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HAZARDOUS AIR POLLUTANT PRIORITIZATION SYSTEM HAPPS

ARGONNE NATIONAL LABORATORY
9700 South Cass Avenue,
Argonne, Illinois 60439

HAZARDOUS AIR POLLUTANT PRIORITIZATION SYSTEM (HAPPS)

by

A.E. Smith and D.J. Fingleton

Energy and Environmental Systems Division

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1 PURPOSE AND RATIONALE

This section discusses the purpose of the Hazardous Air Pollutant Prioritization System (HAPPS) and the rationale used in developing the system. Subsections 1.2, 1.3, 1.4, and 1.5 provide, respectively, the rationale for choosing the particular set of eight factors, the rationale for the specific criteria and weights within each factor, the rationale for grouping the factors and assigning the intragroup weights, and the rationale for the intergroup weights used in the final ranking. These rationales can be properly understood only when the scope of HAPPS and the limitations imposed by this scope are taken into account. Subsection 1.1 discusses these limitations.

Section 2 provides instructions for using HAPPS. Appendix A contains a set of worksheets and tables for documenting a prioritization. Both Section 2 and the Appendix have been placed after the explanatory material in Sec. 1 to aid in copying the working material in the appendix. Section 1 assumes some familiarity with HAPPS and readers may want to scan the instructions and materials in Sec. 2 and Appendix A prior to reading Sec. 1.

1.1 SCOPE AND LIMITATIONS

The strategies and Air Standards Division (SASD) of U.S. EPA's Office of Air Quality Planning and Standards periodically selects new substances for assessment to determine whether regulatory development under the Clean Air Act should begin. Ideally, a full range of toxicological and epidemiological information coupled with detailed estimates of current emissions and human exposure would be available to aid in such decisions. However, such complete information is seldom available and early assessment is often made on the basis of incomplete and/or dated information. This is particularly true of EPA's hazardous air pollutant assessment effort, since a large number of organic and inorganic substances are potential candidates for study. However, even if only a small number of potential candidates existed, the resources involved in producing complete scientific information preclude the development of such information for each substance until there is some certainty that regulation is appropriate. Thus, a procedure for initially prioritizing substances on the basis of limited, readily available information

is needed so that resources for detailed studies might be allocated efficiently, that is allocated first to detailed studies of substances anticipated to be significant air pollution problems and later to substances anticipated to be lesser problems. HAPPS provides a means of producing such a prioritization.

It is recognized that a prioritization with limited data as opposed to extensive, detailed data might produce substantially different results. HAPPS is only intended to provide a reasonable prioritization to aid EPA in deciding which substances to study first based on readily available information. As such HAPPS is intended to be used as part of EPA's internal planning process. It is important to recognize that even substances ranked very high by HAPPS might never be regulated. Many subjective decisions must be made and detailed objective studies done and evaluated between the time a substance is ranked highly by HAPPS and a decision is made to regulate that substance as an air pollutant. In other words, HAPPS must be viewed as an initial, tentative step within the context of the overall regulatory program. Even the initial prioritization produced by HAPPS will be subject to additional screening by experts to eliminate any obvious anomalies. In addition, the methodology will be applied periodically to incorporate new information as it becomes available. Such periodic reviews could result in changes in the relative rankings of various substances, reflecting the new information. There may also be programmatic reasons for overriding the indications given by HAPPS. For example, it might occur that some particular class of compounds like heavy metals is receiving special attention throughout air programs, a consideration which could lead to alterations to a list produced by HAPPS. Regulatory decisions will not be made on the basis of a substance's ranking by the HAPPS procedure. Health assessments, exposure assessments, and other information must all be evaluated prior to making the decision to regulate. It might be found that the health effects associated with a substance ranked highly by HAPPS were not serious enough, that control of the substance was technically infeasible, or that the likelihood of exposure was not sufficiently great to justify regulation.

To be useful, a procedure must be tailored to the expertise and experience of potential users. No matter how complete or precise a procedure is in theory, it is useless if its application requires detailed or specialized

knowledge not available to the user group. With these points in mind, discussions with EPA personnel defined several guidelines which HAPPS would need to follow to be useful in the prioritization effort:

- Generally, readily available summary documents or computerized data bases will be used; searches of primary sources are precluded by the intended use of the procedure and the inability to justify allocating significant resources to this preliminary prioritization step.
- The methodology is purposely designed not to utilize expert judgment in prioritizing chemicals. Such expert judgment is more appropriate as part of subsequent regulatory decision making than to the preliminary prioritization stage where HAPPS is used.
- The preliminary nature of the prioritization means that the procedure should be simple enough to permit a single user to prioritize several substances per day and preferably ten or more.
- Personnel using the procedure should have only limited expertise in toxicology or related subjects and only limited familiarity with some of the sources of emissions of the substances being ranked. Hence, the procedure could not rely on decisions requiring expert judgment or special knowledge related to these areas.
- A particular set of substances should receive the same ranked order when prioritized by two different persons. Thus, insofar as possible, the procedure should be objective and the sources of data should be identical for all users. Complete agreement between two different users of HAPPS is unlikely because the goal of complete objectivity could not be attained; some factors still require the use of informed, as distinct from expert, judgment in choosing between criteria.
- The system should be sufficiently flexible to permit updates for a substance for which additional data becomes available in the standard references.
- The procedure is only intended to produce reasonable, initial rankings. Detailed studies will take place after the prioritization to develop sufficient information to determine whether or not regulation is required. Questions of data interpretation, the validity of data and similar technical items are left for experts to decide at later stages in the assessment process.

These guidelines place considerable constraints upon the procedure by restricting the source of data to be used and by limiting the effort in prioritizing a single compound. In particular, searching the literature and contacting other workers involved in prioritizing hazardous compounds led to an early recognition that the most suitable summary reference appeared to be the

Registry of Toxic Effects of Chemical Substances (RTECS).[1] RTECS is a concise, easily used summary of toxic effects and is kept current by continual updates in a computerized format and by quarterly updates in microfiche copy. RTECS also contains data related to most of the criteria used for ranking substances in the scoring procedure developed by Oak Ridge National Laboratory. As discussed below, the Oak Ridge procedure provided the basis for HAPPS thus making RTECS an excellent match to the data requirements of HAPPS. That RTECS was the most easily accessible reference had a significant impact on the choice of factors and the structure of criteria for individual factors. In addition, the need for consistency between users and the expected expertise of users limit the types of decisions users should be expected to make and make a straightforward approach with little chance for individual deviation desirable.

Many ranking or scoring procedures for prioritizing chemicals exist (see, for example, Refs. 2-25). Rather than develop an entirely new system, consultation with EPA indicated the desirability of using a draft EPA multimedia ranking procedure as the basis for HAPPS. That scoring procedure had been developed by Oak Ridge National Laboratory (ORNL)[21] for EPA's Office of Pesticides and Toxic Substances (OPTS) and itself drew heavily on existing scoring systems. Using an existing procedure as a basis for HAPPS was considered to be efficient in that a significant amount of duplicative work could be avoided. Much thought and developmental work had already gone into the ORNL procedure and its predecessors in choosing factors, criteria, and weights. After an initial review, it was clear that much of what had already been done was relevant to air programs and might need only minor revision or expansion. It should be noted that the ORNL procedure was still in draft form at the time HAPPS was developed. At the date of this report, the ORNL procedure has not been completed and applied because objectives other than prioritization have become priority items in OPTS programs. Thus, the ORNL procedure was used as the principal basis for HAPPS even though still in draft form. In choosing the specific factors and criteria, additional existing scoring systems, frequently those used in developing the ORNL procedure itself, were consulted and used in developing HAPPS.

However, the ORNL procedure differed in scope and purpose from HAPPS. The ORNL procedure was intended to consider multimedia exposures through various routes (air, water, consumer usage, etc.) and was also intended to

present data from the literature and data submitted in compliance with the 8(a)-Level-A rule of the Toxic Substances Control Act (TSCA) in a form suitable for review and final ranking by experts, both intentions making the ORNL procedure inappropriate under the HAPPS guidelines. In developing HAPPS, the ORNL procedure was used to select some of the factors, criteria, and weights and then tailored to the specific concerns of air programs. Since the output of HAPPS will provide program planning information for the Office of Air Programs, it was not necessary to consider total human exposure; consideration of exposure through the air route only is sufficient for such planning purposes.

1.2 RATIONALE FOR HAPPS FACTORS

HAPPS prioritizes substances by scoring them in eight factors chosen to reflect the concerns of air programs and issues deemed important by EPA. Table 1.1 presents the eight factors used in HAPPS and the twenty-five factors used in the ORNL procedure. The broader range of impacts on humans, animals, plants, and the environment in the ORNL procedure shows clearly when the two sets of factors are compared.

Among all the aspects of human health, the Office of Air Programs felt that carcinogenesis should receive special attention in accordance with the public's concern with carcinogens. The ORNL procedure already contained two factors, oncogenicity and mutagenicity, (items 1 and 2 in Table 1.1) related to carcinogenesis and these were retained in HAPPS. The oncogenicity factor contains both malignant and benign tumors. Mutagenicity is related to carcinogenicity and evidence of mutagenic potential is frequently used as an indicator in screening for carcinogens as in the Ames test. Although not a current major concern for air programs, retention of the separate factor for mutagenicity was reasonable for two reasons even though it is later grouped together with oncogenicity under the carcinogenicity group. First, oncogenicity and mutagenicity are distinct effects; all mutagens are not carcinogens; however, most carcinogens are mutagens. In addition, there is only a limited amount of data available from carcinogenicity testing, making the use of the more extensive surrogate data from mutagenicity testing desirable in order to maximize the number of substances that could be scored using data reasonably related to carcinogenic potential. Second, data are available separately for each factor in RTECS, the principal data source, making scoring a compound

Table 1.1 Factors in HAPPS and the ORNL Procedure

Item	Procedure: ORNL[a] Component	Procedure: ORNL[a] Factor	Procedure: HAPPS Factor
1		Oncogenicity	Oncogenicity
2		Mutagenicity.	Mutagenicity
3		Embryo-Fetotoxicity	Reproductive and Developmental Toxicity
4		Reproductive Effects	
5	Chronic Toxicity	Terrestrial Animals	Effects Other than Acute Lethality
6		Aquatic Animals	--
7		Plants, Fungi, Bacteria	--
8	Acute Toxicity	Terrestrial Animals	Acute Lethality
9		Aquatic Animals	--
10		Plants, Fungi, Bacteria	--
11		Production Volume	Potential for Airborne Release
12	Environmental Exposure	Environmental Release[b]	--
13		Transport & Transformation	--
14		Bioconcentration	Bioaccumulation
15		Weighted Quantity Processed[b]	--
16		Weighted Quantity in Products[b]	--
17-21	Occupational Exposure	(Five Separate Factors)[b]	--
22	Consumer Exposure	Weighted Quantity in Products[b]	--
23		Number Exposed	--
24		Frequency of Exposure	--
25		Intensity of Exposure	--
26	--	--	Existing Standards

[a]Adapted from Ref. 21.

[b]Requires information available from manufacturer compliance with 8(a)-Level-A rule of TSCA.

unambiguous if two factors are used while confusion might result with a composite factor based on both oncogenicity and mutagenicity data.

Oncongenicity and mutagenicity were separated from other toxic effects because the Office of Air Programs is primarily concerned with carcinogenicity rather than the toxic effects considered under the other toxicity-related factors: reproductive and developmental effects (items 3 and 4), effects other than acute lethality (item 5), and acute lethality (item 8). It is also generally recognized that oncogens and some mutagens have no thresholds whereas the effects dealt with in the factors for items 5 and 8 normally exhibit thresholds giving the separation a reasonable conceptual basis. Assignment of appropriate weights to the carcinogenicity and toxicity groups, as discussed later, was used to combine all toxic effects including oncogenicity and mutagenicity in the final prioritization. Finally, RTECS provides separate data for oncogenicity, mutagenicity, reproductive and developmental effects, and the two toxic effects factors so that the factors used in HAPPS match the available data, thereby reducing the likelihood of error.

The ORNL factors for items 3 and 4 were combined into a single factor for reproductive and developmental toxicity in HAPPS. Increasing concern for developmental effects has been shown in recent years as evidence accumulates revealing the high sensitivity of human embryos, fetuses, and young to certain substances. Reproductive effects could have long-term impacts on the population and might be considered severe. However, data in RTECS does not distinguish between the two types of effects and hence the separate ORNL factors were combined. As discussed above, these effects were separated from the two factors most directly related to carcinogenicity which is currently the principal focus of air programs. Although it has been theorized that reproductive and developmental effects exhibit thresholds they were also separated from the two factors for toxic effects because this separation matches the form of the data as presented in RTECS.

Since HAPPS emphasizes human health, the ORNL factors for aquatic animals and for plants, fungi, and bacteria (items 6,7,9, and 10 in Table 1.1) were eliminated as being poor indicators of human health effects. In addition, no readily available source of information was found for toxicity effects in plants, fungi, and bacteria making the related factors inappropriate for HAPPS even if they were relevant to the major concern with human

health. Factors for toxic effects in terrestrial animals including humans (items 5 and 8) but distinct from oncogenic, mutaganic, and reproductive and developmental effects were retained. Effects in nonhuman terrestrial species were included as being reasonable indicators of potential effects in humans. Such inclusion, at least for higher mammals, is in accordance with standard toxicological procedures that use animal studies to anticipate health effects or toxicity in humans. Such procedures frequently involve tests on higher mammals and results of such toxicity studies are used in scoring the two toxicity factors in HAPPS.

The factor for production volume (item 11) was modified for HAPPS. In assessing exposure via the ambient air, it is desirable to know how much of a substance becomes airborne. Such detailed information is not available for most substances at the prioritization phase of study so production volume was considered as a surrogate following the ORNL procedure. Because airborne release was the particular interest in HAPPS, the factor was modified to include the consideration of vapor pressure in estimating the potential for airborne release, since, other conditions being the same, a substance with a high vapor pressure will become airborne more readily than a substance with a low vapor pressure. (Vapor pressure was also considered in the ORNL procedure in one of the factors related to occupational exposure.)

Of the five ORNL factors related to environmental exposure (items 12-16), four were eliminated and one was retained. The factors for environmental release (item 12) and for the weighted quantities processed and in products (items 15 and 16) require data that is to be submitted in compliance with the 8(a)-Level-A rule of TSCA and may be of use in the future. However, these factors are aimed at assessing overall environmental exposure and human exposures through routes in addition to ambient air giving them a broader scope than appropriate for air programs. Thus, these factors were dropped from HAPPS. The factor for transport and transformation (item 13) was considered to be important in view of possible chemical transformations and residence time in the atmosphere. However, no summary sources of relevant data were found and no sources seem likely to become available in the near future thus eliminating this factor from consideration under the guidelines.

The factor for bioaccumulation (item 14) was retained in HAPPS. Air pollutants can either be deposited mechanically or absorbed directly by food

or be deposited on soil and absorbed later by plants. Such deposited substances can then either pass up the food chain through animals to humans with possible biological magnification or be ingested directly. In both cases, toxic levels can result directly or build up in the body over time. Data for this factor was available in summary form and consequently was retained in HAPPS.

Overall, then, three factors were used as surrogates for exposure: production volume and vapor pressure combined to estimate the potential for airborne release and bioaccumulation. Information for these three factors is readily available but is not readily available for other indicators of ultimate fate and exposure like residence time in the atmosphere and atmospheric reactions. In addition, these latter two indicators were considered too detailed for the preliminary nature of this prioritization.

The five ORNL factors relating to occupational exposure were deleted in consultation with SASD, because occupational exposure does not fall within the ambit of the Clean Air Act. In addition, only one of the five factors, level of potential occupational exposure, does not depend upon data to be gathered under the 8(a)-Level-A rule of TSCA. This ORNL actor scores compounds based on exposure concentrations experienced by workers. While some of the criteria used for the factor relate to the ease with which workers could contact the airborne chemical, the information required would not generally be available and the factor was dropped from HAPPS. However, vapor pressure could be used for scoring liquids under this criterion in the ORNL procedure and was retained as one of the indicators of the potential for airborne release.

The four ORNL factors for consumer exposure (items 22-25) were dropped from HAPPS. These factors are oriented toward exposures due to use of household and consumer products and would include many routes of exposure inappropriate to air programs. Although indoor air pollution problems due to use of household and consumer products would logically come under the criteria, no summary source of the data required by the criteria for these factors was found. In addition, indoor exposure is not the focus of the air programs office. Thus, these criteria were dropped and the factors for potential for airborne release and bioaccumulation are the only factors related specifically to the potential for human exposure via the ambient air.

A factor for existing standards (item 26), not found in the ORNL procedure, was added to HAPPS. The factor was based on the MITRE procedure[10] and is intended to be scored based on standards set by the Occupational Safety and Health Administration (OSHA). Establishment of an OSHA standard requires a finding of potential toxic effect. Such a finding was considered to be an important indicator that a substance might need to be considered in more detail even though the OSHA standards are intended to apply in the workplace where concentrations are likely to exceed ambient levels. It was also felt that existing standards would be useful for prioritization, especially if data for the other factors was sparse or if two or more substances were scored relatively close.

1.3 RATIONALE FOR CRITERIA

This section discusses the reasons for choosing the criteria and the associated weights within the individual factors. As already noted, the draft ORNL procedure[21] provided the principal model for HAPPS. However, in developing the specific criteria, several other procedures were frequently consulted. References 2, 9, 17, 18, 20, 22, and 23 were found to be particularly useful and include an earlier version of the ORNL procedure itself (Ref. 20) as well as several systems used in the development of that procedure. These references were selected after review of Refs. 2-24 as being most nearly suitable for HAPPS. Thus, the criteria finally used were chosen from among several sets available in the literature with possible additions and modifications to conform to the guidelines for HAPPS and to make them useable with the RTECS data base. With regard to other systems, it should also be noted that the Multimedia Environmental Goals (MEGS)[4] was considered as a basis for HAPPS. Review indicated that for ambient air all the parameters used by MEGS were already represented in HAPPS in a form more appropriate for prioritizing compounds. MEGS establishes "estimated permissable concentrations" (EPC's) and "minimum acute toxicity levels" (MATE's) from threshold limit values (TLV's), National Institute for Occupational Safety and Health (NIOSH) standards, and toxicity data available in RTECS and/or other standard references. The EPC's and MATE's are oriented towards establishing ambient and emission limits for sources rather than toward comparisons between different pollutants. In establishing ambient and emission limits, MEGS provides a tool for

detailed evaluation of the impacts of particular sources, not a means of comparing different substances emitted by sources with many different emission characteristics. Thus, the use of MEGS as a basis for HAPPS was rejected.

Oncogenicity. Table 1.2 compares the criteria used for oncogenicity in HAPPS and the ORNL procedure. It is anticipated that most of the data used in scoring a compound using these criteria will relate directly to carcinogenicity but the definition of the factor and the data in RTECS include neoplastic and equivocal effects as well. It was considered reasonable to use all data related to tumerogenic effects during the prioritization leaving distinctions between types of effects and their relationship to cancer for later consideration by experts.

The HAPPS criteria involve several modifications of the ORNL criteria for this factor. First, since Air Program's principal concern is with human health, criteria explicitly recognizing this concern were added and weighted more heavily than criteria related to evidence based only on animals. Additional weight was also assigned to oncogenetic effects in humans if caused by inhalation giving the highest weight to the route of exposure of interest to air programs (items 1 and 2). The distinction based on inhalation was not made for the criteria based on evidence in animals, because positive studies by any route of administration in nonhuman species were considered as reasonable indicators that additional study would be warranted. As in the ORNL procedure, evidence in two or more animal species was considered a reason for greater concern than evidence in a single species (items 3 and 4). A criterion determined by a substance's status under the National Toxicology Program's (NTP) Carcinogenesis Testing Program was introduced into HAPPS (item 8). Selection for testing under this program requires a determination that concern over a substance's carcinogenic potential is justified and that the degree of concern is greater than that associated with substances not selected for testing. Both of these determinations were considered sufficient reason for air programs to consider looking at a substance in more detail but were not considered as important as actual data. The ORNL criterion based on determining that a substance was a precursor to cancer was dropped because summary data would not be found. Both of the criteria requiring professional judgment were dropped, because such expertise could not be assumed under the

Table 1.2 Criteria for Oncogenicity

	HAPPS			ORNL[a]	
Item	Primary Weight	Secondary Weight	Criteria[b]	Score	Criteria[b]
1	5		Humans by inhalation.		
2	4	0.7	Humans by noninhalation.		
3	3	0.5	Two or more animal species by any route.	9	Humans or two or more animal species by any route.
4	2	0.3	One animal species by any route.	6	One animal species by any route.
5			--	4	Precursor.
6			--	3	Suspect based on mutagenesis screening or suspect based on professional judgment of parametric data.
7			--	1	No data but suspect based on professional judgement.
8	1	0.05	Scheduled for testing.		--
9	0	0.0	Negative evidence.	0	Adequate negative evidence.
10	0	0.0	No data.		--

[a]Adapted from Ref. 21.

[b]Some criteria are presented in shortened form; complete specifications of the HAPPS criteria are given in Appendix A.

guidelines for HAPPS. The criterion based on mutagenicity testing was dropped for two reasons. The data in RTECS could not be used to identify those particular tests for mutagenicity which, like the Ames test, are standard protocols for assessing carcinogenic potential. More important, even if such tests for mutagenicity could be identified in RTECS, it would have been improper to use them to score a substance in both the oncogenicity and mutagenicity factors because such a procedure would amount to a double counting. The HAPPS procedure corresponds to the presentation of the data in RTECS, avoiding both the possibility of error involved in using some mutagenicity data to score the mutagenicity factor and other mutagenicity data to score the oncogenicity factor and, more importantly, the error of double counting. Mutagenicity tests carried out to screen for carcinogens are included in scoring the mutagenicity factor and hence affect the overall scoring of a substance in the carcinogenicity group which depends upon the two separate factors for oncogenicity and mutagenicity. Thus, mutagenicity screening for carcinogenicity is taken into account in the final ranking of a substance even though such tests are not explicitly singled out in a specific criterion under oncogenicity. The criterion for negative evidence was retained but with no judgment as to the adequacy of the evidence being required of the user. Finally, a criterion for "no data" was added to HAPPS.

Weights were assigned in HAPPS to be reasonably consistent with the weights assigned in the ORNL procedure and thus to retain as much as possible of the expert judgment as to the relative importance of the criteria that went into developing the ORNL weights. Generally speaking, an attempt was made to match each HAPPS criterion to a similar ORNL criterion allowing for the differences between the two procedures. Where reasonable matches could be made, the matched criteria were used as benchmarks and assigned weights equal to the corresponding ORNL scores. The weights of unmatched HAPPS criteria lying between two matched criteria were obtained by interpolation and the weights of unmatched HAPPS criteria lying beyond the range of the ORNL criteria were obtained by extrapolation. In some instances, this procedure produced inconsistencies in the relative weights of various HAPPS criteria. These instances are noted in the following discussions of the individual factors. To guarantee complete consistency would have required changing the relative scores (weights) assigned to the benchmark criteria; retention of

these relative weights was considered more important than the achievement of complete internal consistency.

The HAPPS and ORNL criteria for items 3, 4, and 9 in Table 1.2 were felt to correspond reasonably well and these weights were used as benchmarks in developing the other weights in HAPPS. Since the ratios of weights within a factor and not the difference between them give relative measures of the importance of the corresponding criteria, a constant scaling factor can be applied to the individual weights without changing the relative importance of the criteria. For oncogenicity, a factor of 1/3 was chosen. Scaling in this way compresses the scale and thus maximizes the effect of additional secondary weight throughout the range of primary weights. In general, the scaled weights in HAPPS are related to the corresponding ORNL scores by

(Weight in HAPPS) = (Scaling Factor) x (ORNL Score).

Applying this equation with a scaling factor of 1/3, the weight for item 3 in HAPPS is 3 (= 9/3) and the weight for item 4 is 2 (= 6/3). (Note that the ratio of the weights of the two criteria in HAPPS is the same as the ratio of the scores of the corresponding criteria in the ORNL procedure (3/2 = the ratio of the weights in HAPS = 1.5 = 9/6 = the ratio of the ORNL scores).

HAPPS contains two criteria (items 1 and 2) designed to emphasize the primary concern of air programs with human health and exposure by inhalation. Both of these criteria would correspond to a single criterion (item 3) in the ORNL procedure so that assigning weights to them required extropolation beyond the initial correspondences between the HAPPS and ORNL criteria established above. In the ORNL procedure, evidence of oncogenicity in humans would receive a score of 9 (item 3) and evidence of oncogenicity in one animal species would receive a score of 6. Thus, the score (or weight) attributed to evidence in humans is 50% greater than that attributed to evidence in one animal species. It was felt reasonable to use half as great an increase (25%) in HAPPS as a factor for determining the increase in weight to be associated with evidence of oncogenicity in humans by a noninhalation route (item 2) in comparison with evidence from two or more animal species (item 3). This procedure gives additional weight to human data reflecting the concerns of air programs but less additional weight than the ORNL procedure gives to evidence in a second animal species, the lesser weight reflecting the fact that the expert opinion embodied in the ORNL procedure considered human evidence or

evidence in a second animal species equally important. The same factor was also applied to extropolate from evidence in humans by noninhalation (item 2) to evidence in humans by inhalation (item 1). Thus, the weight for item 2 in HAPPS is

(Weight for item 3) x (Extropolation Factor)
= 3 x 1.25 = 3.75 ≈ 4

and the weight for item 1 in HAPPS is

(Weight for item 3) x (Extropolation Factor) x (Extropolation Factor)
= 3 x 1.25 x 1.25 = 4.68 ≈ 5.

The HAPPS criterion for item 8 (scheduled for testing) was considered to correspond most closely to the ORNL criteria requiring expert judgment (items 6 and 7), since it was felt that expert judgment is frequently used in developing testing schedules. The weight for this criterion was chosen to be the geometric mean of the ORNL scores for the two criteria requiring expert judgment taking the scaling factor into account. Thus,

(HAPPS Weight for item 8) = (Geometric Mean of ORNL Scores for items 6 and 7) x (Scaling Factor)
= $\sqrt{3 \times 1}$ x (1/3) = 0.57 ≈ 1.

Finally, the criterion for no data (item 10) was assigned a weight of zero, the same as negative evidence. The references do not reliably distinguish between no data and negative results so equal weights for these two criteria were considered reasonable. Strictly speaking, this weight assignment means that there is less need for concern about a substance for which no data is available in the standard sources (weight = 0) than there is for concern about a substance which has been scheduled for testing (weight = 1). However, in practice, the results of a prioritization will be reviewed and substances with a significant lack of data will be identified and handled separately. In terms of the initial ranked list needed to start a program of detailed evaluation, HAPPS emphasizes substances for which the most data is available and, hence, presumably substances for which additional evaluation will be easiest in the early stages of the evaluation program. Programmatically, this would permit time for data to be gathered on data-deficient substances identified exogenous to HAPPS as being of potential concern. Furthermore, results of prioritization by HAPPS could still be of use in this

effort by indicating the relative need for concern based on the limited available data.

In addition to the primary weights just discussed, HAPPS assigns secondary weights for the oncogenicity factor. Given the criteria, it is possible for a substance to satisfy two or more criteria simultaneously. For example, there could be evidence of oncogenicity in humans by the noninhalation route and evidence from a single animal study. These secondary weights serve the purpose of giving a substance with data satisfying several criteria a total higher score than a substance with data satisfying fewer criteria when the highest weighted criterion satisfied by both substances is the same. Furthermore, the secondary weights have been assigned so that a substance could never receive a total score higher than a substance which satisfied a single more heavily weighted primary criterion simply by satisfying multiple secondary criteria. This relationship between the primary and secondary weights is based on the view that while concommitant evidence should have some positive influence on the final score for a substance, the additional weight should not be sufficient to raise a substance to the score of the next higher ranked criterion. For example, a substance with evidence of oncogenicity in humans by a noninhalation route and evidence of oncogenicity in two animal species should not receive a higher score than a substance with evidence of oncogenicity in humans by the inhalation route. That the secondary weights achieve this aim can be confirmed by noting that, except for a substance whose primary weight is 5, the maximum sum of the secondary weights is 0.55 (= 0.5 + 0.05), because the HAPPS criteria for items 3 and 4 cannot be satisfied simultaneously. This maximum sum for the secondary weights is less than the minimum difference of one between any two primary weights. In making this test it is not necessary to consider the maximum possible secondary weight for a substance whose primary weight is the maximum possible, a substance whose primary weight is 5 in the oncogenicity example, because there are no more highly weighted criteria. The addition of secondary weight can never raise the total weight of a substance with the maximum primary weight above the weight associated with a substance satisfying a more heavily weighted single criterion, because there is no such criterion.

As used in HAPPS, additional secondary weight is assigned only when different criteria are satisfied; additional weight is not assigned when

several data satisfy the same criterion. It was felt that some sense of the quality of the data was necessary in assessing whether multiple data satisfying the same criterion were better than data based on a single study satisfying only one criterion. For example, a substance which has positive evidence in two animal tests of poor quality should probably not be ranked higher than another substance which has positive evidence in only one animal test of superior quality. HAPPS would, however, rank the former compound higher than the latter if additional secondary weight were assigned but since the quality of the studies involved is not reported in the readily available literature, such occurrences could not be checked for in the HAPPS procedure. Therefore, it was decided, based on considerations of this type of situation and the unavailability of data on study quality, not to assign additional weight based solely on meeting the same criterion with data from multiple studies.

Mutagenicity. Table 1.3 compares the HAPPS and ORNL criteria for mutagenicity. Many of the differences between the two sets of criteria are similar to the differences already discussed for oncogenicity and will not be fully discussed in this subsection. Although information specific to humans is likely to be unavailable, evidence of mutagenicity in mammalian test systems was given more weight in both HAPPS and the ORNL procedure than evidence in nonmammalian systems. In HAPPS, evidence obtained from inhalation studies in mammals (item 1) receives additional weight as being directly related to the route of administration of interest in air programs. The ORNL criteria (items 9 and 10) requiring expert judgment were dropped from HAPPS as were the corresponging criteria for oncogenicity. As for the oncogenicity factor, a criterion was added to HAPPS to reflect whether a substance has been scheduled for or is undergoing mutagenicity testing under the National Toxicology Program. Data in RTECS do not unambiguously identify tests showing germinalcell DNA interactions as required by the ORNL criteria for items 7 and 8. Thus, this determination, although desirable, was dropped from HAPPS while the remainder of the ORNL criteria specifying the type of test was retained. Finally, the criterion for no data (item 13) was added.

With these changes, the HAPPS criteria were expanded according to the following scheme. Evidence of mutagenicity from mammalian test systems was considered a better indicator of potential effects in humans than evidence

Table 1.3 Criteria for Mutagenicity

	HAPPS			ORNL[a]	
Item	Primary Weight	Secondary Weight	Criteria[b]	Score	Criteria[b]
1	11		At least one in vivo mammalian test by inhalation.		
2	9	0.7	At least one in vivo mammalian test by noninhalation.	9	One or more whole mammalian tests.
3	8.3	0.5	Two or more in vitro mammalian tests.		
4	7.7	0.4	One in vitro mammalian test.		
5	7.1	0.25	Two or more in vivo nonmammalian tests.		
6	6.5	0.2	One in vivo nonmammalian test.		
7	6	0.15	Two or more in vitro nonmammalian tests.	6	More than one in vitro test or germinal-cell DNA interaction in vivo.
8	4	0.1	One in vitro nonmammalian test.	4	One in vitro test but no germinal-cell DNA interaction.
9	-	-		3	Suspect based on professional judgment of parametric data.
10	-	-		2	No data but suspect based on professional judgment.
11	2	0.25	Scheduled for testing.		--
12	0	0.0	Negative evidence.	0	Adequate negative evidence.
13	0	0.0	No data.		--

[a]Adapted from Ref. 21.

[b]Most criteria presented in shortened form; complete specifications of the HAPPS criteria are given in Appendix A.

from nonmammalian test systems. Thus, mammalian tests were given higher weights than nonmammalian tests just as in the ORNL procedure. Within each of these groups, in vivo tests carried on in the living body of an organism were weighted higher than in vitro tests conducted outside living organisms. This is an extension of the separation of in vivo and in vitro mammalian tests in the ORNL procedure (items 2 and 7). Finally, HAPPS gives additional weight when evidence of mutagenicity is available in more than one test system except for in vivo mammalian tests for which a distinction based on inhalation or noninhalation route of administration was thought to better represent the concerns of air programs. Distinctions based on both the number of tests and the route of administration within the in vivo mammalian category would have been too detailed for this screening level of analysis. Assignment of additional weight for multiple tests is consistent with the treatment of in vitro tests with no germinal cell interaction in the ORNL procedure (items 7 and 8).

As shown on Table 1.3, items 2, 7, 8, and 12 were used as benchmarks in developing the weights in HAPPS. The weight for item 11 (scheduled for testing) was assigned as the geometric mean of the two ORNL criteria requiring expert judgment, just as was done for oncogenicity. Thus, the weight is $2\ (\sqrt{3 \times 2} \approx 2.4 \approx 2)$. For the four criteria listed as items 3-6, interpolation in equal multiplicative steps was used. For five steps between 6 and 9, the factor is about 1.0844 ($6 \times 1.0844^5 \approx 9$). Using this factor and rounding to the nearest tenth, the weights given in Table 1.3 were obtained. For example, the weight for the criterion for two or more in vivo nonmammalian tests (item 5) is $6 \times 1.0844^2 = 7.055 \approx 7.1$, because it lies two steps above the benchmark criterion (item 7). The weight for item 1 was obtained by extrapolation using the same factor as was used for oncogenicity: $9 \times 1.25 \approx 11$. It should be noted that the same factor of 1.25 could be derived by using one-half the increase of 50% applied by ORNL to account for additional in vitro tests or mammalian tests of mutagenicity (see items 2,7, and 8) thus indicating that a consistent approach was applied in developing the ORNL scores.

The type of inconsistency noted in the general discussion shows up for mutagenicity criteria. Several examples, but not a complete list, follow. HAPPS and ORNL increase weights by a factor of 1.5 as evidence becomes available in a second nonmammalian test system in vitro (items 7 and 8). It would be desirable to have the same factor apply to the criteria for nonmammalian

in vivo tests (items 5 and 6) and to mammalian in vitro tests (items 3 and 4) but in these cases the factor involved is only about 1.1 (≈7.1/6.5 and ≈8.3/7.7) which is, of course, simply the interpolation factor used to determine the weights. Similarly, it would be desirable for the ratios between the weights for criteria which are the same except for the type of species involved to be equal. Thus, the ratio of the weights of items 4 and 8 which correspond to evidence from one in vitro test in nonmammals and mammals, respectively, should ideally be equal to the ratio of the weights for items 3 and 7 which correspond to evidence from two or more in vitro tests in mammals and nonmammals, respectively. However, the first ratio is about 1.9 (≈7.7/4) while the second is only about 1.4 (≈8.3/6). The weights could have been assigned to avoid this type of inconsistency but only if experts had been available to provide a reasonable set of weights for the components to be matched. In view of the unavailability of the needed experts, the procedure used here of retaining the expert opinion embodied in the ORNL scores and interpolating and extropolating to express the needs of air programs and to more fully utilize the data in RTECS to spread out the final scores was felt to provide a reasonable approach.

As is the case for oncogenicity, HAPPS assigns secondary weights for mutagenicity when more than one criterion is satisfied by a substance. The previous discussion for oncongenicity is equally applicable to mutagenicity and a similar confirmation can be made that additional secondary weight can never cause a substance with a particular primary weight to receive a greater total score than a substance with the next higher primary weight. Additional weight is not assigned under mutagenicity when a substance has multiple data satisfying the same criterion.

Reproductive and Developmental Toxicity. As noted in Sec. 1.2, the ORNL factor for embryotoxicity and fetotoxicity and the ORNL factor for reproductive effects were combined into the single HAPPS factor for reproductive and developmental toxicity. Since the structure of the ORNL criteria for both factors is very similar, Table 1.4 lists them together in the interests of simplicity for comparison with the HAPPS criteria. For this factor, the rationale for the changes between HAPPS and the ORNL procedure is the same as that for the two previous factors. Additional weight is assigned to evidence

Table 1.4 Criteria for Reproductive and Developmental Toxicity

	HAPPS			ORNL[a]	
Item	Primary Weight	Secondary Weight	Criteria[b]	Score	Criteria[b]
1	5		Humans by inhalation.		
2	4	0.7	Humans by noninhalation.		
3	3	0.5	Two or more animal species by any route.	9	Humans or two oppropriate animal species.
4	2	0.3	One animal species by any route.	6	One animal species.
5			--	4	Inconclusive evidence [c].
6			--	3	Suspect based on professional judgment of parametric data.
7			--	1	No data but suspect based on professional judgment.
8	1	0.05	Scheduled for testing.		--
9	0	0.0	Negative evidence.	0	Adequate negative evidence.
10	0	0.0	No data.		--

[a]Adapted from two factors in Ref. 21 for embryotoxicity and fetotoxicity and for reproductive effects both of which have similar structures for their criteria.

[b]Most criteria presented in shortened form; complete specifications of the HAPPS criteria are given in Appendix A.

[c]This criterion appears only in the ORNL factor for reproductive effects.

of effects in humans and to evidence of effects caused by inhalation in humans to emphasize the interests of air programs. Three ORNL criteria requiring expert judgment (items 5, 6, and 7) were omitted. A criterion related to a substance's testing status and a criterion for scoring substances with no data were added.

The assignment of weights for this factor parallels that for oncogenicity. An overall scaling factor of 1/3 was applied and items 3, 4, and 9 served as the benchmarks. An increase of 25% was used to extropolate to the criteria for humans (item 2) and for humans by inhalation (item 1). This increase is one half the increase of 50% assigned by ORNL for positive results in an additional species (compare ORNL scores of 9 and 6 for items 3 and 4, respectively). The HAPPS weights for items 1 and 2 can be extropolated from the HAPPS weight for item 3 by using an extrapolation factor for a 25% increase just as was done for oncogenicity. Thus, in HAPPS

$$\begin{aligned}(\text{Weight for item 2}) &= (\text{Weight for item 3}) \times (\text{Extropolation Factor}) \\ &= 3 \times 1.25 = 3.75 \approx 4\end{aligned}$$

and

$$\begin{aligned}(\text{Weight for item 1}) &= (\text{Weight for item 3}) \times (\text{Extropolation Factor}) \\ &\quad \times (\text{Extropolation Factor}) \\ &= 3 \times 1.25 \times 1.25 = 4.68 \approx 5.\end{aligned}$$

As for oncogenicity, the criterion for compounds scheduled for testing (item 8) was weighted at the geometric mean of the ORNL criteria (items 5, 6, and 7) requiring expert judgment and taking the scaling factor into account. Thus

$$\begin{aligned}(\text{Weight for item 8 in HAPPS}) &= (\text{Geometric Mean of ORNL Scores for} \\ &\quad \text{Items 5, 6, and 7}) \times (\text{Scaling Factor}) \\ &= (4 \times 3 \times 1)^{1/3} \times (1/3) = 0.76 \approx 1.\end{aligned}$$

Secondary weights were also assigned in the same fashion and subject to the same limitation as was done for oncogenicity and mutagenicity. These latter two effects, however, are generally believed to exhibit either no or very low thresholds while it has been theorized that reproductive and developmental effects exhibit thresholds. However, the thresholds may be very low or even zero so the system of secondary weights was used rather than a system based on lowest effective dose as might be done for effects exhibiting thresholds when

dose-response data is available. In this regard, the criteria for oncogenicity, mutagenicity, and, with the above caveat in mind, reproductive and developmental toxicity should be compared to the criteria for effects which exhibit thresholds. In these factors, no secondary weights are used; a substance's rank depends only upon the lowest recorded dose producing the effect under consideration.

Acute Lethality. Table 1.5 compares the ORNL and HAPPS criteria for the acute lethality factor. Both systems base their rankings on data for lethal dose and lethal concentration. Rather than retain the standard toxicological term "acute toxicity" used in the ORNL procedure, the name of the factor was changed to "acute lethality" in HAPPS to reflect this use of data on lethal doses. This change emphasizes to the nonexpert that only data on lethal doses should be used in scoring this factor and, in fact, HAPPS specifies that only data so identified in RTECS be used. Data on chronic lethality and nonlethal effects both chronic and acute are to be considered in scoring under the factor for effects other than acute lethality. If only chronic effects were considered in the factor for effects other than acute lethality, then the two factors would correspond relatively well to the traditional acute and chronic categories in toxicology. Since both factors are scored using distinct sets of toxicological data as reported in RTECS, the approach taken in HAPPS corresponds to the available data. An appropriate balance between the two factors was obtained by the assignment of their relative weights in developing an overall score for the toxicity group.

The major difference between the two procedures was the deletion of criteria for the intravenous, subcutaneous, and intraperitoreal routes of administration from HAPPS. While these routes of administration are important in detailed toxicological evaluation, they were considered less closely related to exposure through the ambient air than the inhalation, oral, and dermal routes. In addition, these later three routes were the only three considered by the Iteragency Testing Committee[5] and in the Michigan Critical Materials Register[17] which were used in developing the ORNL procedure. ORNL, however, opted to be more detailed in their approach.

A second difference between the two procedures does not show up on Table 1.5 and concerns the definition of the period of exposure which defines

Table 1.5 Criteria for Acute Lethality

Item	Primary Weight	Species	HAPPS Exposure Route and Dose[b,c,d] Inhalation Gas	Inhalation Solid[f]	Oral	Dermal	ORNL[a] Score	ORNL Exposure Route and Dose[b,c,e] Inhalation (Gas)	Oral	Dermal
1	4.7	Human	≤5	≤50	–	–		–	–	–
2	3.7	Human	–	–	≤5	≤5		–	–	–
3	3.0	Animal	≤5	≤50	≤5	≤5	9	<5	<5	<5
4	2.6	Human	5-50	50-500	–	–		–	–	–
5	2.3	Human	–	–	5-50	5-200		–	–	–
6	2.0	Animal	5-50	50-500	5-50	5-200	6	5-50	5-50	5-200
7	0	Human/Animal	50-500	500-5000	50-500	200-500	4	50-500	50-500	200-500
8	0	Human/Animal	500-1000	5000-10,000	500-5000	500-5000	2	500-1000	500-5000	500-5000
9	0	Human/Animal	>1000	>10,000	>5000	>5000	1	>1000	>5000	>5000
10	0	Human/Animal	Negative evidence.				0	Low or no biological activity.		
11	0	Human/Animal	No data.				–	–	–	–

[a]Adapted from Ref. 21.

[b]Criteria presented in shortened form; complete specifications of the HAPPS criteria are given in Appendix A.

[c]Dosage units: Inhalation – ppmv for gases, mg/m^3 for solids.
Oral – mg/kg
Dermal – mg/kg

[d]HAPPS combines items 7, 8, 9 with equal weights into a single criterion.

[e]The ORNL procedure also scores compounds based on intravenous, subcutaneous, and intraperitoneal exposures.

[f]Derived from gas (ppm) scale by using acute lethality line in Fig. 1.

an acute exposure for the inhalation route. The ORNL procedure and its predecessors follow the standard toxicological definition by considering inhalation exposures as acute if they are under about 4 hours in duration but do allow the use of professional judgment in evaluating studies with longer exposure times. Expecting such judgments would, however, violate the HAPPS guidelines and in HAPPS, inhalation exposure times up to 24-hours in duration would still be scored under the factor for acute lethality. This value was chosen because it covers the complete range of the current short-term ambient air quality standards and because it is frequently used in discussing the health effects of air pollution.

As shown in Table 1.5, only inhalation doses for gases given in ppmv could be scored using the ORNL scale. RTECS gives exposure data for solids in units of mg/m^3 which cannot be meaningfully converted to ppmv, a natural unit for gases because equal volumes of different gases at the same conditions of temperature and pressure contain equal numbers of moles. Reference 25 gives a toxicity ranking for dusts and mists in mass concentration units and the corresponding volumetric concentrations for particular gases. For example, a particular mass concentration of a certain solid might be considered "highly toxic" while a particular volumetric concentration of a certain gas would also be considered "highly toxic." Only two pairs of corresponding concentrations were available. In Fig. 1, these pairs have been plotted on log-log graph paper and the straight line labeled "Acute Lethality" has been drawn through them and extropolated. The line so generated was used to establish the mass concentrations measured in mg/m^3 coresponding to the ORNL volumetric concentrations in ppm's. In this way, the HAPPS scale for solids was constructed. Log-log paper was chosen for the extropolation because the toxicity scales are generally close to being logarithmic rather than linear as might be expected, since the exposure ranges involved in toxicological experiments can cover several orders of magnitude. Also shown in Fig. 1 is a line representing the correspondence between volumetric concentrations of gases and mass concentrations of solids for use in ranking existing standards. The development of the points through which this line is drawn is described later in this section. Although developed heuristically, three of the points lie on a straight line that is exactly parallel to the line drawn for acute lethality. This parallelism shows some degree of underlying consistency between the approach used

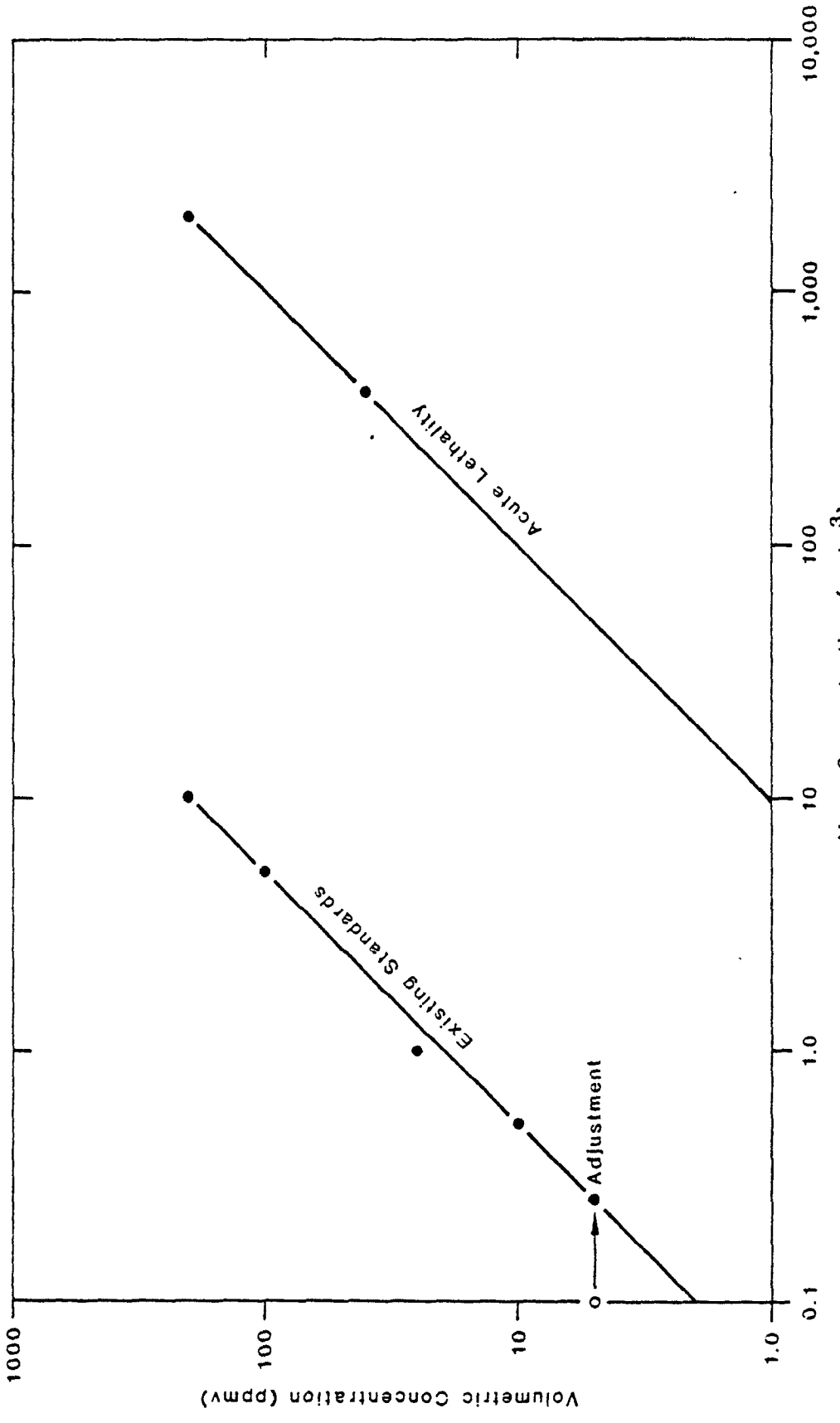

Fig. 1 Scales for Equivalent Volumetric and Mass Concentration Units

for acute lethality and the approach used for existing standards and lends support to the extropolation used for the "Acute Lethality" line. Another approach to ranking both gases and vapors would have been to have converted the volumetric concentrations for gases to mass concentration units. Since such conversions involve the molecular weight of the gas, this approach could lead to cases where two gases with equal lethal volume concentrations but with different molecular weights would be given different weights on a mass concentration scale. On the ORNL scale for volumetric concentrations they would receive the same rank. In addition, Ref. 25 indicated that the mass concentration scale should be used for dusts and mists. To avoid inconsistencies with the established volumetric concentration scale for gases and in view of the recommended use of the mass concentration scale, separate scales for gases and solids were included in HAPPS.

A final difference concerns the relative weights assigned doses greater than those corresponding to item 6 in Table 1.5. In HAPPS, these exposure levels are all scored as having a weight of zero, the same weight assigned to negative evidence. For the inhalation route, the dosages associated with these items are all higher than 50 ppm, a value rarely exceeded in the ambient air unless under accidental conditions. In the absence of other indicators and since the effects being considered exhibit thresholds, these high dosages were thus considered as poor indicators of a need for concern by air programs. Little need for additional study seemed warrented if the threshold was unlikely to be exceeded. Death from nonthreshold effects like cancer, fetal death, and death from developmental disorders are considered in the factors for oncogenicity, mutagenicity, and reproductive and developmental toxicity. Criteria at the corresponding dosage levels for the oral and dermal routes of administration were also given weights of zero, because they are obviously of less concern to air programs than the inhalation route.

The remaining differences between HAPPS and the ORNL procedure were made for reasons similar to those discussed above in connection with other factors. Given the concerns of air programs with human health and exposure via the ambient air, extra weight was assigned to substances documented as being lethal to humans by inhalation at the dosages deemed to be of interest (items 1-6). The ORNL criterion for low or no biological activity was modified to require negative evidence in order to remove any need to make an

expert judgment as to what constituted low biological activity. In HAPPS, low biological activity is operationally defined as dosages above those corresponding to item 6. As with the previous three factors, a criterion for no data was added.

The criteria for animals at low and moderate doses (items 3 and 6) are identical in HAPPS and the ORNL procedure and served as benchmarks. The criteria listed under item 10 were also considered sufficiently related to serve as a third benchmark. Because HAPPS combined the three ORNL criteria for the highest dose ranges (items 7, 8, 9), retention of the ORNL score of 6 for the benchmark item 6 would have created a large gap at the bottom of the HAPPS scale between the criterion for animals at moderate doses (item 6 with a score of 6) and the criterion for high doses (item 7 with a score of 9). To avoid distortion from such a large gap, a scale factor of 1/3 was used to reduce the HAPPS weight for item 6 to 2.0. The weights for items 4 and 5 were determined by interpolation between the benchmark items using a factor of 1.1447 ($6 \times 1.1447^3 = 9$) appropriate to three equal steps. Also, as with the previous factors, the weights for the criteria for human noninhalation exposures (item 2) and human inhalation exposures (item 1) were determined by extropolation using a factor of 1.25.

As noted for the mutagenicity factor, the interpolation and extrapolation from the benchmarks leaves a certain degree of inconsistency in the HAPPS weights. For example, the ratio of the weights for human exposures by different routes of administration should be the same regardless of the dose level. However, in the low dose range the ratio is about 1.3 ($\approx 4.7/3.7$) for items 1 and 2 while in the moderate dose range the ratio is about 1.1 ($\approx 2.6/2.3$) for items 4 and 5. Similarly, the additional importance attached to human data in comparison to animal data should be independent of dose range for a given route of administration. However, for inhalation exposures, the ratio of the weights for humans and animals at low exposure levels is around 1.6 ($\approx 4.7/3.0$) (items 1 and 3) and around 1.3 ($= 2.6/2.0$) at moderate doses (items 4 and 6). As previously noted, this type of inconsistency was deemed less important than retention of the relative importance of the benchmarks; and despite this inconsistency, the ratios are fairly close to being equal.

Secondary weights were not assigned for satisfying more than one criterion under acute lethality. Since these lethal effects generally exhibit

thresholds, the best indication of the need for further assessment of a substance was considered to be the lowest documented dose. In other words, a substance causing death at 1 ppm and 1000 ppm was not considered a better candidate for further assessment than a substance causing death at 1 ppm. Both substances should be and, under HAPPS are, given equal weights, assuming that both sets of data corresponding to 1 ppm are for the same species and route. This situation is different than for the nonthreshold effects, oncogenesis and mutagenesis, for which all the criteria satisfied by the data for a substance are considered in developing an overall score for a particular factor.

Effects Other than Acute Lethality. Unfortunately, little data is available for scoring this factor. Ideally, this catchall factor could be split into several categories such as acute (nonlethal), subacute (lethal and nonlethal), and chronic (lethal and nonlethal) with, perhaps, additional breakdowns into toxic and irritant effects. It is precisely some of these chronic and irritant effects which correspond to the types of exposures and effects frequently of concern in dealing with populations repeatedly exposed to low concentrations over long times. In dealing with toxic pollutants, however, air programs is primarily interested in serious health effects. Very little data on chronic exposures is available due to the time and expense of conducting controlled chronic experiments. Since the data necessary to make distinctions between various types of effects are not readily available, all effects other than acute lethality are scored under a single factor in HAPPS. HAPPS is also an extension of the ORNL procedure which specifically requires chronic exposures with repeated doses over a period of time like weeks or months. In fact, the ORNL factor is titled to indicate that chronic toxicity is being scored. The extension in HAPPS to include acute nonlethal effects makes fuller utilization of the data available in RTECS. It should be noted that the terminology used in HAPPS is employed to match the material presented in RTECS which itself does not always employ the terminology of standard toxicological protocols and that the studies reported in RTECS were not always done under standard protocol. For example, lethality should not occur during standard chronic tests so that the term chronic lethality should not be used

for standard tests. However, since it is used to describe some tests reported in RTECS, it was considered appropriate to use it in HAPPS.

Another important difference between the two procedures involves the absence of the severity subfactor used in the ORNL procedure. A substance is scored by the dose at which an effect is observed and separately according to the severity of that effect, for example, severe incapacitation or mild incapacitation. Then the overall ORNL score for chronic toxicity is obtained by multiplication of the dose score and the severity score. HAPPS uses only a single score which reflects dose but not severity. No standard list of effects categorized by severity was found although typical effects in similar categories of severity are given in Ref. 17. Assignment of effects to the severity categories would require expert judgment and would probably vary with the operator. Thus, assignment of severity rankings was not acceptable for inclusion in HAPPS. Even if a standard list of the relative severity of different effects were available, the primary literature would need to be consulted to determine the nature of the effect in a majority of the cases reported. RTECS distinguishes between toxic effects and irritant effects and ranks the latter according to the degree of irritant severity. However, only dose data with no indication of the type of effect, let alone the severity of the effect, is given for toxic data. Such data could only be found by referencing the primary literature, a procedure precluded by the guidelines for HAPPS as being too detailed at this preliminary stage. In summary, all compounds have the potential to elicit deliterious health effects at some level; however, this methodology emphasizes effects related to carcinogenesis and lethal effects as being most important to air programs at this time and does not address the character or severity of other effects. This procedure was considered reasonable given the preliminary nature of ranking by HAPPS, the judgemental nature of ranking these other effects, and the improbability that such effects would occur at ambient concentrations. Dropping the ranking based on severity also makes the schemes used in HAPPS for the factors for acute toxicity and for other effects consistent in structure and application.

Having noted these differences, the HAPPS criteria for effects other than acute lethality and the ORNL criteria for the dose component of chronic toxicity in terrestrial animals are compared in Table 1.6 The ORNL procedure did not provide a scale for scoring inhalation data given in ppm. Since such

Table 1.6 Criteria for Effects Other than Acute Lethality

Item	HAPPS[a] Primary Weight	Species	Exposure Route and Dose[b] Inhalation Gas	Inhalation Solid[e]	Oral	Dermal	ORNL[a,c,d] Score	ORNL[a,c,d] Dose
1	7	Human	≤1	≤10	-	-	-	-
2	6	Human	-	-	≤1	≤1	-	-
3	5	Human	1-10	10-100	-	-	-	-
4	4	Human	-	-	1-10	1-10	-	-
5	3	Animal	≤1	≤10	≤1	≤1	3	<1
6	2	Animal	1-10	10-100	1-10	1-10	2	1-10
7	1	Human/ Animal	>10	>100	>10	>10	1	>10
8	0	Human/ Animal	Negative or insignificant evidence.				Low or no biological activity.	
9	0	Human/ Animal	No data.					

[a]Most criteria given in shortened form; complete specifications of the HAPPS criteria are given in Appendix A.

[b]Dosage units: Inhalation - ppmv for gases, mg/m^3 for solids
Oral - mg/kg
Dermal - mg/kg

[c]ORNL procedure considers only chronic toxicity.

[d]Adapted from Ref. 21.

[e]Derived from gas (ppm) scale by using acute lethality line in Fig. 1.

data is the primary concern of air programs, an inhalation scale was developed for HAPPS. Reference to the ORNL scales for chronic toxicity (see Table 1.5) shows that at low and moderate dose ranges, the numerical values of the concentrations defining the ranges for ranking inhalation and oral exposures are identical. For inhalation and dermal exposures, the defining concentrations are identical or comparable. The assumption was made that a similar equivalence was reasonable for both chronic and acute nonlethal exposures. The HAPPS scale for inhalation data for gases in volumetric units (ppm) thus assigned defining concentrations in ppm's numerically equal to the ORNL doses (see items 5, 6, and 7). The corresponding mass concentrations for solids were taken from the acute lethality line in Fig. 1 again assuming that the correspondence developed for acute data should be reasonably valid for chronic data as well.

HAPPS distinguishes between effects in humans and those in animals except at high doses above 10 ppm for gases and 100 mg/m^3 for solids for inhalation exposures and above 10 mg/kg for oral and dermal exposures (item 7). Extra weight is assigned to human data to reflect the air programs' charge to protect human health. The distinction was not made at the high dose levels, because it was felt that human exposures at these high levels would probably be experienced only accidentally and even then probably only in occupational settings. Both of these types of exposures were felt not to be indicative of the situation that would be regulated by air programs. Thus, human data at high doses was not considered a better indicator of increased need for additional study than animal data at high doses.

At lower dose levels (items 1-6), HAPPS always weights human data more heavily than animal data whereas the ORNL procedure weights both types of data equally. This additional weight reflects air programs' primary concern with human health but, as just discussed, was not assigned to human data at high dose levels. It was recognized that information on human toxicity is rarely available for this factor. However, where such information is available or where it becomes available in the future it was felt that the significance of human toxicity data should be emphasized by ranking it above animal toxicity data at dose levels near those expected in the ambient air. Similarly, in the HAPPS system, human data at moderate doses (items 3 and 4) is ranked above animal data in the lowest dose range (item 5). This differs from the ORNL

procedure and from the HAPPS assignment of weights for acute lethality in both of which the range in which the dose lies is the primary determinant of the weight assigned. Except where acute lethality is concerned, it was considered more appropriate to weight evidence from humans more heavily than evidence from animals at the low and moderate dose levels. Such a weighting seemed reasonable in view of the many different types of effects and levels of severity of effects which were subsumed under this factor. For example, if dose were the primary determinant of weight, mildly incapaciating effects at low doses would be weighted more heavily than severly incapacitiating but nonlethal effects at moderate doses. Modification of such an assignment would require consideration of the severity of the effects. Since no way to incorporate relative severity was available to HAPPS, it was decided to give more weight to effects in humans regardless of the dose involved as being more valid indicators of the need for additional study in a program concerned primarily with human health. Exactly as for acute lethality, additional weight was assigned for inhalation effects in humans as being most closely related to the goals of air programs.

Since the ORNL procedure did not distinguish between data based on human exposures and data based on animal exposures, the choice of benchmarks was somewhat more arbitrary for this factor than for those discussed previously. By using items 5, 6, and 7 as benchmarks and extrapolating, the ORNL weights were consistently applied to animal data at high, moderate, and low exposure levels. With these benchmarks, the HAPPS weights are easily obtained by extrapolation using the 1.25 factor and rounding the results to the nearest integer for convenience. For example, the weight for item 3, two steps above benchmark item 5 is 5 ($3 \times 1.25^2 = 4.68 \approx 5$).

Additional weight was not assigned when a substance satisfied several criteria simultaneously. The reasons given for acute lethality also apply to this factor for other effects. Finally, a criterion for no data has again been included in HAPPS.

Potential for Airborne Release. As noted in Sec. 1.1, this factor in HAPPS contains two subfactors, production volume and vapor pressure, each of which either is or is associated with a separate factor in the ORNL procedure. Both of these subfactors are being used as rough indicators of potential

exposure and do not reflect other factors like the fraction of production emitted to the atmosphere and the number of people potentially exposed. However, all attempts in the literature reviewed to improve upon the use of these particular subfactors appeared to require data which was generally unavailable or was available under the 8(a)-Level-A rule of TSCA and thus not specific to exposure via the air. When actually implemented, the systems reviewed frequently relied on default values for many of the substances scored. Other proposals have been made such as using the labor intensiveness or price per weight as indicators of how valuable a substance is and thus how well its release might be controlled. However, the indications were that the data required for such efforts are not readily available and that such approaches suffer from as much, if not more, uncertainty than is associated with figures for production volume. In addition, measures of market economics such as downward trends in production volume were not considered in the HAPPS decision process because such data are not readily available and were considered too detailed for this effort. Thus, production volume seems to be the only simple, easily accessible surrogate for exposure. In HAPPS, production volume information was supplemented by scoring a substance by its physical state: solid, liquid, or gas and within liquids by vapor pressure as an additional measure of the potential for a substance to be released into the atmosphere and thus as an additional rough indicator of the quantity potentially released.

Table 1.7 compares the two sets of criteria for scoring production volume. Little need be said to compare the sets because the criteria are essentially identical except for slight differences in rounding and the addition of the criterion for no data (item 8) to HAPPS. The relative weights between various criteria are the same in the two systems and the additional criterion for no data has again been weighted at the same level as the lowest weighted criterion used when data is available.

Both sets of criteria are structured so that substances with high production volumes are considered more likely candidates for additional study than substances with low production volumes. Of course, some substances like sucrose with very high production volumes but with no adverse effects could be ranked higher than a substance with little production but with very high toxicity. However, the reverse situation could occur when the factors related

Table 1.7 Criteria for Production Volume[a]

	HAPPS[b]			ORNL[b,c]		
Item	Weight	10^6 kg/yr	10^6 lb/yr	Score	10^6 kg/yr	10^6 lb/yr
1	10	>450	>1000	10	>450	>990
2	8	450-230	1000-510	8	450-230	990-506
3	6	230-45	510-100	6	230-45	506-99
4	4	45-23	100-51	4	45-23	99-506
5	3	23-.45	51-1.0	3	23-.45	50.6-.99
6	2	.45-.045	1.0-.10	2	.45-.045	.99-.099
7	1	≤.045	≤.10	1	<.045	<.099
8	1	No data.		-	-	-

[a]One of two components used in scoring potential for airborne release in HAPPS.

[b]Most criteria are given in shortened form; complete specifications of the HAPPS criteria are given in Appendix A.

[c]Adapted from Ref. 21.

to toxicity were scored and even if a substance like sucrose were prioritized at a relatively high level, review of the list prior to additional study should eliminate most such anomalies.

The physical state of a substance may affect the potential of that substance for being released to the atmosphere and thus the quantity of the substance actually released. The subfactor for vapor pressure really looks at the physical state and, for liquids, the vapor pressure of a substance. Criteria for vapor pressure are presented in the ORNL procedure as guidelines for use in scoring the level of potential occupational exposure when actual exposure concentration data is unavailable. As modified for use in HAPPS, the scale for scoring vapor pressure is identical to one used in the MITRE scoring procedure (Ref. 9). During testing of HAPPS, it was found that vapor pressure data was unavailable for some substances for which boiling point data was available. A boiling point scale equivalent to the MITRE boiling point scale was added to HAPPS for use when vapor pressure data was unavailable. Table 1.8 compares the two sets of criteria. The weights in HAPPS reflect the fact that gases are generally more difficult to contain than liquids and solids and hence, other things being equal, will be released in greater quantities. Two liquids with equal production volumes will be emitted in proportion to their vapor pressures if all other factors are equal. In the ORNL procedure for scoring occupational exposure, the type of process is categorized by the degree of containment: open, controlled release, or enclosed. Such considerations would also be relevant to determining the quantity released to the ambient air but the required data would not normally be available and such determinations would probably require expert knowledge of the specific processes involved. Such considerations would be unsuitable for HAPPS and are too detailed for a preliminary prioritization. Gases were ranked above all other forms of substances in HAPPS as being the most difficult to contain and thus the most likely to be released in large quantities. Solids are weighted equal in importance to highly volatile liquids, not at the lowest level of importance where their very low vapor pressures would place them. However, the factor of true concern is the quantity of material released and vapor pressure is not the only consideration. The ranking for solids in HAPPS was based upon consideration of the importance of solid particulate matter air pollution and EPA's assessment of how important they considered solids compared to various

Table 1.8 Criteria for Vapor Pressure[a]

		HAPPS[b,c]			ORNL[b,d]						
							Liquid, VP (mm Hg)			
Item	Weight	Vapor Pressure (mmHg)	Boiling Point (°C)	Score	Gas	Solid	>100	100-24	24-1	<1
1	4		Gas	-	-	-	-	-	-	-
2	3		Solid	-	-	-	-	-	-	-
3	3	VP>100	BP<80°	10			X			
4	2	24<VP<100	80°<BP<100°	8				X		
5	1	VP<24	BP>100°	6					X	
6	-		-	1						X
7	1		No data.		-	-	-	-	-	-

[a]One of two components used in scoring potential for airborne release in HAPPS.

[b]Most criteria given in shortened form; complete specifications of the HAPPS criteria are given in Appendix A.

[c]If vapor pressure data is unavailable, the boiling point is used as a substitute.

[d]Adapted from Ref. 21.

liquids in terms of the quantity released, other things being equal. With this ordering of the criteria, the actual weights were assigned. Once again, a scaling factor of 1/3 was used in HAPPS. The identical criteria corresponding to items 3 and 4 were used as benchmarks to the HAPPS weight for item 3 was 3 ($10/3 = 3.3 \approx 3$) and the weight for item 4 was 2 ($8/3 = 2.7 \approx 2$). For item 4, the weight was truncated to 2 rather than rounded to 3 to keep three of the criteria (items 2, 3, and 4) from receiving equal weights. The weight for solids (item 2) also received a weight of 3 equal to the weight for highly volatile liquids as discussed in the previous paragraph. The weight for gases was obtained by increasing the weight for highly volatile liquids by the same factor as ORNL used to go between moderate and high volatility liquids. This factor can be found from

$$\text{(ORNL Score for High Volatility Liquids)} = \text{(ORNL Factor) x (ORNL Score for Moderate Volatility Liquids)}$$

$$\text{or } 10 = \text{(ORNL Factor)} \times 8 \text{ and}$$

$$\text{(ORNL Factor)} = 10/8.$$

The HAPPS weight can be calculated taking the scaling factor into account:

$$\text{(HAPPS Weight for Gases)} = \text{(ORNL Score for High Volatility Liquids) x (ORNL Factor) x (Scaling Factor)}$$

$$= 10 \times (10/8) \times (1/3) = 4.16 \approx 4.$$

As had been done for several other factors, the weight for low volatility liquids which corresponded to two separate ORNL criteria (items 5 and 6) was taken as the geometric mean of the corresponding ORNL criteria. Thus, item 5 received a HAPPS weight of 1:

$$\text{(Weight for item 5 in HAPPS)} = \text{(Geometric Mean of ORNL Scores for items 5 and 6) x (Scaling Factor)}$$

$$= \sqrt{6 \times 1} \times (1/3) = 0.87 \simeq 1.$$

As was the case for previous factors, the criterion for no data was weighted at the lowest level of importance.

The principal difference between HAPPS and the ORNL procedures is that the scores for production volume and vapor pressure are multiplied together in HAPPS to obtain a score for the potential for airborne release rather than being used separately as individual scores for separate factors. Combining

the subfactors provided a convenient way of placing the source-related surrogates for exposure into a single factor. As discussed in Sec. 1.4, this source-related factor is combined with the receptor-related bioaccumulation factor in scoring the exposure group. The individual scores were multiplied rather than added for several reasons.[16] First, at the factor level, it was deemed desirable to avoid the problem of weighting the individual subfactors. Subjective weighting decisions are always required when scores are added in procedures like HAPPS. (The interfactor weightings used in HAPPS are discussed in Sec. 1.4.) Second, use of the multiplicative method normally provides a wider range of scores than does addition. The wider range, even when normalized, tends to avoid equally weighted substances.

Bioaccumulation. The criteria for bioaccumulation are compared in Table 1.9. No summary of bioconcentration factors seem to be available so the criteria based on this parameter were not included in HAPPS. Instead, the criteria were based on the octanol/water partition coefficient which is related to the tendency of a substance to accumulate in fat rather than water and hence to accumulate in animals. The criteria were based upon the fact that higher values of the octanol/water partition coefficient generally correspond to a substance with a greater tendency to dissolve in and accumulate in fat. There are some exceptions to this, particularly for values of

Table 1.9 Criteria for Bioaccumulation

	HAPPS[a,b]		ORNL[a,c]		
Item	Weight	$Log_{10}P$	Score	Bioconcentration Factor	$Log_{10}P$
1	10	>6	10	>4000	>6
2	8	6-4	8	4000-1000	6-4
3	6	4-2	6	1000-300	4-2
4	1	⩽2	1	<300	<2
5	0	No data	-	-	-

[a]P is the octanol/water partition coefficient.

[b]Criteria given in shortened form, complete specifications of the HAPPS criteria are given in Appendix A.

[c]Adapted from Ref. 21.

$\log_{10}P$ greater than 6 but the data to correct for such exceptions is not readily available. HAPPS uses the same criteria and weights as the ORNL procedure uses for items 1-4 and, as with previously discussed factors and for similar reasons, adds a criterion for no data at the lowest importance level.

Existing Standards. Table 1.10 compares the criteria used in HAPPS with those used in the MITRE system[10] upon which this HAPPS factor was based; the factor for existing standards was not used in the ORNL procedure. The criteria for gases are the same except at the low end (item 1) where the criterion for ranking carcinogens was eliminated from HAPPS. Since HAPPS assigns weight for carcinogenic activity under the factor for oncogenicity, to include it again in the factor for existing standards could have resulted in double counting.

A new set of criteria for solids was introduced in HAPPS because both solids and gases are air contaminants. None of the systems reviewed had a model set of criteria for scoring standards for solids. The HAPPS criteria for solids were developed by examination of the current OSHA standards. As an initial attempt, the range of OSHA standards for solids was divided in a manner proportional to the division of the OSHA standards for gases by the MITRE criteria eliminating one substance with an extremely small time-weighted

Table 1.10 Criteria for Existing Standards

	HAPPS[a]			MITRE[a,b]	
Item	Weight	Gas (ppm)	Solid (mg/m^3)	Score	Gas (ppm)
1	6	≤5	≤.25	5	<5 or carcinogen
2	5	5-10	.25-.5	4	5-10
3	4	10-25	.5-1	3	10-25
4	3	25-100	1-5	2	25-100
5	2	100-200	5-10	1	100-200
6	1	>200	>10	0	>200
7	0		No standard	-	-

[a]Most criteria given in shortened form; complete specifications of the HAPPS criteria are given in Appendix A.

[b]Adapted from Ref. 10.

average (TWA) from the process. The criteria so construted ran from <.01 mg/m^3 for item 1 to >.4 mg/m^3 for item 6. However, they were found to deemphasize the importance of solids with respect to gases. Very few solids had standards in the low end of the scale so constructed; only four solid substances would have received weights of four or more given the current standards while many gases would receive such weights. In order not to deemphasize solids with respect to gases, these initial criteria for solids were redefined in a sequence of steps. In the first step, the range of current standards less than 1 mg/m^3 was divided into four ranges corresponding to items 1-4 in the table. The division was done in such a way that approximately equal numbers of standards fell into each of the four ranges. For standards above 5 mg/m^3, a different approach was used. In this first step, the second concentration class (corresponding to item 2 in Table 1.10) covered a concentration range whose width from its lower concentration limit of 0.1 mg/m^3 to its upper concentration limit of 0.5 mg/m^3 corresponded to a factor of 5. This initial division point between the first and second concentration classes is shown as the open circle near the line for existing standards in Fig. 1. Similarly, the width factors corresponding to items 3 and 4 were 2 and 5, respectively. These width factors suggested a repeating sequence of 5,2,5 as one moved from item 2 to item 3 to item 4. It should be noted that this 5,2,5 sequence of width factors is destroyed by the final adjustment of the boundary between the first and second concentration classes from 0.1 mg/m^3 upward to 0.25 mg/m^3 as described below. A tentative width factor for item 5 was chosen to be 2, the next factor suggested by this series. Then,

$$\begin{aligned}\text{(Upper Bound for item 5)} &= \text{(Lower Bound for item 5)} \times \text{(Width Factor)} \\ &= \text{(Upper Bound for item 4)} \times \text{(Width Factor)} \\ &= 5 \times 2 = 10\ mg/m^3\end{aligned}$$

and item 6 would then correspond to any standards exceeding the upper bound of 10 mg/m^3 established for item 5. The corresponding values for gas concentrations in ppm's and for solid concentrations in mg/m^3 were then plotted on log-log graph paper (see the line for existing standards in Fig. 1). As noted in the discussion of the factor for acute lethality, three of these points were found to lie on a straight line parallel to the line already established for acute lethality. As a last step, this standards line was used to adjust

the boundary between items 1 and 2 upward from 0.1 to 0.25 mg/m^3 so that the adjusted point would lie on the line and correspond to 5 ppmv on the MITRE and HAPPS gas scales. Similarly, the boundary between items 3 and 4 (corresponding to 10 ppmv) could also have been adjusted upward from 1.0 to 1.2 mg/m^3. Such a small change was not considered worth making considering the preliminary nature of the use of HAPPS and the heuristic method used to develop the scale for solids.

The weights used in the MITRE system were modified slightly for HAPPS. Even at the highest concentration levels (item 6), the existence of a standard was felt to indicate a positive finding of adverse human health impact. It was desired that the existence of no standard should receive even less weight. The criterion for no standard was given zero weight and the weights for all the other criteria were incremented by one over the corresponding MITRE scores to avoid having any two HAPPS criteria having identical weights.

1.4 FACTOR GROUPS AND WEIGHTS

1.4.1 General

After scoring a substance in each of the factors, HAPPS departs substantially from the ORNL procedure although there are still some points of similarity such as the grouping together of related factors. These differences arise mostly out of the differences in the scopes and purposes of the two systems. In view of these differences, HAPPS will not be compared to the ORNL procedure in discussing the groups of factors nor in discussing the final ranking procedure.

HAPPS ranks substances by proceeding through three levels, beginning with the most detailed level and aggregating at successive levels to provide a final single rank for each substance. The first, most detailed level, scores substances in each of the eight factors chosen as described above in Sec. 1.2. These scores are chosen by comparing the available data against the criteria described in Sec. 1.3. At the second stage, the scores in certain groups of closely related factors are combined to give group scores. Section 1.4.2 describes the groups and the relative weights of the factors in them.

Table 1.11 Utility of Normalization

Type of Scores	Case	Factor 1 Score	x	Weight	+	Factor 2 Score	x	Weight	=	Unnormalized Group Score	Corrected Group Score
Normalized[a]	I	0.5	x	1	+	1.0	x	1	=	1.5	1.5[b]
	II	1.0	x	1	+	0.5	x	1	=	1.5	1.5[b]
Unnormalized[a]	I	5	x	1	+	20	x	1	=	25	15[c]
	II	10	x	1	+	10	x	1	=	20	15[c]

[a]Assumes range of scores of 0-10 for Factor 1 and 0-20 for Factor 2.

[b]No correction required.

[c]Assumes a weight of 0.5, rather than 1 for Factor 2; see discussion in text.

Finally, the group scores are combined to give the overall rank of the substance as described in Sec. 1.5, the overall ranks of different substances giving them a numerical prioritization.

At each stage or level, HAPPS normalizes the score or rank to the maximum value that could be obtained. Thus, the maximum score or rank at any level will be one. This normalization procedure was adopted primarily to aid in the assignment of the interfactor and intergroup weights required in the second and third levels of the procedure. The relative score or rank of different substances remains the same before and after normalization so the important information is unaltered. However, the assignment of relative weights becomes much easier when the factors being combined have all been normalized to one (or to some other single value). For example, suppose that two closely related factors were being grouped and that it was desired to give each factor equal weight in prioritizing substances, that is, both factors were considered as equally important indicators of the need for additional study in relation to the group. Table 1.11 illustrates the utility of normalization in this situation. A substance satisfying the midrange criterion for the first factor and the highest priority criterion for the second factor (Case I) should be ranked the same as a substance satisfying the highest priority criterion for the first factor and the midrange criterion for the second factor (Case II). The table illustrates the problem avoided by normalization. This illustration assumes that equal weights (=1) have been assigned to each factor. When normalized factor scores are used, a score of 1.0 corresponds to the highest criterion and a score of about 0.5 corresponds to the midrange criterion for both factors. In the two cases considered, both substances would receive the same group score (= 1.5) and hence the same priority based on this group alone just as they should. However, if the scores for the two factors range over different sets of values, say 0-10 for the first factor and 0-20 for the second factor, then the unnormalized scores corresponding to the highest and the midrange criteria depend upon the factor being considered with the result that the two substances are no longer given equal group scores. This situation could be corrected in the example by assigning a weight of 0.5 to Factor 2 but then unequal weights would correspond to equal rankings of importance, obscuring for someone interpreting the results of a priorization the relative importance assumed for factors and

groups. Normalization thus aids in assigning the relative interfactor and intergroup weights; elements considered equally important could be assigned equal weights when normalized scores were used without bothering to adjust the weights for differences in the scales of individual elements. Of course, both normalized and unnormalized weights would provide the same ranked list of substances if the unnormalized group scores were corrected appropriately, but normalization was used in HAPPS to aid the clarity of presentation and to make the assignment of weights as simple as possible.

1.4.2 Groups

Certain factors are either closely related or are surrogates for the same effect of real interest. For example, oncogenicity and mutagenicity are closely related and potential for airborne release and bioaccumulation are surrogates for human exposure. Scores for each factors are combined together into group scores prior to final scoring of a substance. This procedure is a matter of convenience only. The same rankings could be obtained by applying an appropriately chosen set of weights to the eight factors individually without going through the intermediate step of scoring within groups. However, use of groups makes it easier to assign relative weights both within a particular group and between different groups.

Within a single group, only a few factors need to be considered at one time. The number of decisions as to the relative weights to be assigned to various factors is thus reduced to a level where the process becomes more managable. In addition, the judgments required are between related factors like oncogenicity and mutagenicity, a situation in which, for example, the decision to weight them both equally or to give one factor five or ten times the weight of the other is relatively easy compared to a situation in which relative weights must be assigned to disparate elements like oncogenicity and production volume. Of course, the use of groups only postpones the assignment of weight to disparate elements until the intergroup weights must be assigned, but because of the grouping of similar factors into groups, the number of decisions to be made has been reduced and the comparisons to be made are between the dissimilar groups. Problems encountered when considering similar and dissimilar elements at the same time are avoided because the similar items have been combined in the groups.

In proceeding in this fashion, HAPPS assumes that linear expressions are acceptable for prioritizating substances, that is, there are no interactions between factors and/or groups. For example, HAPPS assumes that the oncogenicity scores for two substances satisfying the same criterion for oncogenicity should be the same even if one substance is toxic at low levels and produced in high volumes while the other has substantial evidence of no toxic potential and is produced in very small volumes. In fact, interactions between factors may be very important in making decisions and are neglected in HAPPS. Linear systems like HAPPS cannot account for interactions between factors or groups; the weights simply tell how important an element is compared to other elements for a specific set of scores for these elements. Thus, HAPPS is an approximation to an ideal approach but an approximation which is reasonable given the purpose of the system and the available data.

The groups of factors actually used in HAPPS are shown in Table 1.12 along with the relative weight of each factor within a group. Two of the groups (items 2 and 5 in the table) contain only a single factor and need not be discussed further. The remaining three groups are discussed below.

Carcinogenicity Group. As discussed in connection with the oncogenicity and mutagenicity factors in Sec. 1.2, carcinogenic potential provides the

Table 1.12 Groups of Factors

Item	Group	Factor	
		Name	Weight
1	Carcinogenicity	Oncogenicity	1
		Mutagenicity	1/4.40
2	Reproductive and Developmental Toxicity	Reproductive and Developmental Toxicity	-
3	Toxicity	Acute Lethality	1
		Effects Other than Acute Lethality	1
4	Exposure	Potential for Airborne Release	10
		Bioaccumulation	1
5	Standards	Existing Standards	-

basis for EPA's concern with oncogenicity and mutagenicity. Higher scores for the two factors separately are intended to reflect increased concern that the substance being scored is a human carcinogen acting through inhalation. It was thus reasonable to combine these two closely related factors into a single group. Since not all mutagens are carcinogens, somewhat less weight was attached to evidence based on mutagenicity than to evidence based on oncogenicity even though some evidence for oncogenicity could relate to noncancerous tumors. Put another way, the strongest evidence for mutagenicity was considered to be a less reliable indicator of a substance's carcinogenic potential than the strongest evidence for oncogenicity. For both factors, the strongest evidence corresponds to a normalized score of 1.0. For oncogenicity, for example, a normalized score of 1.0 would require evidence of oncogenicity in humans by both inhalation and noninhalation routes, evidence in two or more animal species, and scheduling for carcinogenesis testing under the NTP. The weighting factor of 1/4.40 (= 0.23) was chosen so that the strongest evidence from mutagenicity (normalized score = 1.0) would receive less weight in the group than evidence of noncogenicity in one animal species (normalized score = 2/6.25 = 0.32) but more weight than if the only evidence of oncogenicity was scheduling for testing under the NTP (normalized score = 1/6.25 = 0.16). (The criteria and scores can be checked by reference to the tables in Sec 1.3; normalization factors can be checked by reference to the coring sheets in Appendix A.) Any factor between 0.16 and 0.32 could have been chosen; the one selected was 0.23 ($= \sqrt{0.16 \times 0.32}$), the geometric mean of the two scores of interest. The geometric mean was used to keep the relative ratios of the weights the same, since it is the ratio of weights, not the difference between them that is the measure of their relative importance. (Values quoted in the text have been rounded for presentation and a check of the ratios using the text values will show a slight inequality.)

Toxicity Group. Two of the factors rank substances by their toxic effects: acute lethality and effects other than acute lethality (item 3 in Table 1.12). As discussed previously, both of these factors deal with traditional toxicological data except for the effects of special interest dealt with under oncogenicity, mutagenicity, and reproductive and developmental toxicity. Generally speaking, the acute lethality factor will score data on

acute exposures while the factor for other effects will score data on chronic exposures although nonlethal acute effects would also be scored under the latter factor. Even with this potential mixing of acute and chronic effects in the factor for other effects, it is reasonable to group both factors together into a toxicity group which summarize the need for concern based on data from standard toxicological tests. Were some of the data from other types of tests, say epidemiological studies of human populations, the grouping is still sensible, as both factors measure the degree of concern based on evidence of toxic effects in humans or other species.

Equal weights were assigned to both acute lethality and to other effects in deriving an overall score for the toxicity group. Since most of the concentrations used in the experiments which provide the data used in scoring the two constituent factors exceed the concentrations likely to be encountered in the ambient air, the weights were chosen based on consideration of the lowest concentration ranges scored. Furthermore, since the principal interest of Air Programs is in effects on human health caused by air contaminants, the considerations were restricted to inhalation effects in humans. From the viewpoint of the need for additional assessment, it was felt that a substance producing acute, lethal effects in humans at very low doses should be of as much concern as a substance producing other effects (probably chronic) in humans at very low doses, that is, that the two factors should be equally weighted. Use of weights of one accomplishes this goal. Inspection of Table 1.5 shows that the normalized score for acute lethality in humans in the very low dose range is 1.0 (= 4.7/4.7) for inhalation. Likewise, Table 1.6 shows that the normalized score for other effects in humans in the very low dose range is also 1.0 (= 7.3/7.3) for inhalation. Thus, the choice of equal weighting factors (=1) does provide the intended equal relative weights to the two factors for the species, concentration range, and exposure route of greatest interest in air programs.

Exposure Group. The factors measuring potential for airborne release and bioaccumulation are surrogates for human exposure. As already pointed out, they leave much to be desired in terms of being reliable indicators but within the constraints placed on HAPPs, they appeared to be the only reasonably available indicators; detailed exposure analyses must await further study

in cases where the need for concern indicated in prioritizing by HAPPS is substantiated by additional preliminary information and expert judgment.

In weighting the two factors in the exposure group, the potential for airborne release was considered to be more indicative of the need for additional study than the potential to bioaccumulate. Airborne release is more directly related to the charge of air programs; a substance which accumulated in humans but whose exposure medium was drinking water would not come within the purview of air programs. Specifically, a reasonable weighting scheme was considered to be one which would rank a substance with a high ability to bioaccumulate approximately equivalent, in terms of public exposure potential, to a liquid substance with a moderate production volume and a low vapor pressure. It was also felt reasonable to consider as approximately equivalent a substance with a high ability to bioaccumulate and a gas with a relatively low production volume. In both cases, a high potential to bioaccumulate would correspond to a normalized score of one (see item 1 in Table 1.9). In the first case, the normalized score for potential for airborne release would be 0.10 (= 4 x 1/40) where moderate production volume has been chosen as item 4 in Table 1.7 and a liquid with low vapor pressure corresponds to item 5 in Table 1.8. To make this normalized score weigh equally with the normalized score of 1.0 for bioaccumulation would require multiplication by a weighting factor of 10.0 (10.0 x 0.10 = 1). Similarly, the normalized score for airborne release in the second case would be 0.10 (= 1 x 4/40) where item 7 in Table 1.7 corresponds to low production volume and item 1 in Table 1.8 corresponds to gases. This score would also need to be multiplied by 10.0 to receive equal weight with the score of the high potential bioaccumulator. Although the use of two independent, reasonable ways of determining a weighting factor would not ordinarily result in equal estimates of that factor, such was the case here and 10.0 was taken as the weighting factor for the potential for airborne release factor in the exposure group.

1.5 Intergroup Weights

The final step in the HAPPS procedure combines the normalized scores for the five groups into an overall score or rank. This combining requires that the groups be weighted to indicate their relative importance. As pointed out previously, this task was difficult because it required that decisions be made as to the relative importance of dissimilar elements. Different individuals could reasonably be expected to disagree on the relative importance or

weight to be assigned to a particular group. Procedures like decision analysis capable of assisting in such tasks and of ensuring internal consistency do exist but could not be applied to HAPPS within available resources. Rather, Air Programs developed a set of weights believed to approximate fairly well the importance given to various groups in the past when decisions were required as to whether or not further assessment of a substance was warranted. A sensitivity analysis on the weights indicated that shifts in the priority levels of substances were small for practical purposes. The remainder of this section discusses this process in greater depth.

Table 1.13 lists the relative weights of the five groups. Three of the groups (items 1, 2, and 3) deal directly with data related to health. Of these three, toxicity was considered to be the least important because most of the concentrations used in developing the data for toxicity would exceed ambient levels. Although the same is probably true of the concentrations used in developing the data for the carcinogenicity and the reproductive and the developmental toxicity groups, the effects considered in these latter two groups probably exhibit no thresholds; for carcinogens this lack of a threshold is almost certainly true. It was still felt, however, that traditional toxicity data by itself should provide sufficient justification for a closer look at a compound. Making carcinogenicity twice as important as toxicity was felt to reasonably balance these two considerations. Even though carcinogens are currently a major concern within EPA, reproductive and developmental toxicity was weighted as being of the same importance as carcinogenicity, because both groups deal with severe health effects that may well occur at ambient levels of concentration.

Table 1.13 Intergroup Weights

Item	Group	Weight
1	Carcinogenicity	2
2	Reproductive and Developmental Toxicity	2
3	Toxicity	1
4	Exposure	5
5	Standards	0.5

The exposure group (item 4) was assigned a weight of 5 to make it equal in importance to the three primary health effects groups together. EPA considers both exposure and health effects in making regulatory decisions. For example, it is unlikely that even a potent carcinogen would be regulated unless there were significant exposure via the ambient air. Conversely, it is unlikely that a widely distributed substance exposing many people would be regulated in the absence of severe health effects. A substance ranked at the top of all three health-related groups (the normalized score for each group = 1) would receive an accumulated unnormalized score of 5 for these three groups with the weights shown in Table 1.13 (2 x 1 + 2 x 1 + 1 x 1 = 5). A substance ranked at the top of the exposure group would receive an unnormalized score of 1 for group before the assignment of the relative weight. Choosing a weight of 5 would make the score for the exposure group equal in importance to that of the three health-related groups together. Although the choice of weights made in HAPPS clearly cannot reflect all the nuances involved in considering health effects and exposure for regulatory purposes, the equal weights given to the exposure group and the three health effects groups together were considered to provide a reasonable approximation to the type of thinking done in the past, particularly in terms of determining the order in which substances should receive additional study.

The assignment of the weight to the standards group was perhaps the most arbitrary assignment of weights. This group was considered important because it indicated a past concern with human health. However, the concentrations involved and the exposure conditions assumed in setting these standards are significantly different from those experienced in exposure via the ambient air. It was felt that a similar degree of concern might be appropriate for two substances one of which had a top score of one in either the acute lethality or other effects factors and no data (score = 0) in the other and the second of which had a top score of one in the existing standards factor. In this situation, the toxicity group would have a normalized score of 0.5 (= [1 x 1 + 1 x 0]/2) and the standards group would have a normalized score of 1. To make the standards group equal in importance to the toxicity group in the final ranking thus required the assignment of a weight of 0.5 to the standards group. Again, it should be emphasized that both the toxicity group and the standards group are given low weights because the concentrations needed to

elicit the responses dealt with under these groups are generally higher than those encountered under ambient conditions.

Since there was subjectivity in the assignment of the intergroup weights, a sensitivity analysis was conducted using different values for the intergroup weights. The analysis indicates that the assignment of intergroup weights is not all that critical in determining the rank of a substance within reasonable bounds. Thus, given Air Programs' own uncertainty about what weights are best, the overall rank of a substance is sufficiently accurate for their purposes.

2 PRIORITIZATION METHODOLOGY

The first task that must be completed in a HAPPS analysis is data collection. All the information necessary to identify the criteria satisfied for each of eight factors must be assembled. Seven basic reference sources are needed to complete a HAPPS analysis. Toxicological information, standards, and some physical and structural properties are obtained from RTECS.[26] The status of a compound within the National Toxicological Program (NTP) is available from the NTP Carcinogenesis Testing Program list of Chemicals on Standard Protocol[27] or NTPs Annual Plan.[28] Production volume data is obtained from the SRI Chemical Economics Handbook.[29] The state of matter (solid, liquid, or gas) for the chemical is obtained from The Merek Index[30] while vapor pressure information is from the Handbook of Chemistry and Physics,[31] and octonal/water partition coefficients are from Let et al.[32]

The procedure for completion of a HAPPS analysis is presented in a worksheet format that leads the analyst step-by-step from data collection through prioritization of any substance. Worksheets 1-9 are used for data collection. Each worksheet explains what information is needed and where to find it. Worksheets 10-17 are used in conjunction with Tables 1-9 and Worksheets 1-9 to assign a normalized weight for each of the eight factors. Worksheet 18 helps the analyst combine the eight factors into five groups and calculate normalized group weights. The final prioritization is accomplished using Worksheet 19.

To facilitate their use apart from this document, Tables and Worksheets used in the HAPPS analysis are presented in the Appendix and are numbered from 1-9 and 1-19, respectively. Abbreviations used in RTECS also are presented in the Appendix in Tables A-1 to A-3.

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APPENDIX A

TABLES, WORKSHEETS, AND ABBREVIATIONS USED IN RTECS

Table 1 Criteria and Associated Weights for Oncogenicity[a]

Index	Criteria[b]	Primary Weight	Secondary Weight
1	Evidence of oncogenicity in humans by inhalation route.	5.0	
2	Evidence of oncogenicity in humans by noninhalation route.	4.0	0.7
3	Evidence of oncogenicity in two or more animal species by any route of administration.[c]	3.0	0.5
4	Evidence of oncogenicity in one animal species by any route of administration.[c]	2.0	0.3
5	Compound scheduled for or currently undergoing oncogenicity testing.	1.0	0.05
6	Negative or equivocal results from oncogenicity testing.	0.0	0.0
7	No data.	0.0	0.0

[a]Most available data will relate to carcinogenicity.

[b]See Table A-1 in the appendix for a complete list of abbreviations used in RTECS, Table A-2 for species abbreviations, and Table A-3 for route of administration abbreviations.

[c]If the data satisfy the criteria for Index 3 then Index 4 should not be considered.

Table 2 Criteria and Associated Weights for Mutagenicity

Index	Criteria[a]	Primary Weight	Secondary Weight
1	Evidence of mutagenicity (in vivo) in at least one mammalian test species by the inhalation route.[b]	11.0	
2	Evidence of mutagenicity (in vivo) in at least one mammalian test species by the non-inhalation route.	9.0	0.7
3	Evidence of mutagenicity (in vitro) in two or more mammalian test species.[c,d]	8.3	0.5
4	Evidence of mutagenicity (in vitro) in one mammalian test species.[d]	7.7	0.4
5	Evidence of mutagenicity (in vivo) in two or more nonmammalian test species by any route of administration.[e]	7.1	0.25
6	Evidence of mutagenicity (in vivo) in one nonmammalian test species by any route of administration.[e]	6.5	0.2
7	Evidence of mutagenicity (in vitro) in two or more nonmammalian test species.[f]	6.0	0.15
8	Evidence of mutagenicity (in vitro) in one nonmammalian test species.[f]	4.0	0.1
9	Compound scheduled for or currently undergoing mutagenicity testing.	2.0	0.05
10	Negative or equivocal results from mutagenicity testing.	0.0	0.0
11	No data.	0.0	0.0

[a]See Table A-1 in the appendix for a complete list of abbreviations used in RTECS, Table A-2 for species abbreviations, and Table A-3 for route of administration abbreviations.

[b]If the route of administration is specified the test is in vivo.

[c]If the route of administration is not specified the test is in vitro.

[d]If the data satisfy the criteria for Index 3 then Index 4 should not be considered.

[e]If the data satisfy the criteria for Index 5 then Index 6 should not be considered.

[f]If the data satisfy the criteria in Index 7 then Index 8 should not be considered.

Table 3 Criteria and Associated Weights for Reproductive and Developmental Toxicity

Index	Criteria[a]	Primary Weight	Secondary Weight
1	Evidence for reproductive or developmental effects in humans by inhalation route.	5.0	
2	Evidence for reproductive or developmental effects in humans by noninhalation route.	4.0	0.7
3	Evidence for reproductive or developmental effects in two or more animal species by any route of entry.[b]	3.0	0.5
4	Evidence for reproductive or developmental effects in one animal species by any route of entry.[b]	2.0	0.3
5	Compound scheduled for or currently undergoing testing for reproductive and developmental effects.	1.0	0.05
6	Negative or equivocal results from testing for reproductive or developmental effects.	0.0	0.0
7	No data.	0.0	0.0

[a]See Table A-1 in the appendix for a complete list of abbreviations used in RTECS, Table A-2 for species abbreviations, and Table A-3 for route of administration abbreviations.

[b]If the data satisfy the criteria for Index 3 then Index 4 should not be considered.

Table 4 Criteria and Associated Weights for Acute Lethality

Index	Species	Route of Exposure and Criteria[a]				Primary Weight
		Inhalation		Oral	Dermal	
		Gas(ppm)	Solid(mg/m^3)	(mg/kg)	(mg/kg)	
1	Human	$X \leq 5$	$X \leq 50$	-	-	4.7
2	Human	-	-	$X \leq 5$	$X \leq 5$	3.7
3	Animal	$X \leq 5$	$X \leq 50$	$X \leq 5$	$X \leq 5$	3.0
4	Human	$5 < X \leq 50$	$50 < X \leq 500$	-	-	2.6
5	Human	-	-	$5 < X \leq 50$	$5 < X \leq 200$	2.3
6	Animal	$5 < X \leq 50$	$50 < X \leq 500$	$5 < X \leq 50$	$5 < X \leq 200$	2.0
7	Human/ Animal	$X > 50$	$X > 500$	$X > 50$	$X > 200$	0.0
8	Human/ Animal	Negative or insignificant results in humans or animals.				0.0
9	Human/ Animal	No data.				0.0

[a]See Table A-1 in the appendix for a complete list of abbreviations used in RTECS, Table A-2 for species abbreviations, and Table A-3 for route of administration abbreviations.

Table 5 Criteria and Associated Weights for Effects Other than Acute Lethality

Index	Species	Route of Exposure and Criteria[a]				Primary Weight
		Inhalation		Oral	Dermal	
		Gas(ppm)	Solid(mg/m^3)	(mg/kg)	(mg/kg)	
1	Human	$X \leq 1$	$X \leq 10$	-	-	7.0
2	Human	-	-	$X \leq 1$	$X \leq 1$	6.0
3	Human	$1 < X \leq 10$	$10 < X \leq 100$		-	5.0
4	Human	-	-	$1 < X \leq 10$	$1 < X \leq 10$	4.0
5	Animal	$X \leq 1$	$X \leq 10$	$X \leq 1$	$X \leq 1$	3.0
6	Animal	$1 < X \leq 10$	$10 < X \leq 100$	$1 < X \leq 10$	$1 < X \leq 10$	2.0
7	Human/ Animal	$X > 10$	$X > 100$	$X > 10$	$X > 10$	1.0
8	Human/ Animal	Negative or insignificant results in humans or animals.				0.0
9	Human/ Animal	No data.				0.0

[a]See Table A-1 in the appendix for a complete list of abbreviations used in RTECS, Table A-2 for species abbreviations, and Table A-3 for route of administration abbreviations.

Table 6 Criteria and Associated Weights for Production Volume (PV)

Index	Criteria		Primary Weight
	10^6 kg/yr	10^6 lb/yr	
1	PV>450	PV>1000	10.0
2	230<PV≤450	510<PV≤1000	8.0
3	45<PV≤230	100<PV≤510	6.0
4	23<PV≤45	51<PV≤100	4.0
5	0.45<PV≤23	1.0<PV≤51	3.0
6	0.045<PV≤0.45	0.10<PV≤1.0	2.0
7	PV≤0.045	PV≤0.10	1.0
8	No data.		1.0

Table 7 Criteria and Associated Weights for Vapor Pressure (VP)

Index	Criteria[a,b] VP(mmHg)	bp(°C)	Primary Weight
1	Gas		4.0
2	Solid[c]		3.0
3	VP>100	bp≤80	3.0
4	24<VP≤100	80<bp≤100	2.0
5	VP≤24	bp>100	1.0
6	No data.		1.0

[a]Vapor pressure data should be reported at 25°C and 760 mm Hg.

[b]If vapor pressure data is unavailable use the substance boiling point (bp), at 760 mm Hg, as a substitute.

[c]A substance should be considered a solid if its melting point is greater than 25°C.

Table 8 Criteria and Associated Weights for Bioaccumulation

Index	Criteria	Primary Weight
1	Log $P > 6.0$	10.0
2	$4.0 < \text{Log } P \leq 6.0$	8.0
3	$2.0 < \text{Log } P \leq 4.0$	6.0
4	Log $P \leq 2.0$	1.0
5	No data.	1.0

Table 9 Criteria and Associated Weights for Existing Standards

Index	Criteria Gas (ppm)	Solid (mg/m^3)	Primary Weight
1	$X \leq 5$	$X \leq 0.25$	6.0
2	$5 < X \leq 10$	$0.25 < X \leq 0.5$	5.0
3	$10 < X \leq 25$	$0.5 < X \leq 1.0$	4.0
4	$25 < X \leq 100$	$1.0 < X \leq 5.0$	3.0
5	$100 < X \leq 200$	$5.0 < X \leq 10.0$	2.0
6	$X > 200$	$X > 10.0$	1.0
7	No standard.		0.0

[a]Based on OSHA time-weighted-average (TWA) standards or threshold limit values (TLV) when TWAs are not available.

WORKSHEET 1. GENERAL INFORMATION[a]

Chemical Name: _____

RTECS Number:[b] _____

CAS NUMBER:[c] _____

MOLECULAR WEIGHT:[d] _____ g/g-mol

MOLECULAR FORMULA:[e] _____

MELTING POINT:[f] _____:°C BOILING POINT:[f] _____°C

SUBSTANCE PHYSICAL STATE:[g] Gas Liquid Solid Unknown

RTECS Edition:[h] _____

MERCK INDEX Edition:[i] _____

HANDBOOK OF CHEMISTRY AND PHYSICS Edition:[j] _____

[a]All data taken from the Registry of Toxic Effects of Chemical Substances (RTECS). The latest microfiche edition of RTECS should be used for the analysis and can be obtained from the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C.

[b]Using the RTECS data field RTECS Accession Number, enter the RTECS number.

[c]Using the RTECS data field CAS NUMBER enter the Chemical Abstract Service Registry Number.

[d]Using the RTECS data field MOLECULAR WEIGHT, enter the molecular weight.

[e]Using the RTECS data field MOLECULAR FORMULA, enter the molecular formula.

[f]Using the most recent edition of the Merck Index, enter the melting/boiling points of the substance under analysis. If the substances is not in the Merck Index use the most recent edition of the Handbook of Chemistry and Physics (Tables of Physical Constants of Organic/Inorganic Compounds) for the melting/boiling points.

[g]Using the information on physical characteristics from the Merck Index and the melting/boiling point information determine the physical state of the substance under analysis.

[h]Enter the edition of RTECS used for this analysis.

[i]Enter the edition of the Merck Index used for this analysis.

[j]Enter the edition of the Handbook of Chemistry and Physics used for this analysis.

WORKSHEET 2. ONCOGENICITY

Using the RTECS data field TUMORIGENIC DATA, record the route of administration and test species for all citations that show the Toxic Effect (TFX) as TFX:CAR, TFX:NEO, or TFX:ETA.

ROUTE OF ADMINISTRATION	TEST SPECIES	ROUTE OF ADMINISTRATION	TEST SPECIES

Using the latest edition of the Carcinogenis Testing Program: Chemicals on Standard Protocol[a] from the National Toxicology Program, record the status of the substance in the Carcinogenesis Testing Program.

- ☐ Not on list (should not be scored on Worksheet 10)
- ☐ Scheduled for or currently undergoing testing
- ☐ Negative or equivocal results

Edition Used[b]: _____

[a]A copy can be obtained from: Technical Information Section, Carcinogenesis Testing Program, National Toxicology Program, Landow Building, Room A306, Bethesda, MD 20205.

[b]Enter the edition of the Carcinogenis Testing Program:Chemicals on Standard Protocol used for this analysis.

WORKSHEET 3. MUTAGENICITY

Using the RTECS data field MUTATION DATA, record the test species and route of administration (if applicable) for all citations. Below the heading MUTATION DATA, each mutation data line includes, in sequence, the mutation test system utilized, the species of the tested organism (and where applicable, the route of administration or cell type), and the exposure concentration or dose.

TEST SPECIES	ROUTE OF ADMINISTRATION	TEST SPECIES	ROUTE OF ADMINISTRATION

Using the latest edition of the National Toxicology Program Annual Plan,[a] record the status of the substance in the Mutagenicity Testing Program. Tables in the section on cellular and genetic toxicology should be used for the following analysis (See for example, pages 35-73, Tables 2-8, of the NTP Annual Plan[28]).

☐ Not on list (should not be scored on Worksheet 11)

☐ Scheduled for or currently undergoing testing

☐ Negative or equivocal results

Edition Used[b]: _____

[a] A copy can be obtained from: Technical Information Section, National Toxicology Program, Landow Building, Room A306, Bethesda, MD 20205.

[b] Enter the edition of the National Toxicology Program Annual Plan used for this analysis.

WORKSHEET 4. REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Using the RTECS data field REPRODUCTIVE EFFECTS DATA, record the route of administration and test species for all citations.

ROUTE OF ADMINISTRATION	TEST SPECIES	ROUTE OF ADMINISTRATION	TEST SPECIES

Using the National Toxicology Program Annual Plan[a], record the status of the substance in the Teratogenic Testing Program. Tables in the section on reproductive and developmental toxicology should be used for the following analysis (see for example, pages 125-134, Tables 17-20, of the NTP Annual Plan[28]).

☐ Not on list (should not be scored on Worksheet 12)

☐ Scheduled for or currently undergoing testing

☐ Negative or equivocal results

Edition Used[b]: _____

[a]A copy can be obtained from: Technical Information Section, National Toxicology Program, Landow Building, Room A306, Bethesda, MD 20205.

[b]Enter the edition of the National Toxicology Program Annual Plan used for this analysis.

WORKSHEET 5. ACUTE LETHALITY

Using the RTECS data field TOXICITY AND DATA REFERENCES, record the route of administration, test species, dose, and length of exposure for all citations (other than TFX:CAR, TFX:NEO, or TFX:ETA) that are of the form LD_{Lo}, LD_{50}, LC_{Lo}, and LC_{50} that give the route of administration as ihl, orl, or skn and length of exposure less than or equal to 24 hr.[a]

ROUTE OF ADMINISTRATION	TEST SPECIES	DOSE[b,c]	LENGTH OF EXPOSURE

[a]Any data for LD_{Lo}, LD_{50}, LC_{Lo}, or LC_{50} with exposure times greater than 24 hr should be included in Worksheet 6 (Effects Other Than Acute Lethality).

[b]Concentrations for solid substances should be recorded as mg/m3 and cannot be converted to ppm. If the physical state of the substance is unknown, record the units given in RTECS and do not attempt to convert to ppm. Occasionally, the dose for solids will be given in ppm's (usually when the melting point is near 25°C), the dose then should be recorded in ppm's and not converted to mg/m^3.

[c]For gases and vapors, concentrations in mg/m^3 should be converted to ppm by:

$$ppm = \frac{24.45}{MW} \times \text{concentration } (mg/m^3) \quad @ \ 25°C \text{ and } 760 \text{ mm Hg}$$

where MW = molecular weight (Worksheet 1).

WORKSHEET 6. EFFECTS OTHER THAN ACUTE LETHALITY

Using the RTECS data field TOXICITY AND DATA REFERENCES, record the route of administration, test species, and dose for all citations (other than TFX:CAR, TFX:NEO, or TFX:ETA) that are of the form TD_{Lo}, or TC_{Lo} that give the route of administration as ihl, orl, or skn. Citations of the form LD_{Lo}, LD_{50}, LC_{Lo}, or LC_{50} that give the route of administration as ihl, orl, or skn and length of exposure greater than 24 hr should be included here.

ROUTE OF ADMINISTRATION	TEST SPECIES	DOSE[a,b]

[a]Concentrations for solid substances should be recorded as mg/m^3 and cannot be converted to ppm. If the physical state of the substance is unknown, record the units given in RTECS and do not attempt to convert to ppm. Occasionally, the dose for solids will be given in ppm's (usually when the melting point is near 25°C), the dose then should be recorded in ppm's and not converted to mg/m^3.

[b]For gases and vapors, concentrations in mg/m^3 should be converted to ppm by:

$$ppm = \frac{24.45}{MW} \times \text{concentration } (mg/m^3) \quad @ \ 25°C \text{ and } 760 \text{ mm Hg}$$

where MW = molecular weight (Worksheet 1).

WORKSHEET 7a. PRODUCTION VOLUME (PV)

Using the SRI Chemical Economics Handbook find the total U.S. production for the substance under analysis.

PV = _____ x 10^6 kg/yr or PV = _____ x 10^6 lb/yr

Edition Used[a]: _____

[a]Enter the edition of the SRI chemical Economics Handbook used for this analysis.

WORKSHEET 7b. VAPOR PRESSURE (VP)

Using the information from Worksheet 1, record the physical state (at 25°C and 760 mm Hg) and boiling point (BP) of the substance under analysis.

- ☐ Gas
- ☐ Solid
- ☐ Liquid — BP = _____ °C
- ☐ Unknown

If the physical state is given as gaseous, solid, or unknown, continue on to Worksheet 8.

If the substance is a liquid use the data from the Handbook of Chemistry and Physics[31] to calculate the vapor pressure (VP), at 25°C and 760 mm Hg.[a] Enter constants A and B, and the temperature range for which the equation and constants are valid.

A= _____ B= _____

Temperature Range: _____ °C

VP = _____ mmHg @ 25°C and 760 mmgHg

If 25°C does not fall within the temperature range above continue on to Worksheet 8.

[a] $VP\ (mm\ Hg) = \text{antilog}_{10}\ [(-7.3285 \times 10^{-4} \times A)+B]$

where A = molar heat of vaporization
B = constant.

Constants A and B are obtained from the Handbook of Chemistry and Physics[31] pages D-151 to D-170 for organic compounds and pages D-171 to D-177 for inorganic compounds.

WORKSHEET 8. BIOACCUMULATION

Using Table XVII from Leo et al.[32], find the MOLECULAR FORMULA (Worksheet 1) of the substance under analysis in the column headed EMPIRICAL FORMULA. Find, in the column headed SOLVENT, the line corresponding to octanol. Match the chemical name of the substnace under analysis with the chemical name in the column headed NAME. Enter, in the space provided above, the value from the column headed LOGP OCT. If more than one value of the LOGP OCT is given for the octonal solvent system use the average of the LOGP OCT values. If octonal is not one of the solvents listed for the given MOLECULAR FORMULA and NAME enter the average LOGP OCT estimated from the other solvent systems.

Log_{10} P = _____

WORKSHEET 9. EXISTING STANDARDS

Using the RTECS data field STANDARDS AND REGULATIONS, record the entry for the OSHA time weighted average (OSHA STANDARD-air:TWA) in the space provided below. If OSHA Standard-air TWA is not given use the RTECS data field REVIEW, record the entry for the threshold limit value (THRESHOLD LIMIT VALUE-air:) in the space provided below.

STANDARDS AND REGULATIONS: OSHA STANDARD-air:TWA = _____ ppm (gas)[a,b]

_____ mg/m^3 (solid)[a,b]

REVIEW: THRESHOLD LIMIT VALUE-air: _____ ppm (gas)[a,b]

_____ mg/m^3 (solid)[a,b]

[a]Standards for solid substances should be recorded as mg/m3 and cannot be converted to ppm. If the physical state of the substance is unknown, record the standard in the units given in RTECS and do not attempt to convert to ppm. Occasionally, the standard for solids will be given in ppm's (usually when the melting point is near 25°C), the standard then should be recorded in ppm's and not converted to mg/m^3.

[b]For gases and vapors, standards in mg/m^3 should be converted to ppm by:

$$ppm = \frac{24.45}{MW} \times \text{standard } (mg/m^3) \quad @ 25°C \text{ and } 760 \text{ mm Hg}$$

where MW = molecular weight (Worksheet 1).

WORKSHEET 10. ONCOGENICITY FACTOR SCORE

The completion of Worksheet 10 requires the use of Worksheet 2.

1. Circle the index numbers, in the table below, that correspond to the criteria that are satisfied by the data from Worksheet 2.

2. Starting at Index 1, read down the Index column until the first circled index number is encountered. Record the Primary Weight associated with that index number in the corresponding Criteria Weight column.

3. Continue reading down the Index column to each successive circled index number and record the Secondary Weight associated with each index number in the corresponding Criteria Weight column.

4. Sum all values recorded in the Criteria Weight column and record in the space labeled $\sum$(Criteria Weight) below.

5. Divide the results from Step 4 by 6.25 to obtain the Normalized Factor Score for Oncogenicity (ONCOnorm).

Criteria and Associated Weights for Oncogenicity[a]

Index	Criteria[b]	Primary Weight	Secondary Weight	Criteria Weight
1	Evidence of oncogenicity in humans by inhalation route.	5.0		
2	Evidence of oncogenicity in humans by noninhalation route.	4.0	0.7	
3	Evidence of oncogenicity in two or more animal species by any route of administration.[c]	3.0	0.5	
4	Evidence of oncogenicity in one animal species by any route of administration.[c]	2.0	0.3	
5	Compound scheduled for or currently undergoing oncogenicity testing.	1.0	0.05	
6	Negative or equivocal results from oncogenicity testing.	0.0	0.0	
7	No data.	0.0	0.0	

$$\frac{\qquad}{\sum(\text{Criteria Weight})} \div 6.25 = \frac{\qquad}{\text{ONCOnorm}}$$

[a]Most available data will relate to carcinogenicity.

[b]See Table A-1 in the appendix for a complete list of abbreviations used in RTECS, Table A-2 for species abbreviations, and Table A-3 for route of administration abbreviations.

[c]If the data satisfy the criteria for Index 3 then Index 4 should not be considered.

WORKSHEET 11. MUTAGENICITY FACTOR SCORE

The completion of Worksheet 11 requires the use of Worksheet 3.

1. Circle the index numbers, in the table below, that correspond to the criteria that are satisfied by the data from Worksheet 3.

2. Starting at Index 1, read down the Index column until the first circled index number is encountered. Record the Primary Weight associated with that index number in the corresponding Criteria Weight column.

3. Continue reading down the Index column to each successive circled index number and record the Secondary Weight associated with each index number in the corresponding Criteria Weight column.

4. Sum all values recorded in the Criteria Weight column and record in the space labeled $\sum$(Criteria Weight) below.

5. Divide the results from Step 4 by 12.65 to obtain the Normalized Factor Score for Mutagenicity (MUTnorm).

Criteria and Associated Weights for Mutagenicity

Index	Criteria[a]	Primary Weight	Secondary Weight	Criteria Weight
1	Evidence of mutagenicity (in vivo) in at least one mammalian test species by the inhalation route.[b]	11.0		
2	Evidence of mutagenicity (in vivo) in at least one mammalian test species by the non-inhalation route.	9.0	0.7	
3	Evidence of mutagenicity (in vitro) in two or more mammalian test species.[c,d]	8.3	0.5	
4	Evidence of mutagenicity (in vitro) in one mammalian test species.[d]	7.7	0.4	
5	Evidence of mutagenicity (in vivo) in two or more nonmammalian test species by any route of administration.[e]	7.1	0.25	
6	Evidence of mutagenicity (in vivo) in one nonmammalian test species by any route of administration.[e]	6.5	0.2	
7	Evidence of mutagenicity (in vitro) in two or more nonmammalian test species.[f]	6.0	0.15	
8	Evidence of mutagenicity (in vitro) in one nonmammalian test species.[f]	4.0	0.1	
9	Compound scheduled for or currently undergoing mutagenicity testing.	2.0	0.05	
10	Negative or equivocal results from mutagenicity testing.	0.0	0.0	
11	No data.	0.0	0.0	

$$\frac{\text{}}{\sum(\text{Criteria Weight})} \div 12.65 = \frac{\text{}}{\text{MUTnorm}}$$

[a] See Table A-1 in the appendix for a complete list of abbreviations used in RTECS, Table A-2 for species abbreviations, and Table A-3 for route of administration abbreviations.

[b] If the route of administration is specified the test is in vivo.

[c] If the route of administration is not specified the test is in vitro.

[d] If the data satisfy the criteria for Index 3 then Index 4 should not be considered.

[e] If the data satisfy the criteria for Index 5 then Index 6 should not be considered.

[f] If the data satisfy the criteria in Index 7 then Index 8 should not be considered.

WORKSHEET 12. REPRODUCTIVE AND DEVELOPMENTAL TOXICITY FACTOR SCORE

The completion of Worksheet 12 requires the use Worksheet 4.

1. Circle the index numbers, in the table below, that correspond to the criteria that are satisfied by the data from Worksheet 4.

2. Starting at Index 1, read down the Index column until the first circled index number is encountered. Record the Primary Weight associated with that index number in the corresponding Criteria Weight column.

3. Continue reading down the Index column to each successive circled index number and record the Secondary Weight associated with each index number in the corresponding Criteria Weight column.

4. Sum all values recorded in the Criteria Weight column and record in the space labeled $\sum$(Criteria Weight) below.

5. Divide the results from Step 4 by 6.25 to obtain the Normalized Factor Score for Reproductive and Developmental Toxicity (RDTnorm).

Criteria and Associated Weights for Reproductive and Developmental Toxicity

Index	Criteria[a]	Primary Weight	Secondary Weight	Criteria Weight
1	Evidence for reproductive or developmental effects in humans by inhalation route.	5.0		
2	Evidence for reproductive or developmental effects in humans by noninhalation route.	4.0	0.7	
3	Evidence for reproductive or developmental effects in two or more animal species by any route of entry.[b]	3.0	0.5	
4	Evidence for reproductive or developmental effects in one animal species by any route of entry.[b]	2.0	0.3	
5	Compound scheduled for or currently undergoing testing for reproductive and developmental effects.	1.0	0.05	
6	Negative or equivocal results from testing for reproductive or developmental effects.	0.0	0.0	
7	No data.	0.0	0.0	

$$\frac{\qquad}{\sum(\text{Criteria Weight})} \div 6.25 = \frac{\qquad}{\text{RDTnorm}}$$

[a]See Table A-1 in the appendix for a complete list of abbreviations used in RTECS, Table A-2 for species abbreviations, and Table A-3 for route of administration abbreviations.

[b]If the data satisfy the criteria for Index 3 then Index 4 should not be considered.

WORKSHEET 13. ACUTE LETHALITY FACTOR SCORE

The completion of Worksheet 13 requires the use of Worksheet 5.

1. Circle the index numbers, in the table below, that correspond to the criteria that are satisfied by the data from Worksheet 5.

2. Starting at Index 1, read down the Index column until the first circled index number is encountered. Record the Primary Weight associated with that index number in the space labeled Criteria Weight below.

3. Divide the value obtained in Step 2 by 4.7 to obtain the Normalized Factor Score for Acute Lethality (ALETHnorm).

Criteria and Associated Weights for Acute Lethality

		Route of Exposure and Criteria[a]				
Index	Species	Inhalation Gas(ppm)	Inhalation Solid(mg/m^3)	Oral (mg/kg)	Dermal (mg/kg)	Primary Weight
1	Human	$X \leq 5$	$X \leq 50$	-	-	4.7
2	Human	-	-	$X \leq 5$	$X \leq 5$	3.7
3	Animal	$X \leq 5$	$X \leq 50$	$X \leq 5$	$X \leq 5$	3.0
4	Human	$5 < X \leq 50$	$50 < X \leq 500$	-	-	2.6
5	Human	-	-	$5 < X \leq 50$	$5 < X \leq 200$	2.3
6	Animal	$5 < X \leq 50$	$50 < X \leq 500$	$5 < X \leq 50$	$5 < X \leq 200$	2.0
7	Human/ Animal	$X > 50$	$X > 500$	$X > 50$	$X > 200$	0.0
8	Human/ Animal	Negative or insignificant results in humans or animals.				0.0
9	Human/ Animal	No data.				0.0

_____ ÷ 4.7 = _____

Criteria Weight ALETHnorm

[a]See Table A-1 in the appendix for a complete list of abbreviations used in RTECS, Table A-2 for species abbreviations, and Table A-3 for route of administration abbreviations.

WORKSHEET 14. EFFECTS OTHER THAN ACUTE LETHALITY FACTOR SCORE

The completion of Worksheet 14 requires the use of and Worksheet 6.

1. Circle the index numbers, in the table below, that correspond to the criteria that are satisfied by the data from Worksheet 6.

2. Starting at Index 1, read down the Index column until the first circled index number is encountered. Record the Primary Weight associated with that index number in the space labeled Criteria Weight below.

3. Divide the value obtained in Step 2 by 7.0 to obtain the Normalized Factor Score for Effects Other than Acute Lethality (NLETHnorm).

Criteria and Associated Weights for Effects Other than Acute Lethality

Index	Species	Route of Exposure and Criteria[a]				
		Inhalation		Oral	Dermal	Primary
		Gas(ppm)	Solid(mg/m^3)	(mg/kg)	(mg/kg)	Weight
1	Human	$X \leq 1$	$X \leq 10$	-	-	7.0
2	Human	-	-	$X \leq 1$	$X \leq 1$	6.0
3	Human	$1 < X \leq 10$	$10 < X \leq 100$		-	5.0
4	Human	-	-	$1 < X \leq 10$	$1 < X \leq 10$	4.0
5	Animal	$X \leq 1$	$X \leq 10$	$X \leq 1$	$X \leq 1$	3.0
6	Animal	$1 < X \leq 10$	$10 < X \leq 100$	$1 < X \leq 10$	$1 < X \leq 10$	2.0
7	Human/ Animal	$X > 10$	$X > 100$	$X > 10$	$X > 10$	1.0
8	Human/ Animal	Negative or insignificant results in humans or animals.				0.0
9	Human/ Animal	No data.				0.0

_____ ÷ 7.0 = _____

Criteria Weight NLETHnorm

[a]See Table A-1 in the appendix for a complete list of abbreviations used in RTECS, Table A-2 for species abbreviations, and Table A-3 for route of administration abbreviations.

WORKSHEET 15. POTENTIAL FOR AIRBORNE RESEASE FACTOR SCORE

The completion of Worksheet 15 requires the use of Worksheets 7a and 7b.

Production Volume (PV)

1. Circle the index number, in the table below, that corresponds to the PV interval that the PV data from Worksheet 7a falls into.

2. Read the *Primary Weight corresponding to the index number circled in* Step 1 and record it in the space labeled PV Weight below.

Criteria and Associated Weights for Production Volume (PV)

Index	Criteria		Primary Weight
	10^6 kg/yr	10^6 lb/yr	
1	PV>450	PV>1000	10.0
2	230<PV≤450	510<PV≤1000	8.0
3	45<PV≤230	100<PV≤510	6.0
4	23<PV≤45	51<PV≤100	4.0
5	0.45<PV≤23	1.0<PV≤51	3.0
6	0.045<PV≤0.45	0.10<PV≤1.0	2.0
7	PV≤0.045	PV≤0.10	1.0
8	No data.		1.0

Vapor Pressure (VP)

3. Circle the index number, in the table below, that corresponds to the VP *interval that the VP data from Worksheet 7b falls into.*

4. Read the Primary Weight corresponding to the index number circled in Step 3 and record it in the space labeled VP Weight below.

Criteria and Associated Weights for Vapor Pressure (VP)

Index	Criteria[a,b]		Primary Weight
	VP(mmHg)	bp(°C)	
1	Gas		4.0
2	Solid[c]		3.0
3	VP>100	bp≤80	3.0
4	24<VP≤100	80<bp≤100	2.0
5	VP≤24	bp>100	1.0
6	No data		1.0

5. Divide the Product of PV Weight and VP Weight by 40.0 to obtain the Normalized Factor Score for Potential for Airborne Release (AIRBOnorm).

$$\left[\frac{\text{PV Weight}}{}\times\frac{\text{VP Weight}}{}\right]\div 40.0 = \frac{}{\text{AIRBOnorm}}$$

[a] Vapor pressure data should be reported at 25°C and 760 mm Hg.

[b] If vapor pressure data is unavailable use the substance boiling point (bp), at 760 mm Hg, as a substitute.

[c] A substance should be considered a solid if its melting point is greater than 25°C.

WORKSHEET 16. BIOACCUMULATION FACTOR SCORE

The completion of Worksheet 16 requires the use of Worksheet 8.

1. Circle the index numbers, in the table below, that correspond to the Log_{10} P interval that the Log_{10} P data from Worksheet 8 falls into.

2. Read the Primary Weight corresponding to the index number circled in Step 1 and record it in the space labeled Bioaccumulation Weight below.

3. Divide Bioaccumulation Weight by 10.0 to obtain the Normalized Factor Score for Bioaccumulation (BIOAnorm).

Table 8 Criteria and Associated Weights for Bioaccumulation

Index	Criteria	Primary Weight
1	Log_{10} P>6.0	10.0
2	4.0<Log_{10} P≤6.0	8.0
3	2.0<Log_{10} P≤4.0	6.0
4	Log_{10} P≤2.0	1.0
5	No data.	1.0

Bioaccumulation Weight ÷ 10.0 = BIOAnorm

WORKSHEET 17. EXISTING STANDARD FACTOR SCORE

The completion of Worksheet 17 requires the use of Worksheet 9.

1. Circle the index numbers, in the table below, that correspond to the TWA (or TLV, if TWA unavailable) interval that the TWA (or TLV) data from Worksheet 9 falls into.

2. Read the Primary Weight corresponding to the index number circled in Step 1 and record it in the space labeled Standard Weight below.

3. *Divide Standard Weight by 6.0 to obtain the Normalized Factor Score for Existing Standard (ESTDnorm).*

Criteria and Associated Weights for Existing Standards

Index	Criteria Gas (ppm)	Solid (mg/m^3)	Primary Weight
1	$X \leq 5$	$X \leq 0.25$	6.0
2	$5 < X \leq 10$	$0.25 < X \leq 0.5$	5.0
3	$10 < X \leq 25$	$0.5 < X \leq 1.0$	4.0
4	$25 < X \leq 100$	$1.0 < X \leq 5.0$	3.0
5	$100 < X \leq 200$	$5.0 < X \leq 10.0$	2.0
6	$X > 200$	$X > 10.0$	1.0
7	No standard.		0.0

$$\frac{\text{Standard Weight}}{} \div 6.0 = \frac{}{\text{ESTDnorm}}$$

[a]Based on OSHA time-weighted-average (TWA) standards or threshold limit values (TLV) when TWAs are not available.

WORKSHEET 18. CALCULATE NORMALIZED GROUP SCORE

CARCINOGENICITY GROUP (CAR)

1. Record the Normalized Factor Scores (NFS) for Oncogenicity (ONCOnorm from Worksheet 10) and Mutagenicity (MUTnorm from Worksheet 11) and complete the requested mathematical procedures to calculate the normalized group score for CAR (CARnorm).

$$\left[\frac{\text{ONCOnorm}}{\quad} + \left(\frac{\text{MUTnorm}}{\quad} \div 4.40\right)\right] \div 1.23 = \frac{\text{CARnorm}}{\quad}$$

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY GROUP (REPRO)

2. Record the NFS for Reproductive and Developmental Toxicity (RDTnorm from Worksheet 12). Because there is only one factor in the REPRO group, RDTnorm is equal to the normalized group score for REPRO (REPROnorm).

$$\frac{\text{RDTnorm}}{\quad} = \text{REPROnorm}$$

TOXICITY GROUP (TOX)

3. Record the NFS for Acute Lethality (ALETHnorm from Worksheet 13) and Effects Other than Acute Lethality (NLETHnorm from Worksheet 14 and complete the requested mathematical procedures to calculate the normalized group score for TOX (TOXnorm).

$$\left[\frac{\text{ALETHnorm}}{\quad} + \frac{\text{NLETHnorm}}{\quad}\right] \div 2.0 = \frac{\text{TOXnorm}}{\quad}$$

EXPOSURE GROUP (EXPO)

4. Record the NFS for Potential for Airborne Release (AIRBOnorm from Worksheet 15) and Bioaccumulation (BIOAnorm from Worksheet 16) and complete the requested mathematical procedures to calculate the normalized group score for EXPO (EXPOnorm).

$$\left[\left(\frac{\text{AIRBOnorm}}{\quad} \times 10.0\right) + \frac{\text{BIOAnorm}}{\quad}\right] \div 11.0 = \frac{\text{EXPOnorm}}{\quad}$$

STANDARDS GROUP (STD)

5. Record the NFS for Existing Standards (ESTDnorm from Worksheet 17). Because there is only one factor in the STD group, ESTDnorm is equal to the normalized group score for STD (STDnorm).

$$\frac{\text{ESTDnorm}}{\quad} = \text{STDnorm}$$

WORKSHEET 19. SUBSTANCE PRIORITIZATION

The completion of Worksheet 19 requires the use of Worksheet 18.

1. Record the values for CARnorm, REPROnorm, TOXnorm, EXPOnorm, and STDnorm from Worksheet 18 in the appropriate space below.

2. Calculate the Normalized Substance Rank.

$$\left[\left(2 \times \frac{\quad}{\text{CARnorm}}\right) + \left(2 \times \frac{\quad}{\text{REPROnorm}}\right) + \left(\frac{\quad}{\text{TOXnorm}}\right) + \left(5 \times \frac{\quad}{\text{EXPOnorm}}\right) + \left(0.5 \times \frac{\quad}{\text{STDnorm}}\right)\right] \div 10.5 = \frac{\quad}{\text{Normalized Substance Rank}^{a}}$$

[a]Values for Normalized Substance Rank will range from 0.014 to 1.0.

Table A-1. Comprehensive List of All Abbreviations Used in RTECS[a,b]

ALR - allergenic effects

AQTX- Aquatic Toxicity

asn - Aspergillus nidulans (mold)

ast - Ascites tumor

BCM - blood clotting mechanism effects

bcs - Bacillus subtilis (bacteria)

bfa - body fluid assay

BLD - blood effects

bmr - bone marrow

BPR - blood pressure effects

brd - bird (domestic or lab)

bwd - wild bird species

C - continuous

CAR - carcinogenic effects

cat - cat

cc - cubic centimeter

chd - child

ckn - chicken

CL - ceiling concentration

clr - Chlamydomonas reinhardi (protoza)

CNS - central nervous system effects

COR - corrosive effects

CRIT DOC - NIOSH criteria document

ctl - cattle

CUM - cumulative effects

CVS - cardiovascular effects

cyt - cytogenetic analysis

D - day

dck - duck

DDP - drug dependence effects

DEF - definition

dlt - dominant lethal test

dmg - Drosophila melanogaster (insect)

Table A-1. (Cont'd)

dnd - DNA damage
dni - DNA inhibition
dnr - DNA repair
dns - unscheduled DNA synthesis
dog - dog
dom - domestic
DOT - Department of Transportation
dpo - Drosophila pseudo-obscura (insect)
emb - embryo
EPA - Environmental Protection Agency
esc - Escherichia coli (bacteria)
ETA - equivocal tumorigenic agent
eug - Eugiena gracilis (protoza)
eye - administration into eye (irritant)
EYE - eye effects (systemic)
fbr - fibroblast
frg - frog
GIT - gastrointestinal tract effects
GLN - glandular effects
gm - gram
gpg - guinea pig
grb - gerbil
grh - grasshopper
H - hour
ham - hamster
hla - HeLa cell
hma - host mediated assay
hmi - Haemophilus influenzae (bacteria)
hmn - human
hor - horse
I - intermittent
ial - intraaural
IARC - International Agency for Research on Cancer
iat - intraarterial

Table A-1. (Cont'd)

ice - intracerebral
icv - intracervical
idr - intradermal
idu - intraduodenal
ihl - inhalation
imm - immersion
imp - implant
ims - intramuscular
inf - infant
ipc - intraplacental
ipl - intrapleural
ipr - intraperitoneal
IRDS- primary irritation dose
irn - intrarenal
IRR - irritant effects (systemic)
isp - intraspinal
itr - intratracheal
ivg - intravaginal
ivn - intravenous
kdy - kidney
kg - kilogram
klp - Klebsiella pneumoniae (bacteria)
L - liter
LC_{50}- lethal concentration 50 percent kill
LC_{Lo}- lowest published lethal concentration
LD_{50}- lethal dose 50 percent kill
LD_{Lo}- lowest published lethal dose
leu - keukocyte
lng - lung
lvr - liver
lym - lymphocyte
M - minute
m^3 - cubic meter
mam - mamal (species unspecified)

Table A-1. (Cont'd)

man - man
mg - milligram
MGN - multigeneration
mky - monkey
ml - milliliter
MLD - mild irritation effects
mma - microsomal mutagenicity assay
MMI - mucous membrane effects
mmo - mutation in microorganisms
mmol- millimole
mmr - mammary gland
mnt - micronucleus test
MOD - moderate irritation effects
mol - mole
mppcf - million particles per cubic foot
mrc - gene conversion and mitotic recombination
msc - mutation in somatic mamallian cells
MSK - musculo-skeletal effects
MTDS- mutation dose
MTH - mouth effects
mul - multiple routes
mus - mouse
NEO - neoplastic effects
ng - nanogram
nmol- nanomole
nsc - Neurospora crassa (mold)
nse - non-standard exposure
OBS.- obsolete (trade name)
ocu - ocular
omi - other microorganisms
oin - other insects
open- open irritation test
orl - oral
ORM - Other Regulated Material (DOT)

Table A-1. (Cont'd)

OSHA - Occupational Safety and Health Administration
oth - other cell types
otr - oncogenic transformation
ovr - ovary
par - parenteral
pg - picogram
pgn - pigeon
pic - phage inhibition capacity
pig - pig
Pk - peak concentration
pmol - picomole
PNS - peripheral nervous system effects
post - after birth
ppb - parts per billion
pph - parts per hundred
ppm - parts per million
ppt - parts per trillion
pre - prior to copulation
preg - pregnant
PSY - psychotropic effects
PUL - pulmonary system effects
qal - quail
rat - rat
RBC - red blood cell effects
rbt - rabbit
rec - rectal
REGS - standards and regulations
rns - rinsed with water
RPDS - reproductive effects dose
RTECS - Registry of Toxic Effects of Chemical Substances
S - second
sal - salmon
sat - Salmonella typhimurium (bacteria)
sce - sister chromatid exchange

Table A-1. (Cont'd)

WBC - white blood cell effects
wmn - woman
Y - year
% - percent

[a]From RTECS microfiche edition, October 1981 (Lewis and Tatken 1981).

[b]More recent editions of RTECS may use abbreviations not included on this list. Any abbreviation can be identified by using the Key to Abbreviations in the Appendix of the RTECS edition being used.

Table A-2. Species Abbreviations Used in RTECS[a,b]

Mammalian

cat - cat, adult

ctl - cattle

chd - child

dog - dog, adult

dom - domestic animal (goat, sheep)

grb - gerbil

gpg - guinea pig, adult

ham - hamster

hor - horse, donkey

hmn - human

inf - infant

mam - mammal (species unspecified in reference)

man - man

mky - monkey

mus - mouse

pig - pig

rbt - rabbit, adult

rat - rat

sql - squirrel

wmn - woman

Nonmammalian

asn - Aspergillus nidulans (mold)

bcs - Bacillus subtilis (bacteria)

brd - bird (any domestic or laboratory bird reported but not otherwise identified)

bwd - bird (wild bird species)

ckn - chicken

clr - Chlamydomonas reinhardi (protoza)

dck - duck

dmg - Drosophila melanogaster (insect)

dpo - Drosophila pseudo-obscura (insect)

esc - Escherichia coli (bacteria)

Table A-2. (Cont'd)

eug - Eugiena gracilis (protoza)
frg - frog
grh - grasshopper
hmi - Haemophilus influenzae (bacteria)
Klp - Klebsiella pneumoniae (bacteria)
nsc - Neurospora crassa (mold)
pgn - pigeon
qal - quail (laboratory)
sal - salmon
sat - Salmonella typhimurium (bacteria)
slw - silkworm
smc - Saccharmyces cerevisiae (yeast)
srm - Serratia marcescens (bacteria)
ssp - Schizosaccharomyces pombe (yeast)
tod - toad
trk - turkey

[a]From RTECS microfiche edition, October 1981 (Lewis and Tatken 1981).

[b]More recent editions of RTECS may use abbreviations not included on this list. Any abbreviation can be identified by using the Key to Abbreviations in the Appendix of the RTECS edition being used.

Table A-3. Route of Administration Abbreviations Used in RTECS[a,b]

eye	eyes
ial	intraaural
iat	intraarterial
ice	intracerebral
icv	intracervical
idr	intradermal
idu	intraduodenal
ihl	inhalation
imp	implant
ims	intramuscular
ipc	intraplacental
ipl	intrapleural
ipr	intraperitoneal
irn	intrarenal
isp	intraspinal
itr	intratracheal
ivg	intravaginal
ivn	intravenous
mul	multiple
ocu	ocular
orl	oral
par	parenteral
rec	rectal
skn	skin
scu	subcutaneous
unk	unreported

[a]From RTECS microfiche edition, October 1981 (Lewis and Tatken 1981).

[b]More recent editions of RTECS may use abbreviations not included on this list. Any abbreviation can be identified by using the Key to Abbreviations in the Appendix of the RTECS edition being used.

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16. ABSTRACT

This report presents a preliminary screening technique by which a large number of potentially hazardous compounds can be numerically ranked using readily available information on health effects and release to the ambient air. Factors considered are oncogenicity, mutagenicity, reproduction and developmental toxicity, acute lethality, effects other than acute lethality, production volume, vapor pressure, bioaccumulation and existing standards.

17. KEY WORDS AND DOCUMENT ANALYSIS

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