ARET CRITERIA SUB-COMMITTEE REPORT

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Executive Summary

The Criteria sub-committee of ARET was formed in June 1992 "to select and develop criteria for identifying candidate substances which, due to their physicochemical and toxicological characteristics, warrant action via ARET."

Members of the sub-committee represented industry, labour, environmental group, federal and provincial stakeholders of the ARET committee.

In developing selection criteria for the ARET process, the sub-committee relied heavily on the expertise of the Ontario Ministry of Environment representatives, and the Ontario documents "Candidate Substances List for Bans or Phase-outs", April 1992, and "A Scoring System for Assessing Environmental Contaminants", March 1990.

The criteria used for selecting substances for ARET consideration include toxicity, bio-concentration and persistence. The criteria are simply described, but the interpretation of data for scoring cannot be reduced to a concise formula. It is expected that professional judgement using all of the latest, state-of-the-art information will be used in the application of the ARET criteria. An ARET selection sub-committee will proceed through the criteria application process.

The collection of substances to which the criteria will be applied will initially be those included in the CESARS (Chemical Evaluation Search and Retrieval) database, which has been significantly updated by the Ontario Ministry of the Environment. A second round of selection will be done on substances nominated by ARET stakeholders, to ensure a broader representation of substances on a national basis.

Substances are first ranked based on a normalized scoring of six toxicity elements. Substances scoring above a certain toxicity score will pass on to the next step, which checks the substance's potential to bio-concentrate and persist on the environment. Those which pass all three "screens" are considered to be the highest priority category. Those which pass the toxicity and bio-accumulation or persistence criteria are in the next category, followed by those that pass the toxicity score criterion only.

There will be some substances with insufficient data available to evaluate. These substances will be listed for further data-gathering by industry or government.

Criteria Report

Draft Version 3.0

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Changes from version 1.0, November 15, 1992, are noted in itallics.

I) Background:

The Criteria sub-committee of ARET was formed in June 1992 with the following mandate : "to select and develop criteria for identifying candidate substances which, due to their physicochemical and toxicological characteristics, warrant action via ARET." Members of the sub-committee are:

> David Bennett, Canadian Labour Congress; Geoff Granville, Health & Welfare; Ross Hume Hall, assisting Pollution Probe; Brian Kohler, Canadian Labour Congress; Allan Jones, Canadian Chemical Producers' Association; Roger Keefe, Canadian Petroleum Products Institute; Ian MacLaine, Industry, Science & Technology; Burkhard Mausberg, Pollution Probe; Nancy Sherwin, ARET secretariat; Adam Socha, Ontario Ministry of Environment; *Herb Vandermeulen, Environment Canada*; Stuart Warner, Mining Association of Canada.

In considering the various options for selection criteria, the sub-committee relied heavily on the Ontario Ministry of Environment documents "Candidate Substances List for Bans or Phase-outs", April 1992, and "A Scoring System for Assessing Environmental Contaminants", March 1990. In addition, a document prepared by the Canadian Labour Congress Environment Bureau, "A Critique of the Ontario Hazard Assessment System" was reviewed by the sub-committee.

In early December 1992, a small work group performed a "dry run" of several selection process options on approximately 50 randomly selected substances. Findings from this work have been incorporated in the criteria development and selection process described below. The dry run report is available for further reference upon request.

There are several **points of general note** that should be kept in mind in reading this report:

1) The criteria will be applied to specific substances.

2) *Data used in substance evaluation will preferably be from published and peer-reviewed sources. "Personal communication" data may be used if the validity has been established by ARET.*

3) The proposed criteria for ARET use are simply described, but the interpretation of data for scoring cannot be reduced to a concise formula. It is expected that professional judgement using all of the latest, state-of-the-art information will be used in the application of the ARET criteria.

4) The ARET criteria are not so prescriptive as to prevent the incorporation of the evolving scientific state-of-the-art. The scientific basis for scoring the criteria is expected to move away from descriptive methods and to become more reliant on knowledge of absorption, distribution, metabolism, storage and elimination of substances and their mechanism of action. Similarly, descriptive protocols are expected to change; for example, the use of the new Fixed Dose Method for Acute Toxicity by the Organization for Economic Cooperation and Development (OECD) will be increasingly used to reduce the number of animals formerly used to determine an LD50.

5) In scoring the criteria, all the data should be weighed, including both positive and negative studies for the same endpoint. The data quality must be considered. It also includes knowledge of mechanism of action, consideration of sensitive populations, and what may be known about the behaviour of the substance or its metabolites in the organism.

6) When assessments are available from credible scientific bodies, these may be used in scoring the ARET criteria, with the application of professional judgement. For example, the conclusions of IARC (the International Agency for Research on Cancer), USEPA (United States Environmental Protection Agency), NTP (the U.S. National Toxicology Program), *OECD HPV SIDS (Organization for Economic Co-operation and Development High Product Volume chemicals Screening Information Data Sets), and IPCS (International Program for Chemical Safety)* may be used as the foundation for assessment of the ARET criteria for carcinogenicity.

7) Determinations should be made, where possible, to fill expected gaps where no experimental data exists to score a criteria parameter. Professional judgement should be used which incorporates knowledge of the physical/chemical properties of the substance, Quantitative Structure-Activity Relationships (QSARs), and behaviour of similar substances for the same endpoint.

8) Wildlife data on substance effects will be considered in using professional judgement to assess effects.

9) Policy considerations were not part of the sub-committee's mandate. The proposed ARET criteria and their combination into a classification scheme does not carry any implications with respect to final ARET action(s). The ARET Committee is expected to integrate other considerations into its decisions for action, and may request the criteria sub-committee to adjust their weighting factors or scoring cut-offs to produce either a longer or shorter candidate list for action.

II) *Criteria Elements Used:*

Parameter definitions for the criteria elements are described in Appendix I.

III) *Clarification on selected criteria elements:*

Refer to Table 1 *and accompanying notes* for the scoring system, *which has been* adapted *by the criteria sub-committee* from the Ontario *scoring* method. *The following notes provide additional clarification on several of the elements:*

1. Persistence : The hierarchy of preference in data use is : field measurements are preferred over lab experiments, which are in turn preferred over modelling data. Data on soil persistence is considered to be highly variable, since half-lives in soil are very dependent on environmental conditions and the concentration of the substance in the soil. Therefore, soil persistence will only be considered if the substance receives a zero score for water, *air*, and sediment persistence. When considered, soil persistence *will be flagged for further professional judgement.*

2. Bio-*concentration* data used can be either BCF, bioconcentration factor, or, with professional judgement in view of metabolic considerations, the octanol-water partitioning coefficient, Kow. Preferred data is from tests on freshwater fish in flow-through systems. If fish data are not

available, information from other vertebrate species may be used with judgement. Tissue and organ selection in such studies on which the BCF is based is subject to professional judgement.
Where field measured Bio-Accumulation Factor (BAF) data is available, it should be used, with the same scoring scheme as for BCF.

3. Toxicity : Pharmacokinetics and metabolism of a substance must be considered in relation to its potential to cause genotoxicity and chronic/subchronic toxicity, including cancer.

   a) For **chronic/sub-chronic toxicity**, mammals, preferred data is from studies lasting longer than 90 days. For shorter studies, down to 28 days, divide the end-point concentration results by 5 before scoring. (*This is based on experience with shorter-term tests which indicates that the difference in end-point concentration is less than an order of magnitude*). Data from tests shorter than 28 days will not be considered.

   b) For **carcinogenicity**, either human or animal data may be used. In the case of limited data, where only one laboratory species has been tested, the score will be flagged "L" for "Limited". *For example*, where the one species tested is known to be a cancer-sensitive species, this would be an inappropriate basis, *in the absence of other data (eg. genotoxicity or cytotoxicity)*, to score high on carcinogenicity.

   c) **Genotoxicity or mutagenicity** data will only be used if no reliable data is available on carcinogenic or reproductive endpoints. Data from mammalian studies should be given more consideration than data from mammalian cells in culture, insects, and bacteria.

4. Multi-media partitioning will be used as an informational element only.

   Based on a fugacity model, the equilibrium distribution of a chemical to each environmental medium is estimated, and the percentage to each medium can be recorded. This parameter can be used to identify in which medium persistence is most likely to be critical, and can be used in conjunction with release medium information to provide useful data for application of professional judgement.

IV) *Proposal* for substance selection and prioritization for ARET consideration.

Following a "dry run" test of several options, the sub-committee recommends the following schema for substance selection:

Refer to flow charts A and B.

1. ***The Universe of Chemicals***

To allow the timely preparation of a candidate substance list, the criteria for selection will first be applied to substances in the CESARS (Chemical Evaluation Search and Retrieval System) database. Developed and used by Ontario, this database includes substances that have been found in the Great Lakes basin.

To provide a national scope to the ARET substance list, a second phase list will be prepared using a group of substances nominated in the various regions of Canada through the ARET stakeholders.

2. ***Substances ranked by toxicity***

Obtain toxicity scores for the substances on the six elements noted in Table 1. Where there are no data, set the substance aside for further data search. To calculate the Normalized Toxicity Score (NTS), see below>

<There can be as many as 6 toxicity scores, with a maximum normalized score of 60. If the scores for 5 toxicity parameters were 10, 6, 8, 2, and 4 out of a possible maximum of 10, these would be normalized to 36 out of 60 (total of 30 points out of a potential 50)>.

Note with an asterisk those substances for which a score of 10 is obtained on any element. Set aside for further data-quality review those that score 10 on one toxicity element based on "questionable" (Q) or "limited" (L) data.

3. ***Toxicity screen***

Set an appropriate cut-off NTS at which the substances above the cut-off will continue to be considered for ARET action. Substances below this cut-off that score 10 on any one of the six toxicity elements (based on data that is neither "questionable" nor "limited") will also continue to be considered for ARET action.

4. *Bio-concentration and persistence*

Display bio-concentration scores (0, 4, 7 or 10) and persistence scores (0, 4, 7, or 10) for those substances passing the toxicity cut-off. Substances with bio-concentration and persistence scores of 7 or 10 (i.e. BCF greater than 500 and persistence greater than 50 days) would be given the highest priority for ARET action (Priority List 1). Those with a bio-concentration score of 7 or 10, but with a persistence score lower than 7 would be in List 2.

For bio-concentration scores of 4, display the actual BCF or Kow data. Set aside for further consideration those with a BCF greater than 250.

Those above the BCF cut-off of 500, with persistence greater than 50 days would be in List 3; those with persistence lower than 50 days would be List 4.

V) Next steps:

1. *Agreement by the ARET committee at its February 22/23 meeting to proceed on the basis of this proposal.*

2. *The ARET committee will choose a "Substance Selection Sub-Committee" (SSSC). This small group of individuals should include representatives from government (H&W, DOE, Ontario, and one other province), industry, environmental and labour communities. The members should have sufficient understanding of toxicology to be capable of applying professional judgement. The Selection Sub-committee would operate on an on-going basis, to deal with the nominations for the second phase list and to deal with appeals for changes to the list.*

   ARET will need to define a dispute-resolution mechanism for dealing with situations of differing professional opinions in the sub-committee.

3. *The scoring will be done and criteria will be applied to a large grouping of substances mechanically. The initial grouping of chemicals to be considered as input to the list will be the contents of the CESARS database, held by Ontario Environment. The intent is to complete this task by the end of February.*

4. *The SSSC will look in depth at the data for those substances in List 1 to ensure that the test results used to generate scores were valid. The sub-committee will also do a judgement check on the full mechanically-generated list with respect to the placing of substances in the various*

lists. The intent is to complete selection of the initial-phase lists by late spring 1993.

5. Review of the lists by ARET committee for additions.

6. *Repeat steps 3 to 5 in a second phase using a grouping of substances nominated by ARET stakeholders, to ensure that substances of concern in other areas of Canada than the Great Lakes are also considered. This second phase would likely take place 6 months after Phase 1 to allow time for sufficient nominations to be made.*
   The Mining Association of Canada (MAC) has agreed to provide input on specific metal compounds; several current data bases treat metal compounds as generic groups, while specific compounds would have different scores. Stakeholders will be requested to provide documentation of available data on the substances nominated.

7. *An appeal process should be developed to add or delete substances from the selected list, based on rational positions. Recommendations of list changes, with supporting documentation, would be provided to the ARET secretariat for presentation to the Substances Selection Sub-committee. This group would evaluate the rationale provided and provide a recommendation to the ARET committee for decision.*

VI) Scoring for Substitution Analysis

Although substitution of one chemical for another is not a preferred pollution prevention option, there will be situations where this is the best risk management option available. When such changes are being considered, it is important to know that the substances being considered for the process change are likely to be less harmful than those currently being used. Ranked lists of substances may be useful in this substitution analysis. *It should be noted that the substitution decision can be very complex. A combination of many factors, including the volume of the material to be used, its cost and the energy implications of its use, needs to be considered.*

The lists and detailed data provided by the criteria application process described above could potentially be useful in substitution decisions.

VII) Additional comments to provide to
the ARET committee from the Criteria sub-committee:

1) Although selection criteria are oriented toward specific substances, clusters of substances may naturally arise from the application of criteria. To broaden the focus of ARET, in addressing the substances selected, ARET should consider related emissions, industrial & commercial processes, and sectoral releases. In other words, the candidate substance could serve as a surrogate for a cluster of similar substances.

2) *Consideration of the presence in the environment of the candidate substances, as well as whether they are released, used, imported or produced in Canada, should be a part of the ARET prioritization process.*

3) *In dealing with the candidate substances in the lists to determine appropriate actions, ARET should consider socio-economic factors including, for example, life cycle energy considerations.*

4) Where there is insufficient data to evaluate a substance, it should be flagged for further data-gathering activity. Thus, a list of substances for investigative action may be an outcome of the selection process.

5) *ARET should consider having this criteria methodology and selection process peer-reviewed and published as an example of a process developed by a multi-stakeholder body.*

APPENDIX I : DEFINITIONS

1) Persistence describes the tendency for a chemical to remain in the environment. The net resistance to such processes as sorption, oxidation, hydrolysis and photodegradation can be expressed as the overall persistence of a substance in the environment. Persistence is usually expressed as the length of time required for one-half of the original amount of a substance to be degraded (half-life). Short half-lives generally indicate a lower level of concern.

2) Bio-concentration describes the tendency for a substance to accumulate in biological systems, and more specifically the ability of a substance to accumulate in the tissues of organisms. One of the parameters frequently used to express bioconcentration is the bioconcentration factor (BCF). Most BCF values pertain to fish or other aquatic organisms and are calculated as the ratio of the concentration of a substance in the organism (or some specific tissue) on a wet weight basis to the concentration of a substance in the water at steady state. The tendency of substances to bioconcentrate in tissue frequently has been related to hydrophobicity or lipophilicity. Various regression equations have been suggested for predicting BCF values for aquatic organisms based on the octanol-water partition coefficient (Kow) and other physico-chemical properties.

3) Toxicity elements:

   a) **Acute lethality** describes the acute lethality of a chemical to terrestrial and aquatic animals. Non-lethal or reversible effects are not included. Acute effects other than lethality (irritation, allergic reactions, general narcosis, etc.) are considered in other toxicity elements. Criteria for phytotoxicity are not included in this element because of the difficulties in assessing lethality in plants.

   b) **Chronic/sub-chronic toxicity, non-mammalian species** describes potential effects from long-term exposure of non-mammalian species to chemicals. The effects data may be expressed as median effect concentration (EC50), maximum aquatic toxic concentration (MATC), or no-observed-adverse-effect-concentration (NOAEC).

   c) **Chronic/sub-chronic toxicity data on plants** can be highly varied depending on the toxicant. In some cases, results expressed in concentration units are appropriate, but in most instances the length of exposure time is very important. *Chronic toxicity data on plants should be provided, however, when dealing with phytotoxic substances.*

d) **Chronic/sub-chronic toxicity, mammals** describes potential repeated-dose effects of chemicals in mammals, and is measured in terms of the concentration required to result in the effects. The effects are directed primarily at human health, although the actual data used will largely be from laboratory animals. The toxic effects included in this parameter are restricted to sub-lethal systemic effects but do not include carcinogenic, mutagenic, or teratogenic effects, since these are included in other parameters. This parameter includes reproductive (non-teratogenic) and neurotoxic effects. Pharmacokinetics (absorption, distribution, storage, and elimination) and metabolism, as well as information about the mechanism of action, should be considered in scoring this parameter.

e) **Teratogenicity** *is an interaction of chemical, biological and physical agents with embryonic structure during prenatal life which produces a permanent change in morphology or function.* In scoring this parameter, consideration must be given to the spectrum of minor variations, anomalies, and malformations against their normal background incidence as well as to more subtle effects on the health of newborns and their future development.

f) **Carcinogenicity** *is a potential of a chemical to induce malignant tumours.* Consideration must be given to the pharmacokinetics and metabolism of the substance, its mechanism of action (eg. genetic vs. epigenetic mechanisms), whether the tumours are malignant or benign, whether they reduce the life span, etc.

g) **Genotoxicity/mutagenicity** *is an interaction of chemical and physical agents with the hereditary apparatus of the cell. It can be manifested in either gene alterations or changes in chromosomal structure or number which may be incorporated in the subsequent generations of that cell (i.e. mutations).* Such effects are generally taken as an indication of the potential of a substance to cause cancer or adversely affect reproduction.

Further elaboration of the description of these parameters can be found in the Ontario Ministry of Environment document "A Scoring System for Assessing Environmental Contaminants".

4) Multi-media partitioning describes the tendency of a substance to be distributed amongst air, water and land, and is generally modelled based on fugacity.

Table 1

Recommended Selection Criteria to be Used in Development of Candidates for Consideration by ARET

Scoring Criteria

ELEMENT NAME	ENDPOINT & UNITS	0	4	7	10
Environmental Persistence in water or sediment	t½ (days)	≤ 10	< 10 to 50	< 50 to 100	> 100
Bio-accumulation in freshwater fish[A]	BCF Log k_{ow}	≤20 ≤2.0	> 20 to 500 > 2.0 to 4.0	> 500 to 15000 > 4.0 to 6.0	> 15000 > 6.0

Multi-media partitioning: record % for each medium, based on modelling. (information element)

** Adapted from Table 1.6, in the Ontario Ministry of the Environment document "Candidate Substances List for Bans or Phase-outs"

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Table 1 (continued)

Scoring Criteria

ELEMENT NAME	ENDPOINT & UNITS	0	2	4	6	8	10
Acute Lethality	oral LD_{50} mg/kg	> 5000	> 500-5000	> 50-500	> 5-50	> 0.5 - 5	≤ 0.5
	dermal LD_{50} mg/mg	> 5000	> 500 - 5000	> 50-500	> 5-50	> 0.5 - 5	≤ 0.5
	inhal LD_{50} mg/m^3	> 15000	> 1500-15000	> 150-1500	> 15-150	> 1.5 - 1.5	≤ 1.5
	aquatic LC_{50} mg/L	> 1000	> 100-1000	> 10-100	> 1-10	> 0.1 - 1	≤ 0.1
Chronic/Sub-chronic toxicity, Non-Mammals	aquatic						
	EC_{50}, mg/L	≥ 20	2. < 20	0.2. < 2	0.02. < 0.2	< 0.02*	< 0.02*
	MATC, mg/L	≥ 2	0.2 < 2	0.02. < 0.2	0.002. < 0.02	< 0.002*	< 0.002*
	NOAEC,mg/L	≥ 0.2	0.02 < 0.2	0.002. < 0.02	0.0002. < 0.002	< 0.0002*	< 0.0002*
	terrestrial						
	subchronic						
	NOEL mg/kg/d	≥ 1000	100. < 1000	10. < 100	1. < 10	< 1*	< 1*
	chronic						
	NOEL mg/kg/d	≥ 500	50. < 500	5. < 50	0.5. < 5	< 0.5* *in one genus	< 0.5* *in different genera
Chronic/Sub-chronic toxicity, Plants	Water, mg/L						
	Air, mg/m^3						
	Soil, mg/kg						
	% Growth Reduction:						
	≤5 (= NOEL)						
	water	> 10	> 1.10	> 0.1-1	> 0.01-0.1	0.001-0.01	< 0.001
	air	> 100	> 10-100	> 1.10	> 0.1.1	0.00-0.1	< 0.01
	soil	> 100	> 10-100	> 1.10	> 0.1.1	0.01-0.1	< 0.01
	>5-50 (=EC_{50})						
	water	> 100	> 10-100	> 1.10	> 0.1.1	0.01-0.1	<0.01
	air	> 1000	> 100-1000	> 10-1000	> 1.10	0.1-1	<0.1
	soil	> 1000	> 100-1000	> 10-1000	> 1.10	0.1-1	<0.1
	>50						
	water	> 1000	> 100-1000	> 10-1000	> 1-10	0.1-1	<0.1
	air	> 10000	> 1000-10000	> 100-10000	>10-100	1-10	<1
	soil	> 10000	> 1000-10000	> 100-10000	>10-100	1-10	<1
Chronic/Sub-chronic toxicity, Mammals[a]	oral NOEL mg/kg/day	> 1000	> 100-1000	> 10-100	>1-10	>0.1-1	≤ 0.1
	inhal. NOEL mg/m^3	> 3000	> 300-3000	> 30-300	>3-30	>0.3-3	≤ 0.3
Teratogenicity	mg/kg/day	no terata, or terata only at > 1000	terata or developmental anomalies at > 50-1000	terata or developmental anomalies at > 10-50	terata or developmental anomalies at > 1-10	terata > 0.1-1, without overt maternal toxicity	terata at ≤0.1 without overt maternal toxicity
Carcinogenicity	human and animal bioassay data	no tumours in adequate studies on at least two species, and does not interact with genetic material	tumours in only one animal species, negative results in others	causes benign tumours in more than one species, and does not interact with genetic material; promotor only; or causes cell transformation in vitro only (negative evidence in vivo)	tumourigenic in bioassays at doses causing metabolic enzyme saturation, or associated with lesions that predispose to tumours. No interaction with genetic material	indirect-acting carcinogen, no interaction with genetic material	direct-acting carcinogen that interacts with genetic material
Genotoxicity/ Mutagenicity[c]	in vivo and in vitro cell assays	not genotoxic or mutagenic, negative results in vivo and in vitro	mutagenic in in vitro assays only, negative in vivo	mutagenic in prokaryotic cells only; negative results in eukaryotic cell assays	causes DNA induction or repair, with no direct interaction with nuclear material	causes clastogenic effects, sister chromatid exchange, crosslinks; no evidence of mutation	mutagenic in vivo (no negative results from in vitro assays)

[a] Adapted from Table 1.6, in the Ontario Ministry of the Environment document "Candidate Substances List for Bans or Phase-outs"

Notes on Selection Criteria to Accompany Table 1

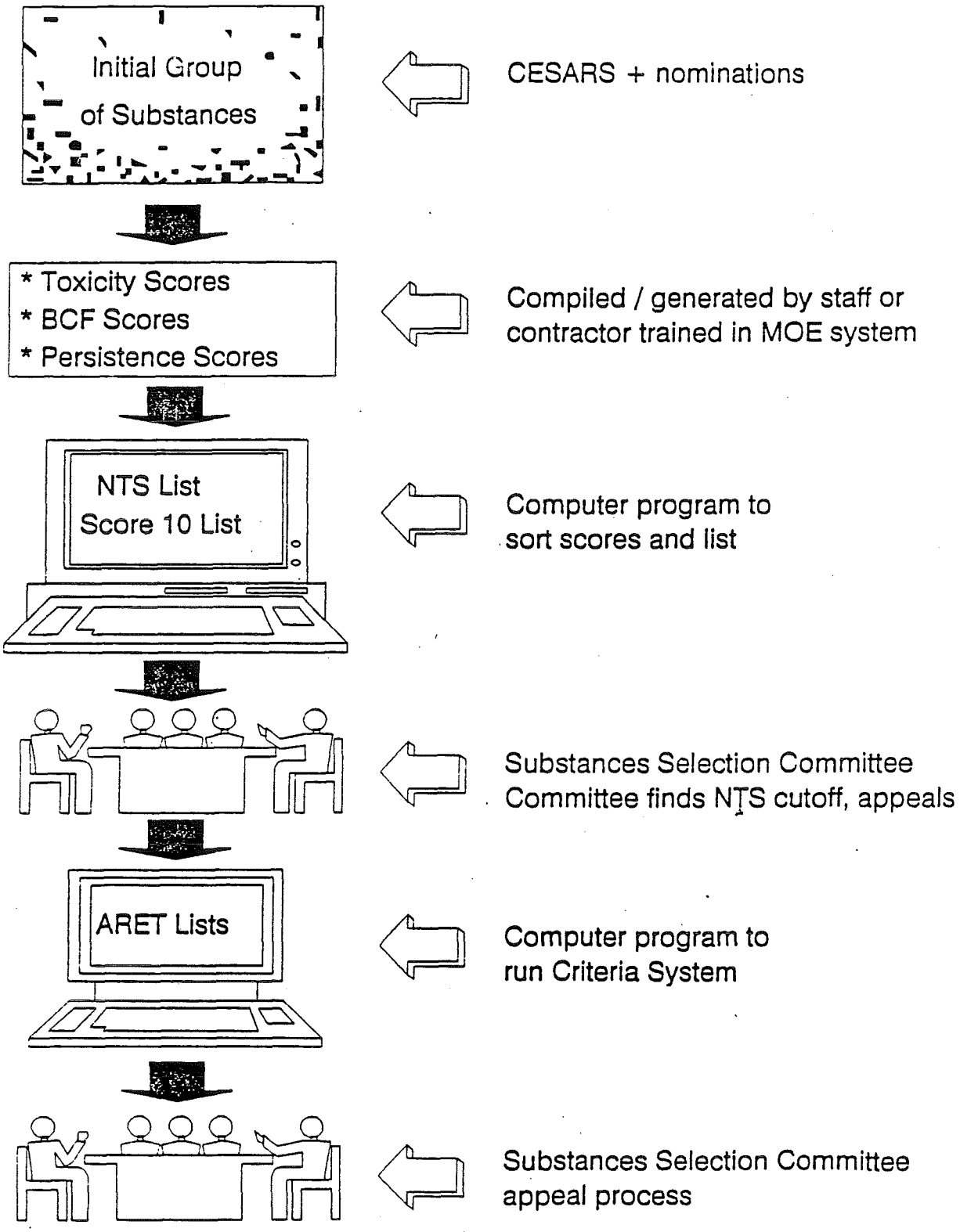
A. If freshwater fish data not available, information from other vertebrate species may be used with judgement.

B. The Sublethal Effects, Mammals criteria are based on studies of $\geq$ 90 days duration. If only shorter-term subchronic studies are available, the end-point concentration data are modified by dividing the result by 5, prior to scoring for toxicity.

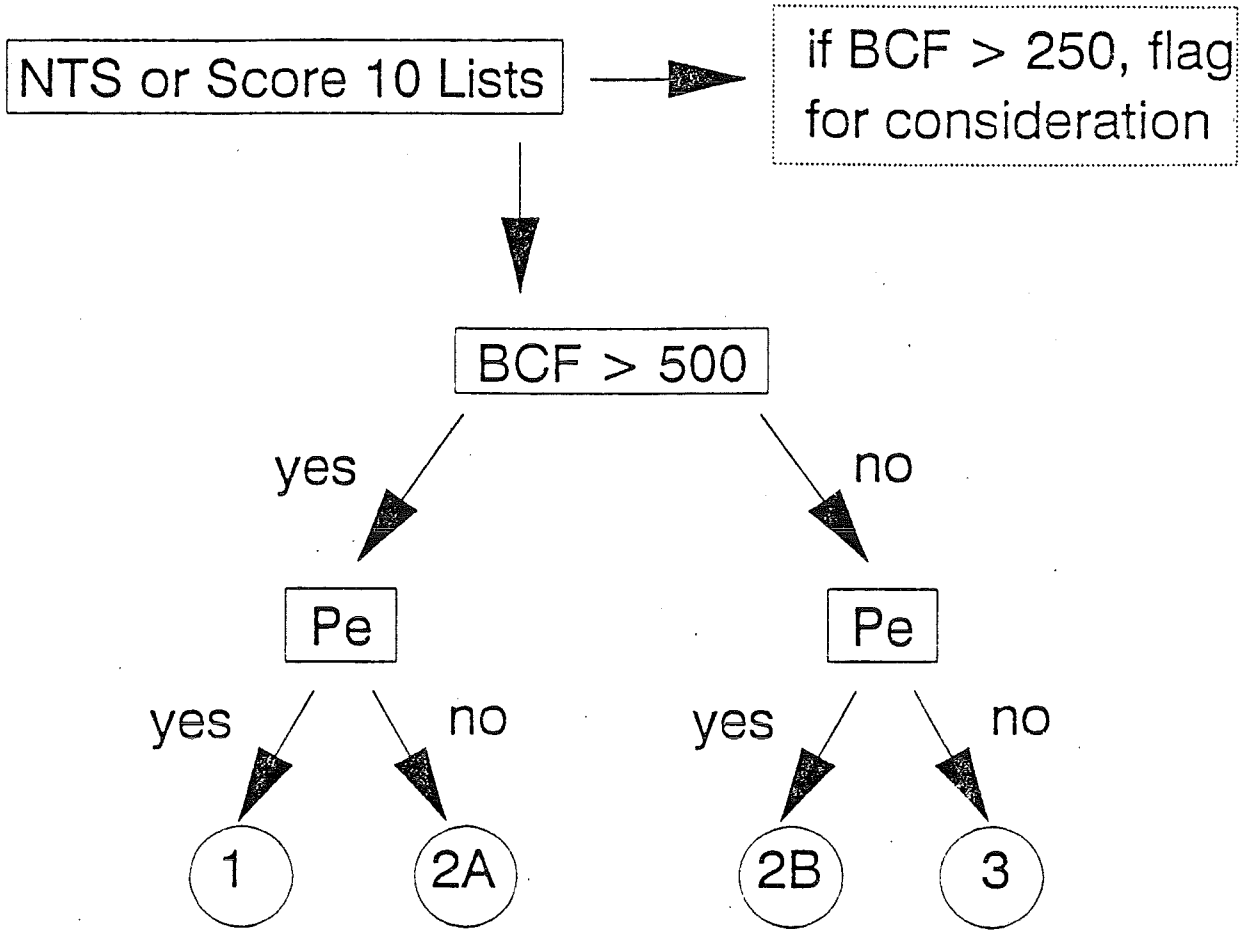
C. This data element is only used if no reliable data is available on carcinogenic or reproductive endpoints.

FLOW CHART A

The Selection Process



Criteria System Flow Chart B



Four different substances lists for ARET, now consider presence, socio-economic factors, etc.

Pe = Persistence > 50 d