there is "inadequate evidence" or "no data" from epidemiologic studies would usually be categorized under Group B2.

Group C—Possible Human Carcinogen

This group is used for agents with limited evidence of carcinogenicity in animals in the absence of human data. It includes a wide variety of evidence, e.g., (a) a malignant tumor response in a single well-conducted experiment that does not meet conditions for sufficient evidence, (b) tumor responses of marginal statistical significance in studies having inadequate design or reporting, (c) benign but not malignant tumors with an agent showing no response in a variety of short-term tests for mutagenicity, and (d) responses of marginal statistical significance in a tissue known to have a high or variable background rate.

Group D—Not Classifiable as to Human Carcinogenicity

This group is generally used for agents with inadequate human and animal evidence of carcinogenicity or for which no data are available.

Group E—Evidence of Non-Carcinogenicity for Humans

This group is used for agents that show no evidence for carcinogenicity in at least two adequate animal tests in different species or in both adequate epidemiologic and animal studies.

The designation of an agent as being in Group E is based on the available evidence and should not be interpreted as a definitive conclusion that the agent will not be a carcinogen under any circumstances.

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SCORES FOR DEVELOPMENTAL AND REPRODUCTIVE TOXICITY FOR 110 CHEMICALS

CHEMICAL	TYPE OF TOXICITY	WEIGHT OF EVIDENCE	LOEL[1]	RISK RATIO[2]	SCORE[3]
Acetaldehyde	Teratogenicity Severe Embryofetal	Suggestive	50 mg/kg/day	10	B
Acetone		No Data			ND
Acrylonitrile	Teratogenicity	Substantial	3 mg/kg/day		A
Ammonia		No Data			ND
Aniline	Post Developmental Maternal Reproductive	Suggestive	560 mg/kg/day		E
Aniline Hydrochloride		No Data			ND
Asbestos		No Data			ND
Benzene	Mild Embryofetal	Suggestive	14.0 mg/kg/day		C
Benzyl Chloride		No Data			ND
Beryllium		No Data			ND
1,3-Butadiene	Maternal Reproductive Paternal Reproductive	Suggestive	397 mg/kg/day		D
n-Butyl Alcohol		No Data			ND
Cadmium	Teratogenicity	Substantial	1.25 mg/kg/day		A

Calcium Chromate		No Data		ND
Carbon Tetrachloride	Mild Embryofetal	Suggestive	164 mg/kg/day	D
Chlordane	Teratogenicity	Suggestive	0.16 mg/kg/day*	B*
Chlorine		No Data		ND
Chlorobenzene		No Data		ND
Chloroethane		No Data		ND
Chloroform	Mild Embryofetal	Suggestive	20.0 mg/kg/day	B
Chloroprene	Mild Embryofetal	Suggestive	1.8 mg/kg/day	B
Chromic Acid		No Data		ND
Chromium (metal)		No Data		ND
Chromium (VI) Compounds		No Data		ND
p-Cresol		No Data		ND
Cyclohexane		No Data		ND
o-Dichlorobenzene		No Data		ND
p-Dichlorobenzene		No Data		ND
1,2-Dichloroethane	Post/perinatal	Suggestive	8.6 mg/kg/day	B

1,2-Dichloroethylene		No Data			ND
Dichloromethane	Severe Embryofetal	Suggestive	381*mg/kg/day		D*
1,2-Dichloropropane		No Data			ND
Diethylamine		No Data			ND
Di(2-ethylhexyl) phalate*	Teratogenicity	Suggestive	70 mg/kg/day	376	B
Dimethylformamide	Severe Embryofetal	Insufficient			E
1,4-Dioxane		No Data			ND
Diphenyl		No Data			ND
Diphenylamine		No Data			ND
Epichlorohydrin	Maternal Reproductive	Suggestive	80 mg/kg/day		B
Ethyl Acetate		No Data			ND

Ethyl Acrylate	Mild Embryofetal	Suggestive	15.35 mg/kg/day		B
Ethyl Benzene		No Data			ND
Ethylene Glycol		No Data			ND
Ethyl Ether		No Data			ND
Fluoride		No Data			ND
Formaldehyde	Paternal Reproductive	Substantial	0.023*mg/kg/day		A*
Heptachlor		Insufficient			E
Hexachloro-cyclopentadiene	Mild Embryofetal	Suggestive	75*mg/kg/day		D*
Hexachloroethane	Severe Embryofetal	Suggestive	39 mg/kg/day		D
Hexachlorophene	Peri/Postnatal	Substantial	5 mg/kg/day	12	A
2-Hexanone		No Data			ND
Hydrazine	Post Developmental Toxicity	Suggestive	8* mg/kg/day		C*
Hydrogen Chloride		No Data			ND
Hydrogen Fluoride		No Data			ND
Hydrogen Sulfide		No Data			ND

Isoamyl Acetate		No Data		ND
Isobutyl Acetate		No Data		ND
Isobutyl Alcohol		No Data		ND
Isopropyl Alcohol		No Data		ND
Lead (metal)	Severe Embryofetal	Substantial	0.113* mg/kg/day	A*
Lead Acetate		No Data		ND
Lead Chloride		No Data		ND
Lead Nitrate	Teratogenicity	Substantial	25 mg/kg/day	A
Lead Subacetate	Paternal Reproductive	Suggestive	1952 mg/kg/day	E

Lindane		No Data			ND
Maleic Anhydride		No Data			ND
Methyl Acrylate		No Data			ND
Methyl Bromide		No Data			ND
2-Methoxyethanol	Paternal Reproductive	Substantial	100* mg/kg/day		B*
Methyl Chloroform	Minor Embryofetal	Suggestive	415 mg/kg/day		D*
Methyl Methacrylate	Severe Embryofetal	Suggestive	435* mg/kg/day		D*
Mirex		No Data			ND
Nickel	Peri/postnatal	Suggestive	0.5 mg*/kg/day		B*
Nickel Carbonyl	Teratogenicity Embryofetal Tox	Suggestive	0.25 mg/kg/day	437	A
Nickel Oxide		No Data			ND
Nitrobenzene		No Data			ND
Pentachlorophenol	Severe Embryofetal	Suggestive	5 mg/kg/day	27	B
Phenol		No Data			ND

Phosphoric Acid		No Data		ND
Phthalic Anhydride		No Data		ND
PCB Arochlor 1242	Maternal Reproductive	Substantial	0.94 mg/kg/day	A
PCB Arochlor 1248	Maternal Reproductive Embryofetal Postdevelopmental	Suggestive	0.08 mg/kg/day	A
PCB Arochlor 1254	Postnatal Development	Substantial	0.06* mg/kg/day 21,583	A*
PCB Kanachlor 300		No Data		ND
PCB Kanachlor 400	Teratogenicity	Insufficient		E
PCB Kanachlor 500	Teratogenicity Postdevelopmental	Substantial	20 mg/kg/day	A
Propyl Alcohol		No Data		ND
Propylene Oxide		No Data		ND
Resorcinol		No Data		ND

Selenium	Teratogenicity Maternal Reproductive	Insufficient		E
Selenium Sulfide		No Data		ND
Styrene	Severe Embryofetal	Suggestive	237.8* mg/kg/day	C*
Sulfuric Acid		No Data		ND
1,1,2,2-Tetrachloro- 1,2,-difluoroethane		No Data		ND
1,1,2,2-Tetrachloroethane		No Data		ND
Tetrachloroethylene	Embryofetal	Insufficient		E
Tetrahydrofuran		No Data		ND
Toluene	Mild Embryofetal	Substantial	300 mg/kg/day	B
o-Toluidine		No Data		ND
1,1,2-Trichloroethane		No Data		ND
Trichloroethylene	Severe Embryofetal	Substantial	27.3* mg/kg/day	A*
Triethylamine	Maternal Reproductive	Suggestive	2.5 mg/kg/day	A

Vanadium		No Data		ND
Vanadium Pentoxide		No Data		ND
Vinyl Acetate		No Data		ND
Vinyl Chloride	Mild Embryofetal	Suggestive	42.6 mg/kg/day	B*
Vinylidene Chloride	Mild Embryofetal	Suggestive	28 mg/kg/day	D
m-Xylene	Severe Embryofetal	Insufficient	900* mg/kg/day	E*
o-Xylene	Maternal Reproductive	Suggestive	45 mg/kg/day	B
p-Xylene	Mild Embryofetal	Suggestive	45 mg/kg/day	B
mixed Xylenes	Teratogenicity Embryofetal Tox	Suggestive	2.06 mg/kg/day	C

1. Lowest Observable Effect Level, when accompanied by an asterisk (*) then value was not taken from a dose response curve, because only one dose used in study.

2. Risk Ratio is equal to LOEL/LD_{50} using same species and route of exposure.

3. Asterisk * signifies that only one dose used in study; score is aligned with effect(s) to which it corresponds.

APPENDIX C

A Simplified Procedure for Scoring Developmental and Reproductive Toxicity

It may not be always possible for the agency to evaluate the literature on reproductive and developmental toxicity of a chemical. In such cases, necessary information should be extracted from the sources listed in Table I. The sources should be used in the following order of preference: EPA Health Assessment Documents > Council on Environmental Quality, 1981 > Barlow and Sullivan, 1982 > Shepard, 1982 > U>S> EPA, 1985a. In all cases, a score is assigned in three steps; first, an effect is classified using Tables C1 and C2; second, the weight of evidence for either reproductive or developmental toxicity is classified using Table C3; third, an appropriate LOEL value (for either reproductive or developmental toxicity) is factored in to derive a score, as shown in Table C4. If more than one LOEL value is available for a particular type of effect, the lowest one is used. Obviously, "Insufficient" weight-of-evidence category does not apply to those situations where only the secondary literature is used because the necessary information is not reported in these sources. Likewise, a distinction between developmental toxicity subcategories I and II will most likely not be possible in those cases. If so, subcategory I should be assumed.

TABLE C1

CLASSIFICATION AND EXAMPLES OF EMBRYO/FETAL TOXIC EFFECTS*

I. Severe Embryo/fetal Effects

- Lethality
- Resorptions
- Individual skeletal variants (missing or poorly ossified sternebrae, vertebral centers, skull)
- Abnormal umbilical corde length, transumbilical distance
- Post implantation loss
- Minor malformations or variations - common in species tested

II. Minor Embryo/fetal Toxic Effects

- Decreased crown-rump length
- Reduced birth weight, weight gain
- Retarded physical development
- Total skeletal variants - no individually increased incidences that are statistically significant

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- Retarded physical development
- Total skeletal variants - no individually increased incidences that are statistically significant

TABLE C3

Weight-of-Evidence Classification for Development and Reproductive Toxicity

CATEGORY	DESCRIPTION OF EVIDENCE
CONFIRMED EVIDENCE	Human evidence showing causal association between exposure to the chemical and adverse effects on development or reproduction
SUBSTANTIAL EVIDENCE Group I	Evidence from two or more positive animal test showing teratogenicity or severe embryo/fetal effects, or perinatal, or postnatal developmental effects, or reproductive effects ——Or Evidence from one positive animal test for teratogenicity and some evidence of teratogenicity in humans, although data are not sufficient to conclusively demonstrate a causal association [same evidence for severe embryo/fetal toxicity, or perinatal, or postnatal developmental effects, or reproductive effects] ——Or, Evidence from one positive animal test demonstrating teratogenicity in animals and one positive test indicating severe embryo/fetal toxicity in animals.
Group II	Evidence from two or more positive animal tests showing minor embryo/fetal effects. ——Or, Evidence from one positive teratogenicity study in animals and one positive test in animals showing minor embryo/fetal toxicity. ——Or, Evidence from one positive animal study showing minor embryo/fetal toxicity and some evidence of embryo/fetal toxicity in humans (of a mild nature), although data are not sufficient to conclusively demonstrate a causal association.
SUGGESTIVE EVIDENCE Group I	Evidence from one positive animal test showing teratogenicity or severe embryo/fetal toxicity, or perinatal, or postnatal developmental effects, or reproductive effects.
Group II	Evidence from one positive animal test showing minor embryo/fetal toxicity.
INSUFFICIENT EVIDENCE	Chemical cannot be classified because tests did not yield statistically significant results, or studies too limited to provide reliable data, or effects found only at very high levels. ——Or, Non-positive results only
NO DATA	No information available in the sources listed.

TABLE C4

SCORING MATRIX FOR DEVELOPMENTAL AND REPRODUCTIVE TOXICITY

Weight of Evidence	LOEL	Score
Confirmed	Any	
Substantial I	0 < LOEL ≤ 50	a
Substantial II	0 < LOEL ≤ 25	
Suggestive I	0 < LOEL ≤ 5	
Suggestive II	0 < LOEL ≤ 2	
Substantial I	50 < LOEL ≤ 200	b
Substantial II	25 < LOEL ≤ 150	
Suggestive I	5 < LOEL ≤ 100	
Suggestive II	2 < LOEL ≤ 75	
Substantial I	200 < LOEL ≤ 400	c
Substantial II	150 < LOEL ≤ 350	
Suggestive I	100 < LOEL ≤ 300	
Suggestive II	75 < LOEL ≤ 300	
Substantial I	400 < LOEL ≤ 500	d
Substantial II	350 < LOEL ≤ 500	
Suggestive I	300 < LOEL ≤ 500	
Suggestive II	300 < LOEL ≤ 500	
Insufficient	500 < LOEL	e
No Data		ND

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TABLE I

SOURCES OF TOXICITY DATA USED FOR EACH HEALTH EFFECTS CATEGORY

Title

SYSTEMIC TOXICITY

- Verified Reference Doses of the U.S. EPA (US EPA, 1985a)
- National Primary Drinking Water Regulations, Federal Register November 13 (US EPA, 1985b)
- Draft Superfund Health Evaluation Manual (US EPA, 1985c)
- EPA Health Assessment Documents (chemical-specific)
- National Academy of Sciences, Drinking Water and Health, Vols. 1-5 (NAS, 1977-1983)

CARCINOGENICITY

- See above
- See above
- See above
- IARC Monographs on the Evaluation of Carcinogenic Risks of Chemicals to Humans (IARC, 1982)
- Carcinogen Assessment Group
- National Toxicology Program. Technical Reports on the Toxicology and Carcinogenicity of Chemicals

MUTAGENICITY

- See above
- See above
- See above
- EPA Gene-Tox data base (Office of Pesticides and Toxic Substances)

REPRODUCTIVE/DEVELOPMENTAL TOXICITY

- Primary literature strongly recommended
- See above
- See above
- Chemical Hazards to Human Reproduction (CEQ 1981)
- Catalog of Teratogenic Agents (Shepard, 1980)
- Reproductive Hazards of Industrial Chemicals (Barlow, Sullivan, 1982)

TABLE II

SCORING MATRIX FOR CARCINOGENICITY[a]

Weight of Evidence Category[b]	Potency Index $(\mu g/kg\text{-}day)^{-1}$			
	$10^{-2}<PI$	$10^{-3}<PI\leq10^{-2}$	$10^{-4}<PI\leq10^{-3}$	$PI\leq10^{-4}$
A, Human Carcinogen	a	a	a	a
B1, Probable Human Carcinogen	a	b	b	b
B2, Probable Human Carcinogen	a	b	b	c
C, Possible Human Carcinogen	b	b	b	c
D, Not Classifiable	d	d	d	d
E, Evidence of Non-Carcinogencity	e	e	e	e

[a]Scores "d" and "e" are derived on the basis of weight of evidence alone.

[b]Weight of evidence categories, A, B1, B2, C, D, E, have been previously defined by the Environmental Protection Agency (US EPA, 1986)

TABLE III

SCORING MATRIX FOR REPRODUCTIVE TOXICITY

WEIGHT-OF-EVIDENCE[a]	LOEL	SCORE
Confirmed Evidence	NA	a
Substantial Evidence	$0 < LOEL \leq 50$	a
Suggestive Evidence	$0 < LOEL \leq 5$	a
Substantial Evidence	$50 < LOEL \leq 200$	b
Suggestive Evidence	$5 < LOEL \leq 100$	b
Substantial Evidence	$200 < LOEL \leq 400$	c
Suggestive Evidence	$100 < LOEL \leq 325$	c
Substantial Evidence	$400 < LOEL \leq 500$	d
Suggestive Evidence	$325 < LOEL \leq 500$	d
Insufficient Evidence	$500 < LOEL$	e
No Data		ND

[a]Weight-of-Evidence categories have been previously defined (Ref)

TABLE IV

SCORING MATRIX FOR DEVELOPMENTAL TOXICITY

WEIGHT-OF-EVIDENCE[a]	LOEL mg/(kg-day)		RISK RATIO	SCORE
Confirmed Evidence	NA		NA	a
Substantial Evidence				
Group I	$0 < LOEL < 50$	or	$100 < RR$	
Group II	$0 < LOEL \leq 25$	or	$150 < RR$	a
Suggestive Evidence				
Group I	$0 < LOEL < 5$	and	$200 < RR$	
Group II	$0 < LOEL \leq 2$	and	$250 < RR$	a
Substantial Evidence				
Group I	$50 < LOEL < 200$	or	$20 < RR < 100$	
Group II	$25 < LOEL \leq 150$	or	$30 < RR \leq 150$	b
Suggestive Evidence				
Group I	$5 < LOEL < 100$	and	$40 < RR < 200$	
Group II	$2 < LOEL \leq 75$	and	$50 < RR \leq 250$	b
Substantial Evidence				
Group I	$200 < LOEL < 400$	or	$2 < RR < 20$	
Group II	$150 < LOEL \leq 350$		$3 < RR \leq 30$	c
Suggestive Evidence				
Group I	$100 < LOEL < 325$	or	$4 < RR < 40$	
Group II	$75 < LOEL \leq 300$	or	$5 < RR \leq 50$	c
Group III	$LOEL \leq 25$		NA	
Substantial Evidence				
Group I	$400 < LOEL < 500$	or	$1 < RR < 2$	
Group II	$350 < LOEL \leq 500$	or	$1 < RR < 3$	d
Suggestive Evidence				
Group I	$325 < LOEL < 500$	or	$1 < RR < 4$	
Group II	$300 < LOEL \leq 500$	or	$1 < RR < 5$	d
Group III	$25 < LOEL \leq 500$		NA	
Substantial or Suggestive Evidence (Groups I, II, or III)	$500 < LOEL$	or	$RR < 1$	e
Insufficient Evidence	NA		NA	e
No Data				nd

[a]Weight-of-Evidence categories and subcategories (I, II, III) have been previously defined (Ref)

TABLE V

SCORING CRITERIA FOR MUTAGENICITY

CATEGORY	TEST TYPE AND NUMBER OF POSITIVE RESULTS[a]	LETTER SCORE
Sufficient Evidence	Group I: Two or More	a
	or	
	Group II: Four or More	a
	or	
	Group III: Six or More	a
	or	
	Group I:	
	and	a
	Group II: One or More	
	or	
	Group I: One	
	and	a
	Group III: Two	
Substantial Evidence	Group I: One	b
	or	
	Group II: Three	b
	or	
	Group III: Four or Five	b
	or	
	Group II: One or Two	
	and	b
	Group III: Three	
Suggestive Evidence	Group II: One or Two	c
	or	
	Group II: Two or Three	c
	or	
	Group II: One or Two	
	and	
	Group III: One or Two	c
Limited Evidence	Group III: One	d
Inadequate Evidence	Inconclusive Data (results equivocal) or Non-positive results only	e
No Data	Chemical not tested	ND

[a]Screening assays classified into Groups I, II and III have been previously defined (Ref)

TABLE VI

SCORING MATRIX FOR SYSTEMIC TOXICITY BY ORAL ROUTE

Acceptable Daily Dose (ADD) (mg/kg-day)	Severity Factor 1	2	3
ADD≤0.001	c	b	a
0.001<ADD≤0.01	c	c	b
0.01<ADD≤0.1	d	c	b
0.1<ADD≤1	e	d	c
1<ADD	e	d	c

TABLE VII

MATRIX FOR SCORING EXPOSURE CATEGORY

Measured Average Concentration	Score	
ppm (µg/gm - wet)	Typical Variation[a]	Potentially High Variation
> 30	a	a
3 - 30	b	a
.3 - 3	c	b
< .3	d	c

[a]Variation is defined by three numbers: the average concentration, the maximum concentration measured, and the number of samples;

Typical Variation

More than 100 samples *and* Maximum/Average < 20

or

20 - 100 samples *and* Maximum/Average < 10

Potentially High Variation

Fewer than 20 samples

or

Fewer than 100 samples *and* Maximum/Average > 10

or

Maximum/Average > 20

TABLE VIII
HEALTH EFFECTS AND EXPOSURE SCORES FOR 20 SAMPLE CHEMICALS

Chemical Name	Toxicity			Carcinogenicity			Mutagenicity	Reproductive/Developmental Toxicity				Exposu
	ADD[a]	Severity Factor	Score	PI	WOE	Score	Score	LOEL	WOE	RR	Score	
Arsenic & compounds	0.2	3	a	1.5×10^{-2}	A	a	b	-	a	-	a	NI
Barium & compounds	50	2	c		D	d	e				ND	NI
Benzo(a)pyrene				1.1×10^{-2}	B2	a	a				ND	NI
Cadmium & compounds	0.55	3	a		D	d	ND	1.25	Subst.	-	a	d
Chlordane	0.9	3	a	1.7×10^{-3}	B2	b	d	0.16	Sug.	-	b*[b]	NI
Chromium & compounds	5	3	b		D	d	ND				ND	c
Copper & compounds	40	1	d		D	d	e				ND	b
DDT	20	1	d	3.4×10^{-4}	B2	b	e	50	Sug.		b	NI
Epichlorohydrin	2	3	b	1.8×10^{-6}	B2	c	a	80	Sug.	-	b	NI
Heptachlor	0.07	2	b	3.4×10^{-3}	B2	b	d		Insuf.		e	NI
Heptachlor Epoxide	0.03	2	b	5.4×10^{-2}	B2	a	d		Insuf.		e	NI
Lead & copper	0.6	3	a		D	d	d	0.11	Subst.	-	a*	c
Lindane	0.3	2	b	1.3×10^{-3}	C	c	ND		Insuf.		e	NI
Mercury (org)	0.1	3	a		D	d	ND		Suff.		a	d
Methoxychlor	50	2	c		D	d	e				ND	NI
Nickel & compounds	10	2	c		D	d	ND	0.5	Sug.		b*	b
PCBs	2	1	c	4.3×10^{-3}	B2	b	ND	0.06	Subst.	-	a	NI
Pentachlorophenol	30	3	b		D	d	d	5	Sug.	27	a	ND
Selenium & compounds	3	2	c		D	d	ND		Insuf.		e	ND
Zinc & compounds	200		e		D	d	ND				ND	a

[a]Abbreviations and units used: ADD, acceptable daily dose (ug/kg-day); PI, potency index $(ug/kg\ day)^{-1}$; WOE, weight-of-evid RR, risk ratio; LOEL, lowest observed effect level (mg/kg-day)

[b]Asterisk signifies that the score was assigned on the basis of qualitative evidence only.

TABLE IX

ASSUMPTIONS ABOUT SEAFOOD CONSUMED BY MEMBERS OF HYPOTHETICAL EXPOSED POPULATION

Size of a meal: 200 g (wet) of cleaned seafood

AVERAGE CONSUMER

Annual consumption: 7.2 kg = 20 g/day = .1 meal/day

Monthly during peak month: 2.4 kg = 80 g/day = .4 meal/day

Daily during peak 2 hrs: 400 g = 2 meals

HIGH CONSUMER

1 - 3% of population may consume 3 x these values

Assumptions based on data from Hu (1985)

TABLE X

FACTOR BY WHICH INTAKE OF A TOXIC SUBSTANCE MIGHT EXCEED AVERAGE INTAKE FOR THE HIGHEST CONSUMING 1-3% OF THE HYPOTHETICAL EXPOSED POPULATION

	TYPICAL VARIATION	POTENTIALLY HIGH VARIATION
Day	10X	100X
Month	3X	10X
Year	3X	6X

The variation in intake, expressed as a factor X average intake, depends on the time period over which it occurs, variation in fish consumption behavior of the population, and the expected variability in concentrations found in fish.

TABLE XI

CONCENTRATIONS OF SEVEN METALS IN QUAHOGS CLAIM MEATS FROM NARRAGANSETT BAY[a]

Location	Cadmium Mean	Cadmium SD[b]	Chromium Mean	Chromium SD	Copper Mean	Copper SD	Mercury Mean	Mercury SD	Nickel Mean	Nickel SD	Lead Mean	Lead SD	Zinc Mean	Zinc SD
Fall '85														
Q-GR1	0.12	0.03	0.31	0.19	3.44	0.82	0.02	0.01	2.52	1.19	0.17	0.01	27.50	3.39
Q-MH55	0.14	0.04	0.99	0.42	3.29	0.70	0.08	0.04	3.17	1.19	0.59	0.24	31.54	10.71
Q-MH61	0.15	0.06	0.67	0.32	3.35	0.46	0.09	0.01	2.95	0.59	0.47	0.25	35.11	8.75
Q-MH62	0.09	0.05	0.73	0.22	2.81	0.61	0.11	0.03	2.76	0.29	0.42	0.11	30.47	1.74
Q-MH63	0.10	0.03	0.52	0.24	4.11	0.97	0.09	0.01	3.33	0.50	0.42	0.13	25.47	2.13
Q-MV1	0.19	0.07	0.82	0.68	4.14	1.60	0.04	0.02	3.26	1.28	0.18	0.05	25.97	6.17
Q-OL1	0.14	0.02	0.77	0.50	3.22	0.80	0.03	0.02	3.14	1.30	0.43	0.15	31.31	8.90
Q-PR13	0.18	0.01	0.48	0.27	5.54	0.69	0.02	0.02	4.04	0.77	0.76	0.34	41.13	6.10
Q-PR2	0.18	0.03	1.17	0.50	9.27	3.92	0.06	0.02	4.18	1.82	0.97	0.47	47.46	14.94
Q-PR30	0.38	0.18	0.74	0.54	7.04	3.60	0.01	0.02	4.29	1.48	0.85	0.60	52.60	29.18
Q-PR47	0.21	0.02	1.33	1.61	4.22	1.40	0.04	0.03	4.06	1.02	0.25	0.13	29.04	5.02
Q-PR49	0.19	0.05	1.53	0.41	6.04	1.20	0.07	0.01	6.43	2.29	0.62	0.33	43.10	6.87
Spring '86														
Q-GR2	0.11	0.01	0.18	0.01	3.45	0.56	0.02	0.01	2.25	0.30	0.23	0.06	30.90	9.00
Q-MH55	0.15	0.04	1.07	0.57	5.37	1.22	0.10	0.01	5.19	1.31	0.83	0.45	40.17	12.71
Q-MH61	0.15	0.01	0.57	0.40	3.10	0.50	0.12	0.09	2.70	0.64	0.68	0.15	34.00	6.30
Q-MH62	0.15	0.01	1.58	0.10	3.85	0.01	0.15	0.02	4.01	1.33	1.03	0.23	46.40	18.40
Q-MH64	0.15	0.01	1.73	0.36	4.43	0.57	0.14	0.03	3.34	0.81	0.77	0.16	35.93	3.65
Q-MV1	0.09	0.02	0.31	0.21	3.54	0.54	0.03	0.02	2.68	0.70	0.39	0.13	27.40	8.12
Q-MV2(1)	0.32	0.09	1.50	0.50	11.12	1.55	0.13	0.03	11.54	3.63	1.51	0.31	82.23	5.35
Q-MV2(2)	0.08	0.07	0.18	0.01	3.90	0.54	0.02	0.01	2.81	0.57	0.69	0.19	29.30	6.56
Q-OH1	0.17	0.06	0.53	0.21	5.18	0.72	0.04	0.04	3.77	1.12	1.24	0.19	39.44	7.43
Q-PR15	0.13	0.02	0.45	0.16	6.41	1.12	0.03	0.01	4.46	0.91	0.99	0.34	49.52	15.03
Q-PR1	0.21	0.05	0.98	0.03	9.92	3.44	0.07	0.03	5.07	0.99	1.03	0.33	49.87	6.60
Q-PR30	0.21	0.04	0.41	0.36	3.96	0.42	0.03	0.01	3.26	0.65	0.52	0.14	40.11	7.37
Q-PR47	0.15	0.03	0.59	0.32	4.74	0.43	0.03	0.01	4.15	1.00	0.55	0.18	26.78	4.75
Q-PR49	0.15	0.06	0.85	0.39	7.51	3.73	0.06	0.01	4.75	1.22	0.67	0.38	47.36	24.87

[a]From Thibault/Bubly Associates (1986).

[b]Mean of between four and ten measurements taken at the same location where each measurement represents a composite of four clams.

TABLE XII

COMPARISON OF TOXICITY INDICES WITH DAILY INTAKE OF METALS THROUGH CONSUMPTION OF QUAHOG CLAMS FROM NARRAGANSETT BAY[a]

	ADD (score)[b] ug/kg-day	LOEL (score)[b] ug/kg-day	Daily Mean Intake from Clams, ug/kg-day	Suggested Action
Cadmium	0.5 (a)	1250 (a)	0.1 - 0.45	Detailed assessment. No urgency
Chromium	5 (b)	---	0.2 - 2.0	No further analysis
Copper	40 (d)	---	3.0 - 13	No further analysis
Mercury	0.1 (a)	--- (a)	0.02 - 0.17	Detailed assessment. No urgency
Nickel	10 (c)	500 (b*)	2.5 - 13	Detailed assessment. No urgency
Lead	0.6 (a)	113 (a)	0.2 - 1.7	Detailed assessment. Priority
Zinc	200 (e)	---	30 - 60.0	No further analysis

[a]Assuming 80g of clams per day. 1-3% of the population may consume two- to three-fold quantity.

[b]ADD, Acceptable Daily Dose to protect from chronic toxicity (see Table VI); LOEL, Lowest Observed Effect Level for developmental/reproductive toxicity (see Tables III and IV).